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Contents

Trust in Conventional Healthcare and Utilization of Complementary and Alternative Medicine in South Tyrol, Italy: A Population-Based Cross-Sectional Survey

Verena Barbieri[1], Stefano Lombardo[2], Timon Gärtner[1], Giuliano Piccoliori[1], Adolf Engl[1], Christian J. Wiedermann[1,3]

Abstract

Background. This study explored the link between trust in conventional healthcare and consultations with complementary and alternative medicine (CAM) providers in South Tyrol, Italy's linguistically diverse region.

Methods. A representative cross-sectional survey of 1,388 South Tyrolean adults assessed trust in conventional healthcare, general practitioners, and complementary and alternative medicine consultation frequencies and their determinants using chi-square tests and Kendall-Tau-b correlations.

Results. Seventy percent trusted the traditional healthcare system, with general practitioners as the primary trusted professionals. Trust is correlated with higher education and linguistic compatibility. A 5% subgroup, mostly women and multilinguals with lower education levels, showed uncertain trust. Over 80% had seen a general practitioner in the last year, while distrust was correlated with complementary and alternative medicine consultations. German and Ladin speakers, with higher education levels, were notably inclined towards complementary and alternative medicine consultations.

Conclusions. Trust in South Tyrolean healthcare varied according to education level and language. While general practitioners remain central, there is a marked shift towards complementary and alternative medicine among specific groups.

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[1] *Institute of General Practice and Public Health, Claudiana – College of Health Professions, Bolzano (BZ), Italy*

[2] *Provincial Institute for Statistics of the Autonomous Province of Bolzano-South Tyrol (ASTAT), Bolzano (BZ), Italy*

[3] *Department of Public Health, Medical Decision Making and Health Technology Assessment, University of Health Sciences, Medical Informatics and Technology – Tyrol, Hall, Austria*

Introduction

Trust in healthcare influences patient decisions and compliance, but has declined pre- and post-pandemic (1-5). It serves as a metric for healthcare effectiveness (6) and is affected by demographic factors such as language and education (7-9). Mistrust can lead to the overuse or underuse of services (10-12) and has contributed to an increase in Complementary and Alternative Medicine (CAM) use (13, 14). The popularity of CAM, particularly in the Western World, remains a subject of debate (15-22) and is partly driven by mistrust in conventional medicine (23-25).

Italy's CAM regulations are complex and vary by region (26, 27). South Tyrol has a unique CAM integration model, but lacks comprehensive usage data (28, 29). Vaccine hesitancy is high among the German-speaking population and is linked to lower education levels and distrust in conventional healthcare (30, 31).

This study aims to examine variations in trust in South Tyrol's bilingual context, focusing on demographic factors such as language and education, assessing which healthcare providers and institutions in South Tyrol are the most and least trusted, investigating regional CAM usage patterns and their relation to trust in conventional healthcare, and examining perceptions of healthcare professionals and their influence on health choices, including CAM inclination. Based on these findings, informed and evidence-based strategies may be proposed to improve trust in the South Tyrolean healthcare system.

Methods

1. Study participants sampling and recruitment

The survey was conducted by the Provincial Statistical Office (ASTAT) in scientific collaboration with the Institute of General Practice and Public Health of the College of Health Professions Claudiana in Bolzano, Italy. According to Italian law, approval by the ethics committee and written informed consent are not required for non-clinical questionnaire-based or register-based population studies (Legislative Decree No. 121 of May 5, 2001). This study was conducted in accordance with the principles of the Declaration of Helsinki. The provision of information about the survey, its purpose, and voluntary participation in the interview constituted implicit consensus. This study was conducted in compliance with the European Union's General Data Protection Regulation (GDPR), which supersedes the Italian Personal Data Protection Law (Legislative Decree No. 196 of June 30, 2003). Informed consent was obtained from all subjects involved in the study.

The administration of the questionnaires to participants was conducted through a structured approach. Each participant received a personalized invitation letter, which included the specified date for participation. The letter contained a link to an online questionnaire, designed to gather a comprehensive range of demographic, clinical, and socio-behavioral data relevant to our study. To ensure the privacy and confidentiality of participant's responses, a personalized password was provided with each invitation. This password served as a pseudonymization code, allowing participants to securely access and complete the questionnaire online. Additionally, to accommodate participants who might face challenges with the online format or have any queries regarding the questionnaire, telephone support was made available.

A total of 1,388 questionnaires were completed. The estimated response rate, which is the ratio of the number of units responding to the number of eligible units, is 39%. The average time taken to complete the questionnaire was 26 minutes. The dropout rate ("people who started to fill in the questionnaire but did not finish") was 5%.

1.1. Questionnaire

The questionnaire assessing trust was an adapted version of the COSMO questionnaire (32) using a 6-point Likert scale (1= no trust…6=big trust) with a seventh option for "I don't know." Trust in local institutions (regional free emergency numbers, civil protection, local Government), national medical institutions (national Ministry of healthcare, "Istituto Superiore di Sanità"), regional medical institutions (healthcare professionals colleges, leaders of the regional sanitary system) and in the WHO was asked as well as trust in specific healthcare professionals (pharmacists, vaccine staff, nursing staff, general practitioners (GPs), pediatricians, private specialists, specialists in hospitals, physiotherapists, nutrition consultants, director of the local sanitary system).

The International Questionnaire (I-CAM-Q) was used to measure CAM use. It is a widely recognized instrument designed to capture detailed data on CAM consumption patterns. To ensure accuracy and inclusivity in the bilingual context of South Tyrol, the survey employed both its German and Italian versions (15, 33).

Demographic variables were asked in accordance with the COSMO questionnaire (32), and a question to assess the local mother tongue was added with the options "German, Italian, Ladin, other language/more than one language according to the local mother tongues.

As primary outcome variable "trust in health care professionals" was analyzed, and "trust in the national healthcare system" as secondary outcome variable.

1.2. Statistics

The total study population included an adult population residing in South Tyrol. Individuals permanently residing in nursing homes or other community institutions were excluded from this study. The statistical unit, which is the same as the survey unit, is the individual unit. This study used a stratified probability-sample survey. A total of 3,800 names were randomly selected from the population registers of the South Tyrolean municipalities using Statistical Analysis System (SAS) software (SAS Institute, Cary, NC). Stratification was based on the following variables: municipality of residence, age, and gender. Estimates were obtained using calibration estimators. For this purpose, post-stratification was carried out on the known totals according to the following variables: nationality, geographical area (three zones), municipality size (two classes), age, and sex. The weights were calibrated using the software "R Functions for Calibrated Weighting and Complex Variance Estimation in Survey Data Analysis" (ReGenesees; Italian National Institute of Statistics, Rome, Italy). The estimated percentages were rounded to the nearest total number. Therefore, the sum of the percentage distributions may differ from 100 (99 or 101).

To assess trust, the 6-point Likert scale was redefined as dichotomous (1–3: low trust; 4–6: high trust) (34, 35). The responses were analyzed separately.

Nominal and ordinal data were presented as absolute and relative frequencies, and age was presented as mean (M) ± standard deviation (SD). Significant differences between groups were assessed using chi-square tests, and correlations were calculated using Kendall's tau-b. Significance levels were defined as $p<0.05$ (*), $p<0.01$ (**), and $p<0.001$ (***).

Results

1.1. Demographics

A total of 1,388 participants completed the questionnaire, and their demographic patterns are presented in Table 1. The mean age was 50.3 years and 51% were female. Household income increased in the last three months for 5% of the participants, remained the same for 66.9%, decreased for 25.2%, and 2.9% did not know whether it had increased or decreased. Education level was reported by 18.1% of the participants as primary school, 28.7% as vocational school, 31.3% as high school, and 21.8% as university. German was the mother tongue of 63.1% of the participants, Italian 27.1%, and Ladin 3.7%, whereas 6.1% declared that they had another mother tongue. Of the participants, 40.5% reported living in an urban area, 90.2% reported having Italian nationality, and 18.2% reported having a chronic disease.

1.2. Trust in healthcare professionals and institutions

Table 1 shows demographic and health characteristics of the 1,388 participants, categorized by their trust in healthcare professionals: low trust (28.5%), high trust (66.5%), and "don't know" (5%). No significant differences were found in sex, age, residence, or chronic diseases between the groups. Trust levels are linked to household income, education, native language, and nationality. Stable income was correlated with higher trust, whereas low education, multiple mother tongues, and non-Italian citizenship were associated with uncertainty in trust.

Variances were observed in the percentage of participants who were unfamiliar with the different health professionals. The rates of unfamiliarity were as follows: GPs, 4.1%; vaccination professionals, 4.5%; pharmacists, 4.6%; care professionals, 7.6%; hospital specialists, 11.3%; general directors of the regional health system, 20.7%; private sector specialists, 21.8%; pediatricians, 35.1%; physiotherapists, 29.1%; and nutrition specialists, 36.1%.

Figure 1 provides a detailed breakdown of trust in various healthcare professionals and institutions, reflecting responses from participants familiar with each entity. Trust is measured on a 1 to 6 scale, with 1 indicating no trust and 6 indicating high trust. General Practitioners (GPs) and hospital specialists garner the highest trust at 78.6%, closely followed by specialists in the private sector at 79.4%, and pediatricians at 76.1%. The overall trust in healthcare professionals stands at 70%, akin to trust in nursing staff (71.8%) and pharmacists (70.8%). Vaccination specialists command a trust level of 67.7%. On the lower end, physiotherapists are trusted by 61.4% of respondents, while the general directors of the provincial health system and nutrition specialists see lower trust levels at 49.2% and 48.4%, respectively.

Table 1. Basic characteristics of the participants based on their trust in health care professionals.

	Total (N=1388)	Low trust in health care professionals (N=396)	High trust in health care professionals (N=923)	Don't know (N=69)	p-value
Women (%)	51	50.5	50.6	59.4	n.s.
18–34 years (%)	23.8	22.9	23.6	30.9	n.s
35–49 years (%)	24.1	29.0	21.9	25.0	
50-64	29.8	28.7	30.8	23.5	
65+	22.3	19.4	23.7	20.6	
Household Income within the last 3 months					
Better	5.0	3.8	5.4	5.8	<0.001
Equal	66.9	61.0	70.5	52.2	
Lower	25.2	31.6	22.0	31.9	
Don't know	2.9	3.5	2.2	10.1	
Years of Education					
Primary school	18.1	17.9	17.2	31.9	0.003
Vocational school	28.7	28.3	28.7	31.9	
Secondary school	31.3	34.3	30.1	29.0	
College/university	21.8	19.2	23.9	7.2	
Mother tongue					
German	63.1	64.6	63.0	55.9	<0.001
Italian	27.2	26.0	28.4	17.6	
Ladin	3.7	3.8	3.7	2.9	
More than one/ other	6.1	5.5	5.0	23.6	
Urban residency	40.5	41.9	40.0	39.1	n.s.
Italian nationality	90.2	94.2	89.9	72.5	<0.001
Chronic disease	18.2	16.4	19.0	18.8	n.s.

Figure 1 also presents the trust levels in national and regional institutions as well as in the WHO on a scale of 1 (no trust) to 6 (high trust). Trust in both national and international entities was relatively consistent, at approximately 60%. This was evident in institutions such as the Italian National Health System, the "Istituto Superiore di Sanità," the WHO, regional free emergency numbers, and the directory of the regional health system. Among these, civil protection recorded the highest trust at 69.2%, whereas regional government registered the lowest at 45.5%. Regarding unfamiliarity with certain institutions, 17.8% of respondents were unfamiliar with regional free emergency numbers and 17.2% were unaware of the "Istituto Superiore di Sanità." For the remaining institutions, between 5% to 8% of participants opted for the "I don't know" response.

1.3. CAM Usage Patterns

1.3.1. Consultations with CAM Providers within the last 12 months

Table 2 provides a breakdown of patients' consultations with various health practitioners in the past year, the perceived efficacy of these consultations, and the primary reasons for seeking such services. Overall, the table illustrates the preferences and experiences of participants regarding various health practitioners, emphasizing the importance of GPs in healthcare consultations and underscoring the role of both conventional and alternative health practices in addressing acute and chronic conditions as well as the pursuit of holistic well-being.

A substantial percentage (81.7%) of the participants reported consulting a GP in the past year. Among
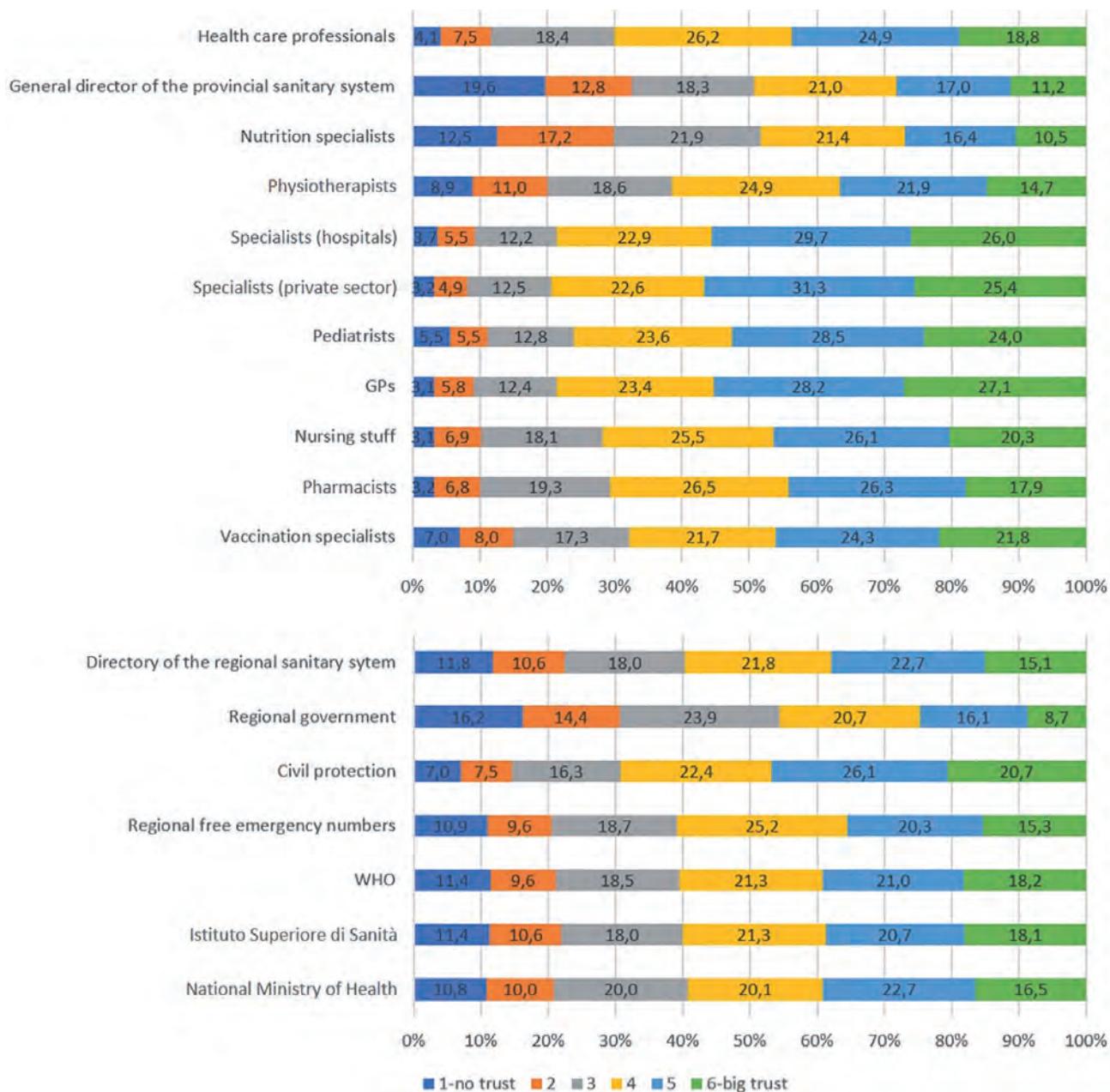
Figure 1. Trust spectrum in healthcare professionals and institutions. This figure visualizes the spectrum of trust in various healthcare professionals and national and regional institutions, rated on a scale from 1 (no trust) to 6 (high trust). The graph categorizes trust levels into six segments, illustrating the percentage of respondents within each trust bracket. The x-axis represents the percentage of responses, while the y-axis lists the professional groups and institutions. Responses of 'I don't know' are excluded for visual clarity but are discussed in the manuscript text.

Table 2. Consultation Rates, Efficacy, and Reasons for Seeking Different Health Practitioners in the Past Year

Health practitioner	Consulted within the last year (%)	Consultations very/ rather helpful (%)	Reason for consultation (%)		
			Acute illness	Chronic disease	Improve wellbeing
GP	81.7	86.1	43.0	19.7	37.4
Osteopath	9.9	75.1	24.0	24.9	51.1
Homeopath	8.7	65.4	15.0	27.2	57.8
Medical CAM specialist	4.8	74.5	9.7	29.1	61.5
Non-medial CAM specialist	4.5	69.1	11.5	26.7	61.8
Other	4.4	66.3	10.7	28.1	61.8
Acupuncteurist	3.8	65.7	11.9	36.3	51.7
Chiropractor	3.4	69.0	23.0	25.7	51.4

those who consulted GPs, 86.1% found consultations helpful. The main reasons for consulting GPs included acute illness (43%), chronic diseases (19.7%), and desire to improve overall well-being (37.4%).

Osteopaths were consulted by 9.9% of participants, with 75.1% receiving beneficial consultations. Reasons for seeking osteopathic care varied as follows: 24% for acute illness, 24.9% for chronic diseases, and 51.1% for well-being. Homeopathy services were sought by 8.7% of participants, with 65.4% perceiving consultations as very helpful. The reasons for consultation were acute illness (15%), chronic disease (27.2%), and the goal of improving well-being (57.8%). Medical CAM

specialists were consulted by 4.8% of the participants and 74.5% deemed the sessions beneficial. These specialists were primarily approached for chronic conditions (29.1%) and with the purpose of enhancomg wellbeing (61.5%). Consultations with non-medical CAM specialists were reported by 4.5% of the participants, with 69.1% finding them useful. Sessions were sought for acute illness (11.5%), chronic diseases (26.7%), and pursuit of better well-being (61.8%). The "Other" category of practitioners was consulted by 4.4% of participants, with 66.3% appreciating the efficacy of the sessions. The consultations were primarily for acute health concerns (10.7%), chronic conditions (28.1%),
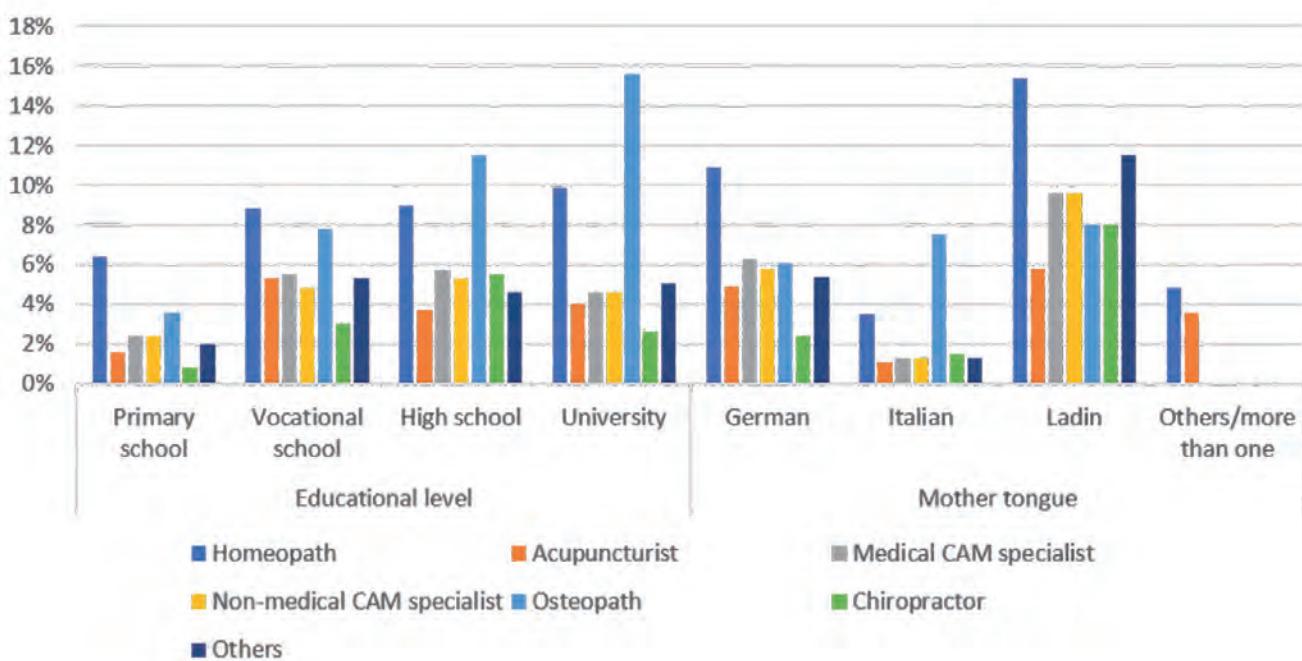
Figure 2. Consultation of CAM-providers within the last 12 months per educational level and mother tongue.

and general well-being (61.8%). Acupuncturists were seen by 3.8% of respondents, with 65.7% deeming their sessions beneficial. The reasons were spread among acute illnesses (11.9%), chronic ailments (36.3%), and enhanced wellbeing (51.7%). Finally, 3.4% of participants consulted chiropractors. Of these, 69% found their care very helpful. Consultations were predominantly for acute health issues (23%), chronic conditions (25.7%), and the enhancement of overall well-being (51.3%).

Most participants found the treatment beneficial (over 65%, Table 2). GPs were consulted mainly for acute conditions (43%), whereas CAM providers were consulted mainly for improving well-being (over 50% each) and for chronic conditions (over 20%). Acupuncturists were consulted for chronic conditions in 36.3% of cases, followed by medical CAM specialists (29.1%).

Women consulted GPs (85.6% vs. 77.5%, p<0.001), homeopaths (11.7% vs. 5.4%, p<0.001), acupuncturists

(4.9% vs. 2.6%; p=0.026), medical CAM specialists (6.1% vs. 3.5%; p=0.027), non-medical CAM specialists (5. 9% vs. 2.9%; p=0.007), and osteopaths (13.1% vs. 6.5%; p<0.001) more often than men within the last 12 months, whereas no significant sex difference was found for chiropractors and others.

The 35–49 years age group consulted CAM providers significantly more often than the 65+ (p<0.001) and 50–64 years age groups (p<0.001). Among the individual CAM providers, a significant difference between age groups was only found for osteopaths (p=0.009):18-34 years old participants:8.5%; 35-49:13.2%; 50-54:12.4%, and 65+:5.8%.

1.3.2. Influences of Education and Linguistic Backgrounds on differences in CAM consultations

The influence of education and linguistic background is shown in Fig. 3. Participants with different levels of education considered CAM providers
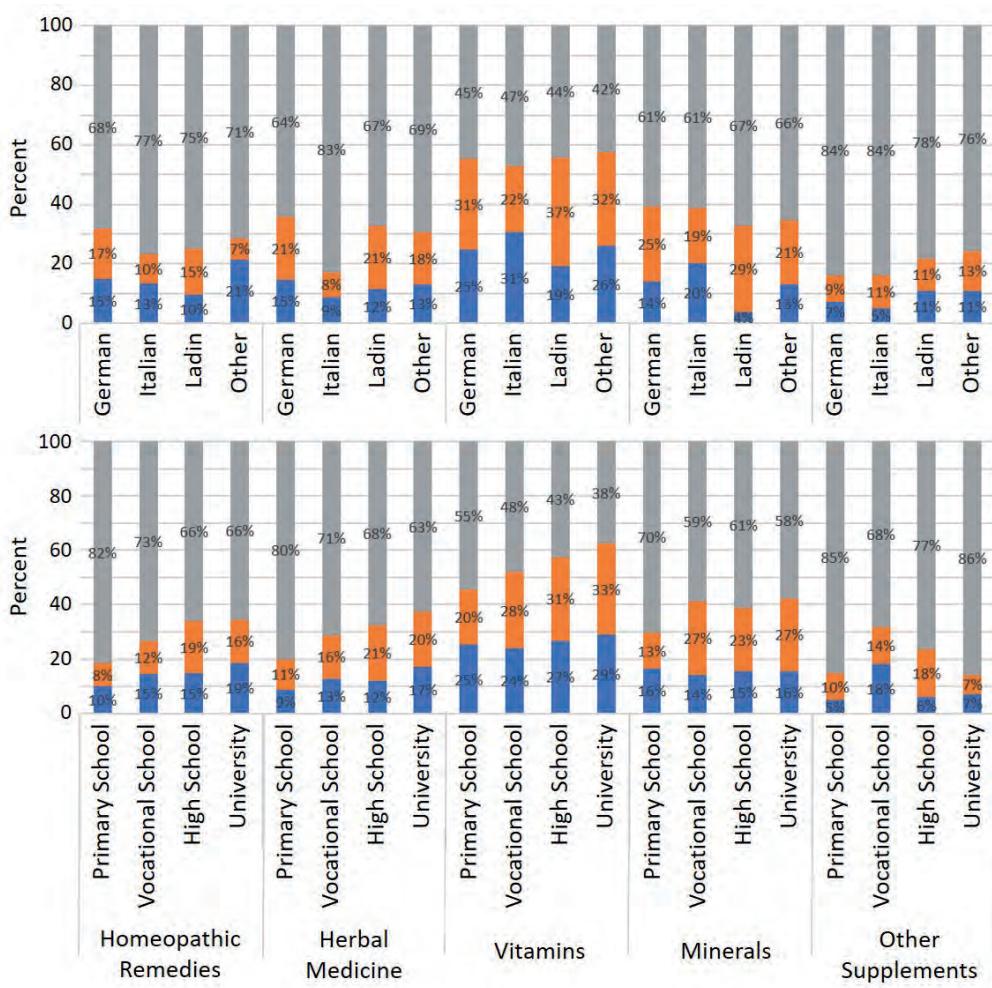
Figure 3. Use of herbal remedies per mother tongue and educational level. (Blue - Yes, by prescription; Orange - Yes, without prescription; Grey - No)

significantly different (p<0.001). Participants with primary education consulted CAM providers in 4.9% of cases, those. With vocational education in 10.1% of cases, those with secondary education in 12.6% of cases, and those with university degrees in 13.2% of cases. Significant differences were found between primary education and all other educational levels (p<0.001 for both).

Regarding consultations with individual CAM providers, significant differences were found between the educational levels for osteopaths and chiropractors. Osteopaths were consulted by 3.6% of the participants with primary education, 7.8% with vocational education, 11.5% with high school education, and 15.6% with university education. Significant differences were found between participants with primary education and those with other levels of education (vocational school, p=0.031; high school and university, p<0.001 each). The difference in osteopath consultations between participants with vocational school and university education was significant (p=0.001). Chiropractors were consulted by 0.8% of primary school participants, by 3.0% of vocational school participants, by 5.5% of high school participants, and by 2.6% of university participants. The only significant difference was found between the participants with primary and high school education (p=0.002).

Differences between German, Italian, Ladin, and more than one native tongue were also investigated. No significant differences were found between participants with German and Ladin mother tongues in total consultations with CAM providers, consultations with GPs, or individual consultations with CAM providers. Significant differences were found between the German (12.3%) and Italian (6.8%) language groups (p<0.001), the Italian and Ladin (12.8%) language groups (p=0.027), and the German language group and the group of participants who reported having more than one native tongue (6.8%, p=0.026).

There was also a significant difference in the number of consultations with the GPs between the German and Italian groups (80.1% vs. 85.9%, p=0.014). For individual CAM providers, a significant difference between the German and Italian groups was found for homeopaths (10.9% vs. 3.5%; p<0.001), acupuncturists (4.9% vs. 1.1%, p=0.001), medical CAM specialists (6.3% vs. 1.3%; p=0.001), non-medical CAM specialists (5.8% vs. 1.3%; p<0.001), and other CAM providers (5.4% vs. 1.3%, p=0.001). No significant differences were found between the osteopaths and chiropractors. Significant differences between the Italian and Ladin groups were found for homeopaths

(3.5% vs. 15.4%, p<0.001), acupuncturists (1.1% vs. 5.8%, p=0.012), medical CAM providers (1.3% vs. 9.6%, p<0.001), non-medical CAM providers (1.3% vs. 9.6%, p<0.001), and others (1.3% vs. 11.5%, p<0.001).

1.3.3. Self-help Practices

Approximately 78% of the participants reported using at least one self-help technique in the past 12 months. The most popular treatment modalities were prayer (29.1%), relaxation (21.4%), yoga (14.7%) and meditation (13.4%). Self-help practices were mainly used to improve well-being (usually more than 80%), followed by chronic conditions (approximately 10%) and less often acute conditions (less than 10%). Most participants considered all modalities to be very helpful. Painting/music-making was very helpful in 90.6% of the cases, yoga in 85.8%, and meditation in 82.9%. QiGong (64.9%) and Prayer (68.6%) were the least effective techniques.

In general, females used self-help techniques more than males (77.6% vs. 57.8%; p < 0.001), with only ThaiChi and prayer for personal health showing no significant gender differences. Differences between language groups were found only for yoga (German, 18.1%; Italian, 8.7%; Ladin, 15.4%; other/more than one language, 7.2%; p=0.002), praying for personal health (German, 32.2%; Italian, 22.6%; Ladin, 32.7%; more than one/other, 21.5%; p<0.001), and other self-help techniques (German, 13.0%; Italian, 7.7%; Ladin, 1.5%; more than one/other, 15.1%).

Educational level significantly influenced the use of self-help techniques (primary school: 46%; vocational school: 54%; high school: 50%; university: 57%; p<0.001). While no significant difference was found in panting/music-making, there was a significant decrease in praying for personal health with increasing educational level (primary school, 38%; vocational school, 31%; high school, 26%; university, 23%, p<0.001). For Thaichi and participation in ritual healing, there were small significant differences between levels of education. For all other techniques such as meditation, yoga, QiGong, relaxation, and visualization, there was a significant increase in their use with increasing levels of education.

1.3.4. Use of Natural Remedies

Nearly 68% of the participants used natural remedies, most commonly vitamins (54.8%), and minerals (38.5%). Females were more likely to use them than were males (59.9% vs. 43.7%, p<0.001). Use increased with education as follows: 55.4%

(primary), 64.2% (vocational), 73.2% (high school), and 75.9% (university) (p<0.001) (Fig. 3). Language also influenced use: German (68.9%), Italian (67.2%), Ladin (59.6%), and multilingual (65.5%) (p<0.001). Germans favored herbal and homeopathic remedies, Italians preferred dietary supplements, and multilinguals mainly used vitamins.

For all single natural remedies, a significant association was found between increasing age and increasing use of natural remedies (homeopathic remedies, p=0.003; herbal remedies, p<0.001; vitamins, p=0.04; minerals, p=0.01; others, p<0.001).

2. Trust in Health Care System Components and CAM Use

2.1. Healthcare Professionals

Kendall's tau-b correlation coefficient was calculated for trust in healthcare professionals and the CAM parameters. There was a significant negative correlation between trust in healthcare professionals and CAM consultations (rho= −0.084**), and a slightly positive correlation between trust and GP consultation (rho=0.063*). There was also a significant positive correlation between the GP and CAM consultations (rho=0.109**). The highest correlations were found between CAM consultation and the use of natural remedies (rho=0.227**) and between CAM consultation and the use of self-help techniques (rho=0.249**). The use of self-help techniques and natural remedies were positively correlated (rho=0.266**).

While trust in healthcare professionals seems to deter CAM consultations, it encourages GP consultations. Moreover, those engaged in CAM consultations were particularly inclined to use natural remedies and self-help techniques. The overall percentage of CAM consultations in the last 12 months was approximately 21.2%, GP consultations were 81.7%, use of natural remedies (prescribed or not) was about 67.9%, and use of self-help techniques was about 78.1%. These four subgroups were analyzed in detail (Fig. 4).
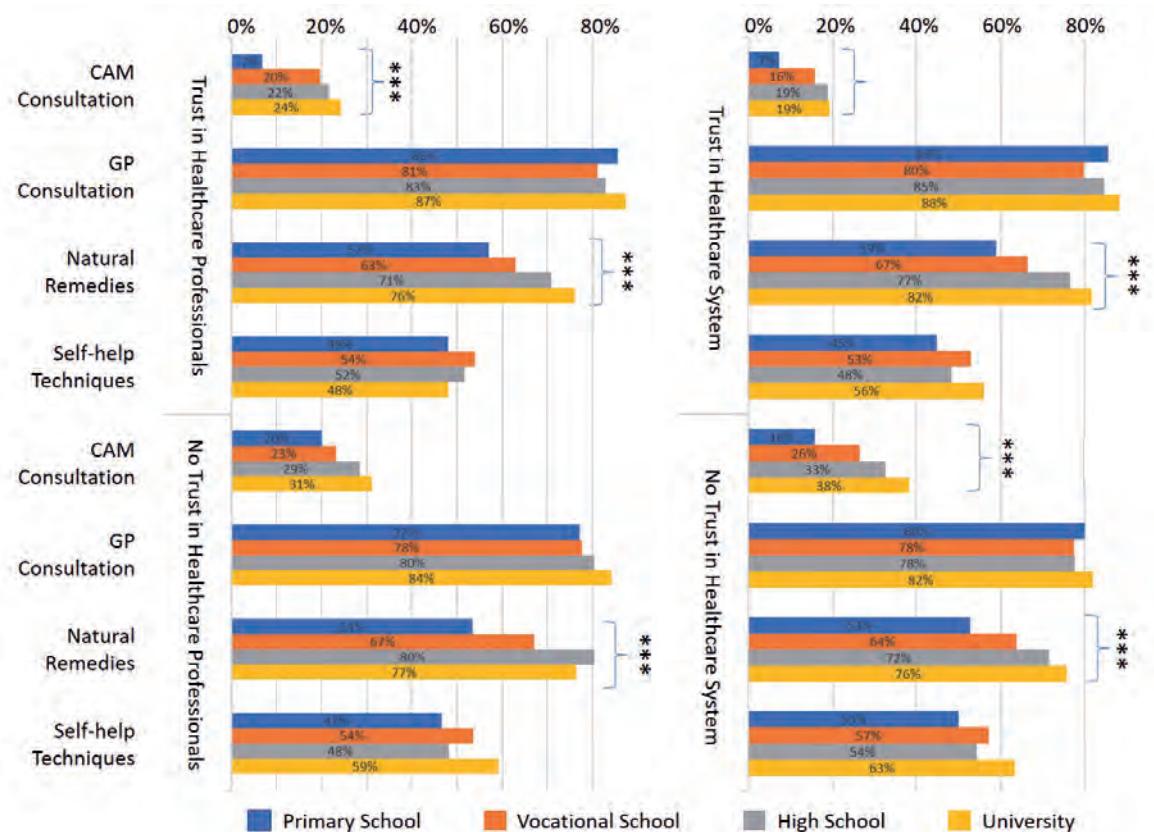
Figure 4. Consultation of CAM-specialists and GPs, use of natural remedies and self-help techniques per educational level for subgroups of persons trusting and non-trusting in health care professionals and the health care system.

CAM practitioner consultation: People with low or no trust in health professionals consulted CAM practitioners significantly more often (26.3% vs. 19.2%, p=0.004) than those with high or high trust. No significant differences were observed in consultations with GPs, use of natural remedies, or self-help techniques. The following individual CAM practitioners were consulted significantly more often by participants with low or no trust in healthcare providers than by those with high or low trust: homeopaths (14.1% vs. 6.4%; p<0.001), medical CAM practitioners (8.6% vs. 3%; p<0.001), non-medical CAM practitioners (8.3% vs. 2.9%; p<0.001), and others (8.3% vs. 2.7%, p=0.001). No significant differences were found among acupuncturists, osteopaths, and chiropractors.

In both the trust and mistrust subgroups, language significantly affected CAM consultations. Among the trusters, Italians consulted CAM specialists the least (12.6%), followed by Ladins (20.6%), Germans (21.8%), and multilinguals (22.2%), with p=0.004. Among the distrusters, Germans (30.5%) and Ladins (46.7%) consulted CAM specialists more than Italians (15.5%) and multilinguals (13.6%) did.

GP consultation, use of natural remedies, and self-help techniques for the groups of participants who had consulted a GP in the last 12 months, who had used natural remedies, and who had used self-help techniques, showed no significant difference between the language groups.

There was a clear significant increase with an increasing level of education in CAM consultation (p<0.001), use of natural remedies (p<0.001), and use of self-help techniques (p<0.001) in the group of people who trusted health professionals. In the mistrust group, only a significant increase in the use of natural remedies was observed (P <0.001) (Fig. 4). Regarding individual CAM providers, homeopaths were consulted significantly more often by mistrusting participants than by trusting participants (14.1% vs. 6.4%, p<0.001) as well as by medical CAM providers (8.6% vs. 3.0%; p<0.001), non-medical CAM providers (8.3% vs. 2.9%; p<0.001), and other CAM providers (8.3% vs. 2.7%). No significant differences were found among acupuncturists, osteopaths, and chiropractors.

Individuals with little or no trust in healthcare professionals were significantly more likely to use homeopathic (35.5% vs. 26.9%; p=0.002) and herbal remedies (37.1% vs. 28.0%; p=0.004). No significant differences were found in vitamin, mineral, or other dietary supplements.

2.2. National Ministry of Health

Those with little or no trust in the Ministry of Health were significantly more likely to consult CAM specialists (28.4% vs. 16.3%, p<0.001) and significantly less likely to consult GPs (78.8% vs. 84.6%, p=0.007) than were those with high trust. The following CAM specialists were consulted significantly more often by participants with no or low trust in the Ministry of Health: homeopaths (14.6% vs 4.8%), acupuncturists (5. 5% vs. 2.7%, p=0.011), medical CAM providers (8.1% vs. 2.5%; p<0.001), non-medical CAM providers (6.6% vs. 3.1%; p=0.003), chiropractors (5.6% vs. 1.9%; p<0.001), others (7.0% vs. 2.7%; p=0.001). No significant differences were observed between the osteopaths.

No significant differences in trust were found in the use of natural remedies or among the native speakers towards the Ministry of Health. However, trust varied by educational level, with university graduates showing the highest level of trust at 67.8%. While education did not affect trust in GP consultations or self-help use, it significantly increased CAM consultation and natural remedy use in both the trusting and mistrusting subgroups (Fig. 4).

Discussion

This study investigated trust in healthcare and CAM consultation patterns among adults in Northern Italy. Most participants (70%) trusted healthcare providers, particularly the GPs. Higher education and linguistic compatibility were positively associated with trust, whereas the geographic location within the region had no impact. A vulnerable 5% subset— primarily women, multilinguals, those with low education, or non-Italians—expressed uncertainty in their healthcare trust, indicating a need for targeted information interventions.

Over 80% of the participants consulted a GP in the last year, indicating a high utilization rate of GP services. This rate of consultation does not directly equate to trust, as evidenced by the fact that 30% of our sample expressed mistrust in healthcare professionals, particularly among German speakers and the highly educated, which led to increased CAM use. Trust did not affect GP visits, but influenced the choice of CAM providers. Distrust in health authorities has pushed people towards CAM and away from GPs. Higher education increased CAM and natural remedy use regardless of trust, underlining the role of trust in

steering patients between mainstream and alternative healthcare (6).

While a preference for CAM can suggest some level of skepticism towards conventional treatments, it does not invariably imply a complete rejection of conventional healthcare. In many instances, individuals may choose CAM due to personal health beliefs, cultural influences, or as a complement to conventional medical treatments, rather than as an outright alternative. Individuals with higher education levels may exhibit a more cautious and informed approach to using certain medications, such as antibiotics, and may favor natural remedies not necessarily as a manifestation of mistrust but as part of a broader, "informed" healthcare strategy from their part.

Economic stability was a crucial determinant of trust in healthcare professionals in this study. Those with stable incomes expressed higher trust, aligning with the notion that personal financial well-being shapes perceptions of healthcare system reliability (36). Importantly, trust correlates not only with perceptions but also with better health outcomes (37). These findings underline the role of socioeconomic factors in healthcare disparities and trust, offering actionable insights into areas that require targeted intervention.

Contrary to the expectations, conventional demographics such as age and gender did not significantly impact trust levels, possibly due to the uniform quality of care in Italy's National Health Service. Larger influences, such as healthcare policies or tools for measuring trust, may explain this (38). More nuanced sociocultural factors, such as education and language, affect trust (39). Linguistic diversity, notably among multilinguals, indicates uncertainty in trust and potentially signals communication barriers in healthcare (40). Higher education levels often lead to better-informed opinions and varied trust levels, highlighting the role of information access in shaping trust.

In South Tyrol (Alto Adige in Italian), a Region with german-speaking people are a majority and the there is a kind of autonomous regionalcgovernment, healthcare policies allow to search for specialized services in Germany and Austria. This option may inadvertently influence trust, particularly among German-speaking residents who frequently use these foreign services. This suggests that linguistic factors can create disparities in trust in healthcare.

High trust in GPs and hospital specialists underscores their pivotal role in healthcare (41, 42). Most participants had consulted a GP in the past year, primarily for acute illnesses. While CAM providers are consulted less often, they often address overall well-being or chronic conditions, indicating their role in holistic or long-term care (23, 43).

Education level was correlated with CAM consultation frequency and herbal remedy use, suggesting increased openness to alternative healthcare among the more educated (43). Linguistic background significantly influenced CAM consultations; Italian speaking people were less inclined towards CAM than their German or Ladin counterparts. Those distrusting the Ministry of Health notably favored CAM specialists. Trust varied across educational levels but was not significantly influenced by language. The data show that women tend to consult a more diverse range of healthcare providers, particularly in the CAM sector. This trend suggests that females may have unique health care needs and preferences that differ from males, possibly due to biological, psychological or social factors (23). In order to develop more effective gender-specific health strategies, it is essential to recognize these differences. Such strategies should take into account women's different health-seeking behavior and ensure that health services, whether conventional or CAM, are tailored to their specific needs. This approach aims to provide more personalized healthcare and improve outcomes and patient satisfaction for females.

High trust levels correlate with frequent GP consultations, whereas lower trust is associated with CAM consultations and natural remedy use (44). Understanding trust factors in Italian and German communities is vital for aligning healthcare practices with evidence-based medicine in southern Tyrol. Higher education levels were correlated with increased use of natural remedies and self-help techniques, except for prayer. Linguistic groups displayed different preferences for these practices (23).

Among all the providers, GPs were rated as the most beneficial, followed by osteopaths and medical CAM specialists. Osteopathy and chiropractic pain are perceived as more manual and structural and require specialized training, unlike homeopathy and acupuncture, which are more holistically perceived and culturally rooted (45). Immediate relief from osteopathic or chiropractic treatments may explain their "tangible" benefit perception.

In light of WHO's encouragement for integrative healthcare practices (46), it is recommended that South Tyrol's CAM center seek to establish a collaborative relationship with conventional healthcare, especially with GPs. This integration should not be

unidirectional but rather a mutual effort, recognizing the need for open-mindedness and cooperation from both conventional healthcare providers and CAM practitioners. Tailoring treatments for South Tyrol's linguistic and cultural diversities are crucial. Cultural sensitivity training of CAM practitioners can improve the relationship with the patient. A synchronized approach incorporating empirical methods and community involvement will address South Tyrol's diverse needs.

Distrust in healthcare is correlated with more CAM consultations (23). Among German and Ladin speakers in South Tyrol, this trend does not extend to self-help or natural remedy. The impact of educational level on CAM use was independent of trust. The drive towards CAM may stem from a desire for personalized care, which self-guided remedies do not offer. The skeptics of conventional healthcare may seek reassurance from CAM professionals, instead of self-management.

This study revealed that trust in South Tyrol's healthcare system is influenced by language, education, and income. The GPs were exceptionally trusted, with a 78% trust rating, indicating a focal point for enhancing overall trust. Lower trust in mainstream healthcare is linked to higher CAM use, which is influenced by linguistic and educational factors. This suggests that CAM could serve as an alternative to conventional healthcare.

In South Tyrol, efforts to increase trust in conventional healthcare should not only target healthcare professionals, who are instrumental in creating patient's trust, but also address the complex healthcare preferences of the better educated. While this group tends to have higher levels of trust in the healthcare system, their increased inclination towards CAM providers suggests a desire for diverse healthcare options. Healthcare strategies should therefore aim to build trust in conventional medicine while recognizing and accommodating the educated group's preference for CAM. The GP-patient relationship is crucial and should be reinforced through clear and understandable communication. The unique linguistic landscape of South Tyrol, especially the needs of Italian and German speakers, should be prioritized in these communication strategies. A specific subset of the population, mainly consisting of females, multilinguals, and those with lower education or non-Italian ethnicity, has an information gap. Targeted outreach and communication programs can bridge this gap effectively. Investment in strengthening the GP-patient relationship is further justified by the high consultation rates within this segment.

Limitations

This study has some limitations, including its focus on South Tyrol's unique sociocultural dynamics, which may not be generalizable to other regions. There is ambiguity in responses like "I don't know" when questioned about trust's complicate interpretation. The study only looked at consultations with CAM specialists, natural remedies, and self-help practices, without a comprehensive CAM-Use score. Additionally, the study relied on older research, potentially making the findings less relevant to the current healthcare landscape (38).

Conclusions

In South Tyrol, trust in healthcare is influenced by education, language, and nationality. GPs are the primary trust figures, but there has been a shift towards CAM, especially among specific language groups and the educated. Addressing language barriers and strengthening GP relationships could improve public healthcare outcomes.

Strengthening the relationship between GPs and patients is crucial, with a particular emphasis on linguistic compatibility to cater to South Tyrol's diverse language groups. Specialized communication and outreach programs should be developed to target vulnerable subgroups such as females, multilingual individuals, and those with lower education levels. To bridge the existing trust gap, it is advisable to better integrate complementary and alternative medicine services with conventional healthcare, especially since German and Ladin speakers in South Tyrol are more inclined to consult CAM providers. Finally, enhancing social support mechanisms that focus on economic stability could significantly boost trust in healthcare given the correlation between financial security and better health outcomes.

Riassunto

Fiducia nella Sanità Tradizionale e Utilizzo della Medicina Complementare ed Alternativa in Alto Adige, Italia: Un'Indagine Trasversale su Base di Popolazione

Premessa. Questo studio ha esplorato il legame tra la fiducia nei servizi sanitari e le consulenze con fornitori di medicina complementare e alternativa in Alto Adige, regione d'Italia di lingua diversa (tedesco).

Metodi. Un'indagine trasversale rappresentativa su 1.388 adulti altoatesini ha valutato la loro fiducia nei servizi sanitari, le frequenze di consultazione con medici di medicina generale e con i fornitori di medicine complementari ed alternative ed i determinanti di questi comportamenti, utilizzando test del chi quadrato e le correlazioni di Kendall-Tau-b.

Risultati. Il 70% dei partecipanti ha fiducia nel sistema sanitario, con i Medici di medicina generale come professionisti più fidati. La fiducia è correlata con un più alto livello di istruzione e con la compatibilità linguistica. Un sottogruppo del 5%, prevalentemente donne e multilingue con livelli di istruzione inferiori, ha mostrato una fiducia incerta. Oltre l'80% ha consultato un Medico di Medicina Generale nell'ultimo anno, mentre la sfiducia era correlata con le consultazioni con i fornitori di medicine complementari ed alternative. I parlanti tedesco e ladino con livelli di istruzione più elevati erano particolarmente inclini verso le medicine complementari ed alternative.

Conclusioni. La fiducia nei servizi sanitari altoatesini variava secondo l'istruzione e la lingua. Benchè i Medici di Medicina Generale rimangano centrali, si nota un marcato spostamento verso le medicine complementari ed alternative in gruppi specifici.

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Corresponding author: Prof. Christian J. Wiedermann, MD, Institute of General Practice and Public Health, Claudiana – College of Health Professions, Lorenz-Böhler-Street 13, 39100 Bolzano (BZ), Italy
e-mail: christian.wiedermann@am-mg.claudiana.bz.it

Primary care doctors retirements in the context of an ageing population in Italy

Zeno Dalla Valle[1], Carlo Signorelli[1], Cristina Renzi[1,2]

Abstract

Background. *Ongoing shortages in primary care doctors/primary care paediatricians and increasing healthcare needs due to ageing of the population represent a great challenge for healthcare providers, managers, and policymakers. To support planning of primary healthcare resource allocation we analyzed the geographic distribution of primary care doctors/primary care paediatricians across Italian regions, accounting for area-specific number and age of the population. Additionally, we estimated the number of primary care doctors/primary care paediatricians expected to retire over the next 25 years, with a focus on the next five years.*

Study design. *Ecological study.*

Methods. *We gathered the list of Italian general practitioners and primary care paediatricians and combined them with the data from the National Federation of Medical Doctors, Surgeons and Dentists. Using data from the National Institutes of Statistics, we calculated the average number of patients per doctor for each region using the number of residents above and under 14 years of age for general practitioners and primary care paediatricians respectively. We also calculated the number of residents over-65 and over-75 years of age per general practitioner, as elderly patients typically have higher healthcare needs.*

Results. *On average the number of patients per general practitioner was 1,447 (SD: 190), while for paediatricians it was 1,139 (SD: 241), with six regions above the threshold of 1,500 patients per general practitioner and only one region under the threshold of 880 patients per paediatrician. We estimated that on average 2,228 general practitioners and 444 paediatricians are going to retire each year for the next five years, reaching more than 70% among the current workforce for some southern regions. The number of elderly patients per general practitioner varies substantially between regions, with two regions having >15% more patients aged over 65 years compared to the expected number.*

Conclusions. *The study highlighted that some regions do not currently have the required primary care workforce, and the expected retirements and the ageing of the population will exacerbate the pressure on the already over-stretched healthcare services. A response from healthcare administrations and policymakers is urgently required to allow equitable access to quality primary care across the country.*

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1 Faculty of Medicine, University Vita-Salute San Raffaele, Milan Italy

2 Epidemiology of Cancer Healthcare & Outcomes (ECHO) Research Group, Department of Behavioural Science and Health, Institute of Epidemiology & Health Care, University College, London, UK

Introduction

In Italy, primary care medicine is funded by the National Health Service ("Servizio Sanitario Nazionale", SSN) and is provided by general practitioners ("medici di medicina generale", GPs) and primary care paediatricians ("pediatri di libera scelta", PLSs). All citizens are registered with a GP or a PLS, and the switch from PLS to GP usually occurs when patients are aged between 6 and 14 years of age (1).

GPs and PLSs are the first point of contact for patients, playing a crucial role in providing appropriate healthcare, especially for individuals with chronic conditions. Additionally, GPs and PLSs provide preventive healthcare and contribute in reducing the number of unnecessary specialist visits, diagnostic investigations and Emergency Department (ED) visits, increasing the efficiency and appropriate use of healthcare resources (2).

In order to guarantee high-quality care, the current legislation and the national collective contract of Italian GPs allow a maximum of 1,500 registered patients per GP, with some exceptions, and recommending 1,000 patients per GP as the optimal number (3,4). Similarly, the current legislation and the national collective contract of PLSs allow a maximum of 880 registered children per PLS, with the optimal number being 600 per PLS (1).

To address the shortage of primary care doctors and to guarantee primary care to the entire population, some regions and Local Healthcare Trusts ("Aziende Sanitarie Locali", ASLs) raised the limit of registered patients (5,6). Primary care doctors are eligible for retirement at age of 68, but they can choose to prolong their working activity for the SSN up to age 70 (7). The recent law n. 14/2023 extended the possibility to work for the SSN up to age of 72, until the end of 2026, in response to the current shortage of physicians (8).

The burden of care faced by primary care doctors is primarily related to the ageing population and the high prevalence of multi-morbidity, defined as the simultaneous presence of two or more chronic diseases (9,10). The increase in the average age of the Italian population, caused by a reduced fertility rate (11) and a lengthening of life expectancy (12), will continue to lead to a rising primary care burden in the future years (13).

Reports by Healthcare Organizations at regional, national and international level, have highlighted the shortage of GPs and PLSs in Italy, attracting a large media attention (14–16). The National Agency for Regional Healthcare Services ("Agenzia Nazionale per i Servizi Sanitari Regionali", AGENAS) pointed out that between 2019 and 2021 the number of primary care doctors has decreased in many Italian regions and in the country overall. A negative balance between new GPs and newly retired GPs is expected in many regions and in the entire nation by 2025, with a loss of more than 3,600 GPs (17). The Italian Public Accounts Observatory ("Osservatorio Italiano dei Conti Pubblici") published a report in 2021, declaring that in 2019 every Italian GP had an average of 1,408 registered patients, slightly below the European average (1,430), which is however strongly conditioned by eastern European countries, with a much higher ratio (18).

The aim of this ecological study was to analyze the characteristics of primary care doctors currently working in Italy, considering regional differences and expected retirements over the next few years, to support future staffing needs estimates.

Methods

We used all the data available on the website of the National Federation of Medical Doctors, Surgeons and Dentists ("Federazione Nazionale degli Ordini dei Medici, Chirurghi e Odontoiatri", FNOMCeO) which contains an entry for every physician working in Italy. The dataset was updated on January 4, 2023. We also downloaded the list of GPs and PLSs working in Italy from each regional and national healthcare trust website and combined them. Every website is updated at different time periods, so we reported the data as available in each site (details in Supplementary Table 1).

The two datasets were then merged, trying to match as many fields as possible (including first name, last name, birthdate, and birthplace). We used the list of GPs and PLSs to integrate the FNOMCEO dataset with information on the job title (GP, PLS, other), the region and, when available, the province of work for every physician.

We unequivocally matched 40,933 (96.3%) primary care doctors, while for the remaining 1,594 physicians this was not possible, mainly due to homonyms and name transcription errors in the FNOMCeO dataset or in the list of primary care doctors.

From 40,933 primary care doctors, 172 entries were excluded due to lack of medical registration number, because they unsubscribed or their license was revoked, and nine entries were excluded as their medical license was temporarily suspended. The final analyses included a total of 40,752 medical doctors.

We examined differences between GPs and PLSs, described the age and gender distribution, overall and by Italian regions. We also evaluated the concordance between both province and region of work and province and region of birth, as well as the concordance between both province and region of work and province and region of Order registration, respectively. Moreover, we analyzed the number of resident population per GP and PLS (hereafter patients per GP and patients per PLS), a proxy indicator of the number of registered patients per GP and PLS, calculated as resident population in the region (≥14 years and <14 years of age per GP and PLS respectively). Then we estimated the expected number of retirements, calculated as the number of physicians who are turning 68 during the year of analysis, for each year over the next 25 years among the entire nation and over the next five years for each region. In such analyses, in order to produce estimates based on the total number of primary care doctors, we also considered the number of GPs and PLSs that were not matched and applied the age distribution of their matched colleagues.

The Italian territory was divided in the following geographic areas: north, including the north-eastern and north-western regions, centre, and south, including the two major islands.

To evaluate between-group differences, we used ANOVA for the continuous variables and chi-squared test for the categorical ones. Student's t test for independent samples was used in the post-hoc analysis.

P-values <0.05 were considered statistically significant. The Holm-Bonferroni method was applied to counteract the problem of multiple comparisons that occurred in the post-hoc analysis.

Analyses were conducted using Python v. 3.10.9 and the following libraries: pandas v. 1.5.3, scipy v. 1.10.1, statsmodels v. 0.13.5, matplotlib v. 3.7.1, seaborn v. 0.12.2. The library italy-geopop v. 0.6.2 was used to retrieve geographical and demographic data, as it includes data from 2022 from the National Institute of Statistics ("Istituto Nazionale di Statistica", ISTAT).

Results

Among the 40,752 Italian primary care doctors, there were 34,348 (84.3%) GPs and 6,404 (15.7%) PLSs. On average PLSs were older than GPs (mean age 58.3 vs. 56.8 years, p<0.001). PLSs were more frequently women than GPs (71.1% vs. 43.9%, p<0.001) (Tab. 1).

The lists contained the job province information for 20,740 primary care doctors. Province of work and province of Order registration were concordant in 91.6% of cases (Cramer's V=0.929); the region of work, available for all primary care doctors, matched the region of Order registration in 97.4% of the cases (Cramer's V=0.963).

We analysed the distribution by age classes for GPs and PLSs (Fig. 1A and 1B respectively). For both groups the majority were aged 64-67 years, followed by 60-63 years. We assessed gender differences, calculated on a subset of primary care doctors not eligible for retirement (GP n=29,994, PLS n=5,868), by age class and working region for both GPs and PLSs and they all resulted statistically significant (p<0.001) (Fig. 1C and 1E for GPs; 1D and 1F for PLSs). We found differences in the frequency distribution of female GPs between Italian geographic areas (north 50.1%, centre 49.5%, south 41.2%) with statistically significant differences between the north and the

Table 1. Characteristics of primary care physicians registered in Italy.

	GPs (n=34,348 or 84.3%)		PLSs (n=6,404 or 15.7%)		p-value
	N (%)	Min-Max	N (%)	Min-Max	
Age (years) Mean (SD)	56.8 (11.9)	24 - 83	58.3 (9.3)	27 - 79	<0.001
Graduation age (n=34,342) (years) Mean (SD)	27.8 (3.6)	21 - 63	26.0 (2.0)	22 - 47	<0.001
Sex (F)	15,063 (43.9%)		4,551 (71.1%)		<0.001
Birth province same as registration	23,494 (68.4%)		4,039 (63.1%)		<0.001
Birth region same as registration	26,993 (78.6%)		4,953 (77.3%)		<0.001

GP: general practitioner ("medico di medicina generale"), PLS: primary care paediatrician ("pediatra di libera scelta"), N: number of, SD: standard deviation, F: female
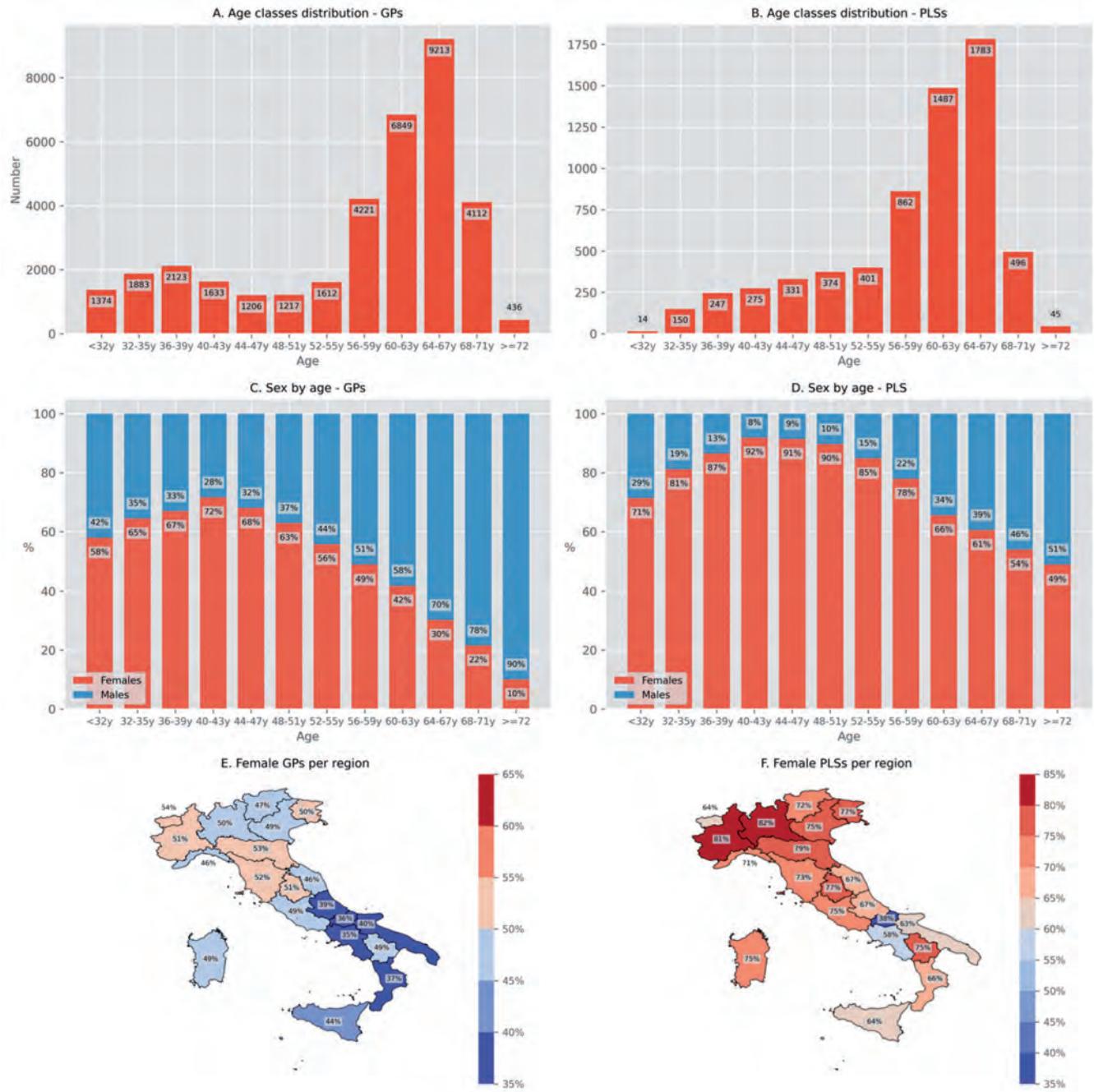
Figure 1. Age classes distribution, sex distribution by age class and sex distribution by region for GPs and PLSs
GP: general practitioner ("medico di medicina generale"), PLS: primary care paediatrician ("pediatra di libera scelta")

south and between the centre and the south (p=0.001, p=0.022, respectively).

On average the number of patients per GP was 1,447 (SD: 190) (Fig. 2A). The region with the highest number of patients per GP was Puglia (1,879), followed by Calabria (1,717). The number of patients per GP did not differ by geographic areas (p=0.111). Puglia was also the region with the highest number of older patients per GP, both patients over-65 and over-75 (Fig. 2B and 2C). We also estimated the expected number of over-65 and over-75 patients per GP using the Italian demographic age class distribution and 1,500 as the number of patients per GP. We then represented the percentage of variation between expected and observed values. The regions with the highest percentage of variation were Puglia, Basilicata and Calabria for the over-65 and Puglia, Liguria and Friuli-Venezia Giulia for the over-75. On average the
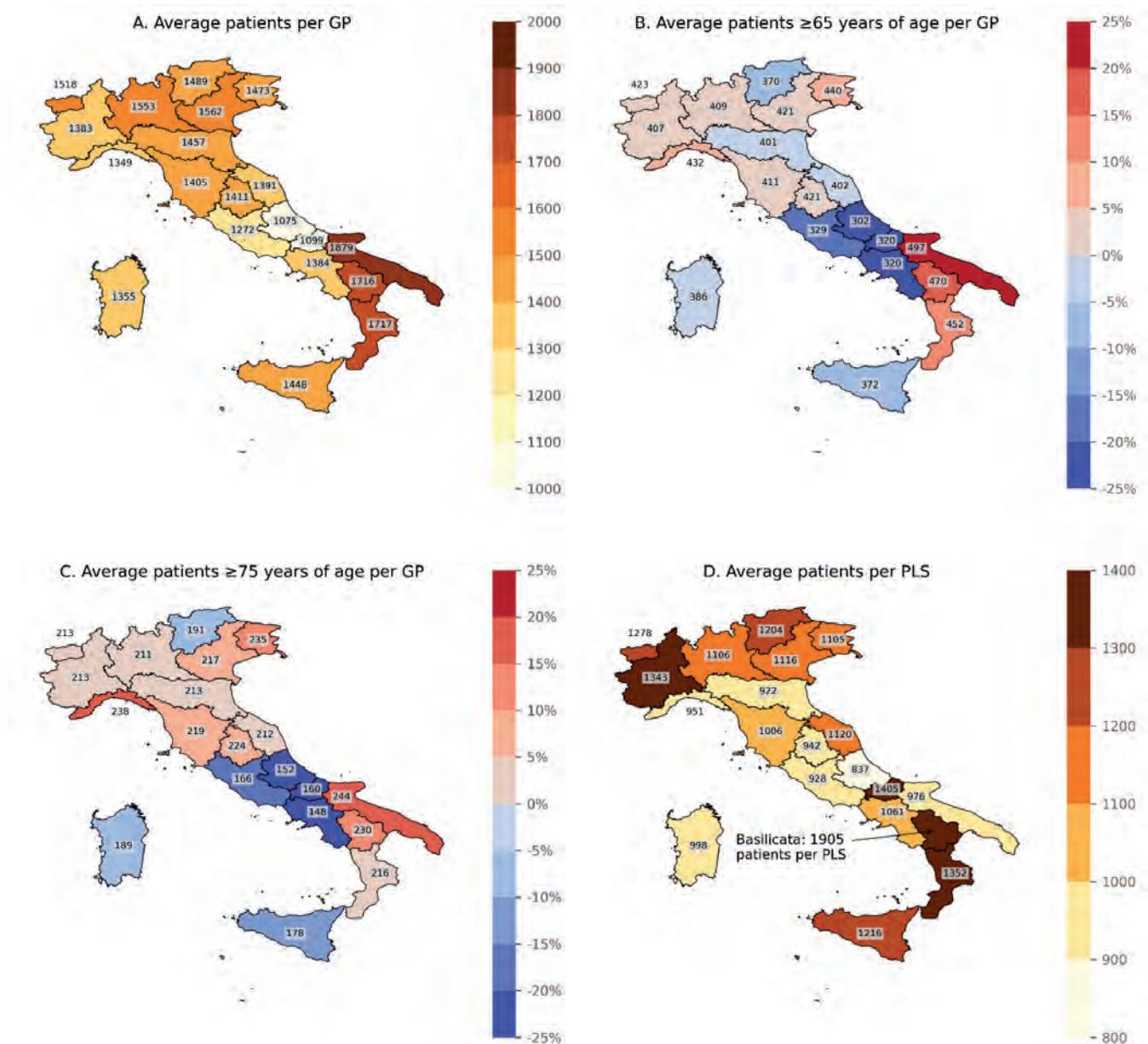
Figure 2. Average patients, average patients ≥65 years (with percentage variation from the expected value), average patients ≥75 years (with percentage variation from the expected value) per GP and average patients per PLS
GP: general practitioner ("medico di medicina generale"), PLS: primary care paediatrician ("pediatra di libera scelta")

number of patients per PLS was 1,139 (SD: 241) (Fig. 3D). The region with the highest number of children per PLS was Basilicata (1,905), followed by Molise. The number of children per PLS did not differ between geographic areas (p=0.123).

We estimated the expected retirements between 2023 and 2047, a 25-year span (Fig. 3A). In the next five years, until 2027, there will be on average 2,228 retirements each year, with a peak of 2,540 in 2024; this will be followed by a decreasing trend during the subsequent years, and it will settle to 305 on average from 2038. We calculated the percentage of GPs that already turned 68 before 2023 and were therefore eligible for retirement (Fig. 3B). The regions with
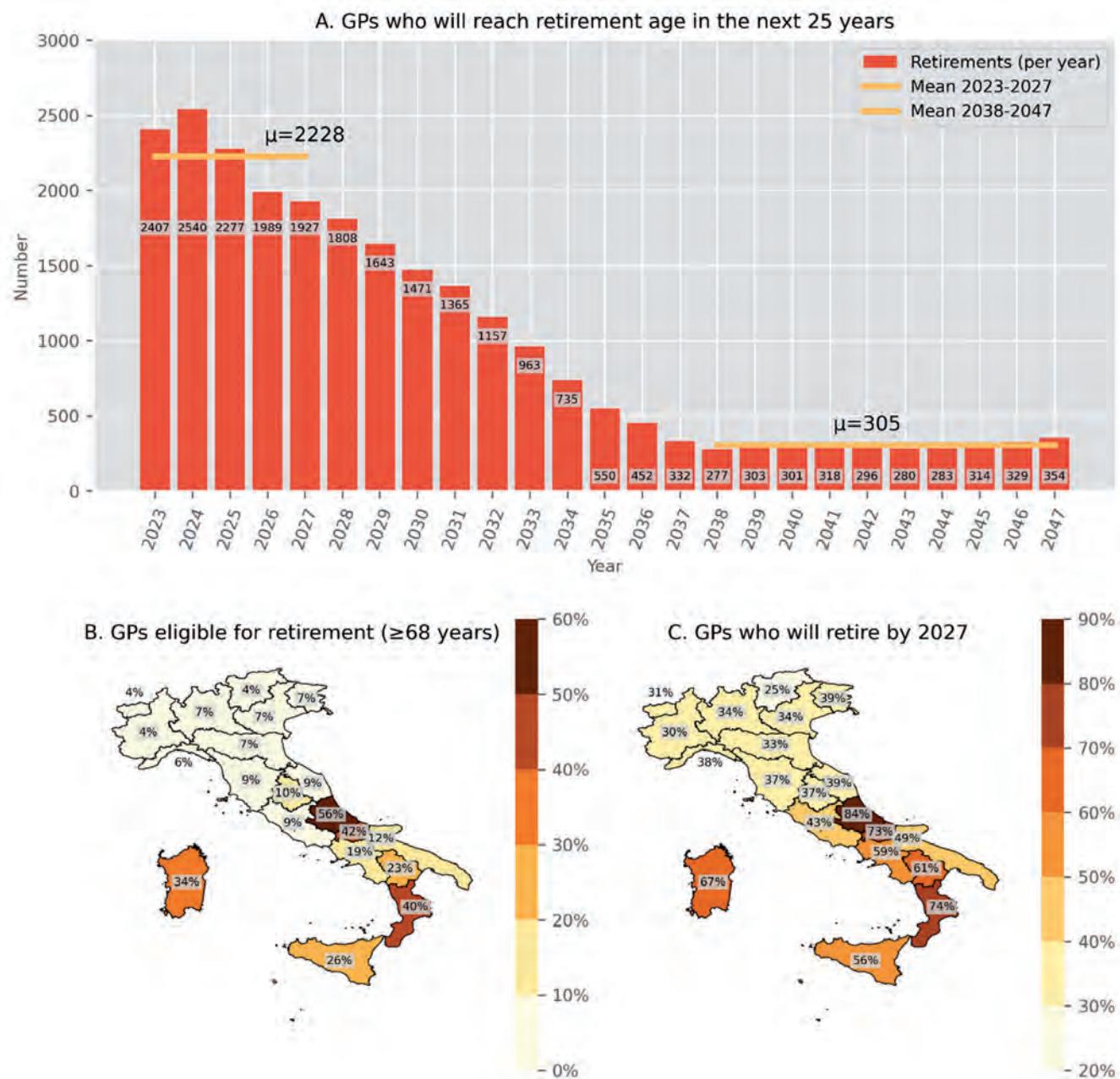
Figure 3. Retirements in the next 25 years for GPs, GPs already eligible for retirement and expected retirements by 2027 by region
GP: general practitioner ("medico di medicina generale"), μ: mean

the highest value were Abruzzo (56.0%) and Molise (41.8%). The regions with the lowest value were Valle d'Aosta (4.3%) and Piemonte together with Trentino-Alto Adige (4.4%). We found a statistically significant difference in the percentage of GPs that were eligible for retirement across Italian regions (p<0.001), with a north-south gradient (north 5.8%, centre 9.4%, south 31.6%).

The percentage of GPs that will turn or have already turned 68 by the end of 2027, five years from now, will span from 84.1% of Abruzzo to 25% of Trentino-Alto Adige (Fig. 3C).

The expected retirements for PLSs in the next five years will be 444 PLSs per year on average; this will be followed by a decreasing trend, and they will be 85 on average after 2038 (Fig. 4A). We calculated the percentage of PLSs who already turned 68 before 2023 (Fig. 4B). There was a statistically significant difference in the employment of PLSs eligible for retirement between Italian geographic areas (north 3.6%, centre 7.6%, south 20.4%, p=0.002), with north vs. south being significantly different (p=0.002). The percentage of PLSs that will turn or have already turned 68 by the end of 2027, five years from now, will span from 81.8% of Abruzzo to 26.4% of Trentino-Alto Adige (Fig. 4C).

We also calculated the number of GPs and PLSs who decided to extend their activity from 68 years of age to 70. In this analysis, we focused on the northern and central regions of Italy, for which the lists of primary care doctors were more updated (GP n=17,998, PLS n=3,281). The number of doctors aged 68 and 69 were 682 (3.8%) and 397 (2.2%), respectively, for GPs, while for PLSs they were 88 (1.4%) and 46 (0.7%).

Discussion

The study provides an overview of primary care doctors characteristics across Italian regions, accounting for the number and age distribution of the resident population. The findings highlighted that currently six regions, both in the northern and southern areas of the country, have an average number of patients per GP exceeding the threshold of 1,500. Overall, the average number of patients per PLS is 1,139, with only one region under the threshold of 880 patients per PLS. The study estimated that a large number of primary care doctors are expected to retire in the next five years (2,228 GPs and 444 PLSs every year on average), reaching more than

70% of retirements among the current workforce for some southern regions. The analysis also emphasized that the number of elderly patients, who typically have higher healthcare needs, varies substantially between regions, with two southern regions (Puglia and Basilicata) having >15% of patients aged over 65 years.

Insights into the geographic distribution of ageing populations, combined with data on the estimated large number of primary care doctors retiring over the coming years in some regions, can inform healthcare planners, aimed at reducing the pressure on already stretched services and allowing equitable access to quality care across the country.

The average number of residents per GP, which is in line with previous reports of 1,408 residents per GP for the year 2019, with a continuous increase compared to past years (18), highlights a heterogeneous picture across Italian regions. The region with the highest number of residents per GP is Puglia; while Abruzzo and Molise are the regions with the lowest number of residents per GP, they are the regions with the highest number of GPs eligible for retirement. The number of over-65 patients per GP varies substantially across regions due not only to the different number of primary care doctor workforce, but also due to a different demographic distribution. Our data show that the peak of retirements for GPs will occur during the year 2024, followed by a decrease in the number of retirements. This phenomenon will particularly concern southern regions, where the percentage of workforce retirement often exceeds 50%, and up to 84% in Abruzzo. Critical situations have been highlighted due to GPs' retirements and the impossibility of finding replacements or successors. Costa et al. described the activation of a territorial facility of primary care assistance where the local ASL couldn't find new GPs to replace those who retired. Thanks to nursing and administrative support it was possible to deliver care for more than 6,200 patients with a relatively small number of doctors (19). For PLSs, the largest age class is 64-67 years and, together with 60-63 years, it represents more than 50% of the Italian PLSs current workforce. Therefore, a big wave of retirements is expected also for PLSs in the next few years. In this case, a temporarily solution could be to facilitate the transition of patients to GPs.

The national governments tried to address the problem of retirements introducing the possibility for doctors to work for the SSN up to age 72 (8). The current study cannot fully evaluate the effectiveness of this measure but, considering that currently the
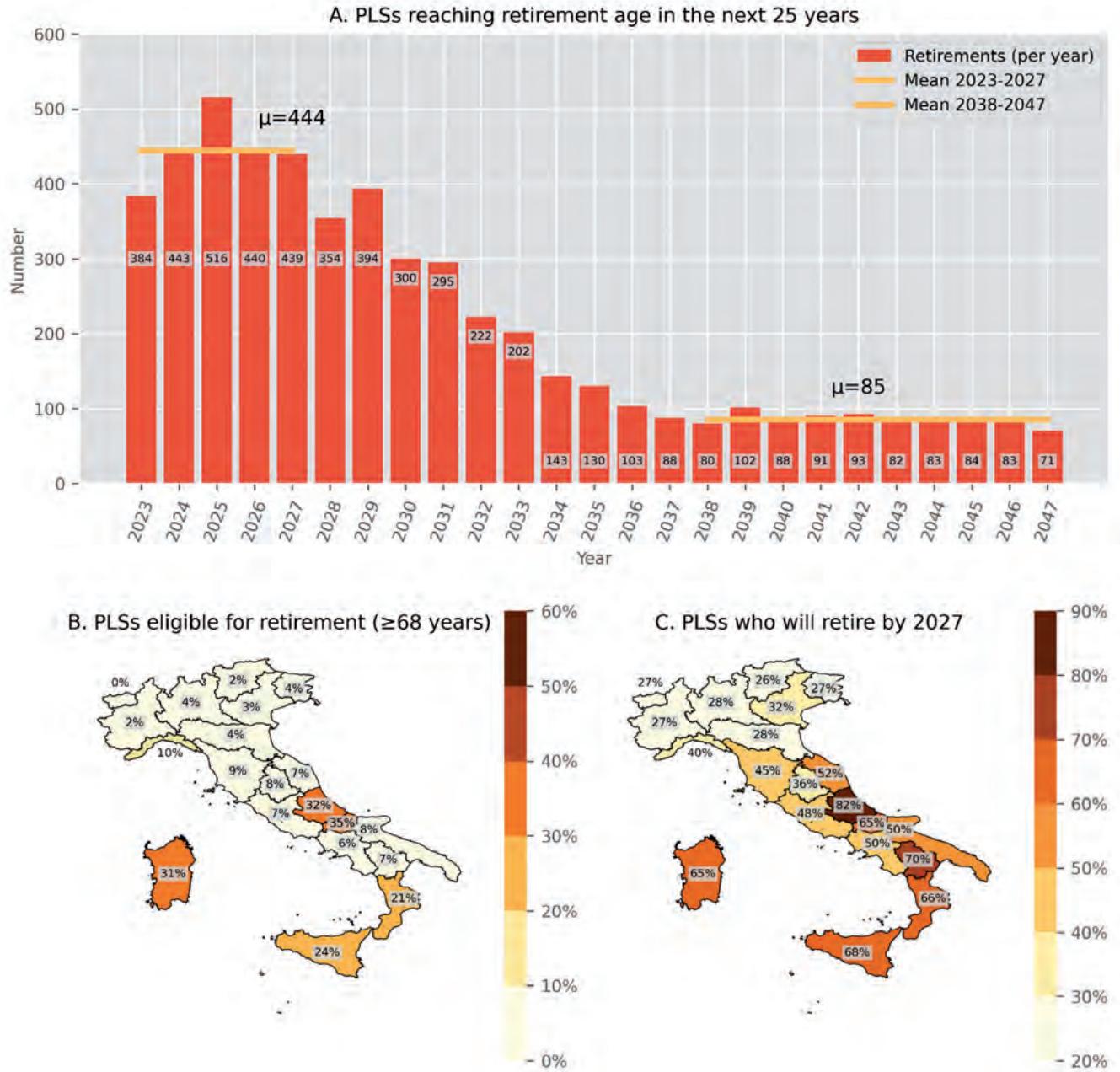
Figure 4. Retirements in the next 25 years for PLSs, PLSs already eligible for retirement and expected retirements by 2027 by region
PLS: primary care paediatrician ("pediatra di libera scelta"), μ: mean

percentage of doctors choosing to continue working after age 68 is only 6% for GPs and 2% for PLSs, we believe this measure can only have marginal benefits. Our data is not comparable with the AGENAS report about primary care doctors, due to the different time frame of analysis and the different method adopted by AGENAS for the calculation of the expected retirements, i.e. 70 years of age. However, the expected deficit of approximately 3,600 general practitioners that they calculated appears an under-estimation, as our data show that most doctors choose not to extend their activity. Moreover they calculated the number of new GP entries as the number of scholarships available for GP training courses, assuming all available scholarships will be assigned, and no dropouts during the three-year course, which are unlikely (17).

In addition to the retirement wave, primary care medicine will have to face the problem of ageing populations and multi-morbidity. As reported in the National Plan of Chronic Diseases (Piano Nazionale delle Cronicità), a substantial increase in the proportion of people aged over-65 years is expected, from the current value of 23.8% to 27.6% (corresponding to approximately 17.6 million people) in 2032 (13). In the region Emilia-Romagna, in the year 2016, the prevalence of multi-morbidity was 61.0% in the over-65-year-old age class and 72.5% in the over-80. Multi-morbidity was responsible for increased use of healthcare resources, accounting for approximately 89.0% of home care assistance (assistenza domiciliare integrata) (20). Thus, even assuming equal numbers of patients, a greater share of older populations entails a greater workload for GPs, with substantial differences between regions. A GP working in Puglia has on average 497 over-65-year-old patients, a 23.1% excess compared to the expected numbers, and 195 more than colleagues working in Abruzzo, the region with the lowest value (302 per GP, -25.1% than the expected). This, combined with the expected retirements, suggests a critical situation with serious repercussions on primary care in southern Italy.

The great concordance found between province and region of work and province and region of Order registration respectively suggests that the latter are a good proxy indicator of the place where doctors carry out the professional activity.

Our study has some limits. The lists of GPs and PLSs were not consistently updated, which might have influenced some of the findings. The number of residents per doctor is assumed to be a valid proxy for the number of patients registered with a primary care doctor, but the aggregated average value does not provide information about the between-doctor variability, considering that doctors can also limit the number of registered patients. Furthermore, accuracy of some data sources could not be verified and could be influenced by lists being out of date or affected by errors (e.g. 1,905 children per PLS in Basilicata). More studies would be needed to gain insights into the willingness of doctors to extend their working activity up to 70 or 72 years. Moreover, the quality of primary care medicine does not depend solely on the number of primary care doctors, but also on other aspects that must be assessed through other indicators.

Healthcare planning after estimating the required personnel has been less than optimal in the last years. Now the time has come to find solutions for dealing with the ongoing and expected personnel shortage and the increasing complexities in primary care needs. Surely investing in the administrative and nursing support can help primary care doctors providing care to more patients. Creating groups of doctors (medicina di gruppo), supported by healthcare administrations, is recommended. The National Recovery and Resilience Plan funded by the European Union also encourages this with the development of Community Health Centres (Case Della Comunità), which include administrative and nursing support for primary care doctors, potentially increasing the number of patients per GP.

Considering that six years of university plus three to five years of specialization are necessary to train primary care doctors, planning should take demographic trends of the population at a national and regional level into account. Moreover, it's important to identify factors that may prevent new graduates from choosing primary care medicine and strengthen the appeal of the profession among medical graduates.

The number of patients over-65 and over-75 per GP could be used, together with the overall number of patients, to better estimate the workload of GPs and establish new limits for the maximum number of registered patients, in order to guarantee a high-quality assistance.

Conclusions

The study provided an overview of primary care doctors characteristics across Italian regions, highlighting that some regions do not currently have the workforce needed to provide primary healthcare to all citizens, while respecting the limit of 1,500 patients per GP. The expected number of retirements

and the ageing population will exacerbate the situation of already over-stretched healthcare services. A response from regional healthcare administrations and policymakers is urgently required to allow equitable access to quality primary care across the country.

Riassunto

Pensionamenti dei medici di assistenza primaria e invecchiamento della popolazione in Italia

Introduzione. La carenza di medici nelle cure primarie (medici di medicina generale e pediatri di libera scelta) e l'aumento della domanda di prestazioni sanitarie dovuta all'invecchiamento della popolazione pone una grande sfida per manager e coordinatori dell'assistenza primaria. Per supportare la pianificazione dell'allocazione di risorse nelle cure primarie abbiamo analizzato la distribuzione geografica regionale dei medici delle cure primarie, considerando il numero di residenti e la loro età. Inoltre abbiamo stimato il numero di pensionamenti attesi nei prossimi 25 anni, con un focus particolare sui prossimi cinque anni.

Disegno dello studio. Studio ecologico.

Metodi. Abbiamo recuperato la lista dei medici di medicina generale e pediatri di libera scelta attivi in Italia e l'abbiamo combinata con i dati della Federazione Nazione degli Ordini dei Medici Chirurghi e Odontoiatri. Usando i dati dell'Istituto Nazionale di Statistica abbiamo calcolato il numero medio di pazienti per medico per ciascuna regione, utilizzando il numero di residenti di età maggiore e minore di 14 anni per i medici di medicina generale e per i pediatri rispettivamente. Abbiamo inoltre calcolato il numero di residenti con più di 65 e 75 anni per medico di medicina generale dal momento che i pazienti più anziani tipicamente hanno necessità assistenziali maggiori.

Risultati. Mediamente il numero di pazienti per medico di medicina generale era 1447 (DS: 190) mentre per i pediatri di libera scelta era 1139 (DS: 241), con sei regioni oltre il limite di 1500 pazienti per medico e solo una regione al di sotto del limite di 880 pazienti per pediatra. Abbiamo stimato che in media 2228 medici di medicina generale e 444 pediatri di libera scelta raggiungeranno l'età pensionabile ogni anno nei prossimi cinque anni, superando il 70% della forza lavoro corrente per alcune regioni del Sud Italia. Il numero medio di pazienti anziani per medico di medicina generale varia considerevolmente tra le regioni, con due regioni che hanno >15% in più di pazienti di età maggiore di 65 anni per medico rispetto al valore atteso.

Conclusioni. Lo studio ha evidenziato come alcune regioni non abbiano la forza lavoro necessaria per erogare l'assistenza primaria e come l'invecchiamento della popolazione accentuerà la già elevata pressione sui servizi sanitari. È urgentemente richiesta una risposta da parte degli amministratori e dei policy maker che permetta di introdurre strategie volte a mantenere l'accesso a cure primarie di qualità in tutto in territorio nazionale.

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Supplementary Table 1. Date of update of the lists of GPs and PLSs provided by regions or national health trusts.

Region	Frequency of update, distribution method, date of the list used in the study (day/month/year)	
	GPs	PLSs
Piemonte	Continuous update, website, 23/05/2023	
Valle d'Aosta	Continuous update, website, 23/05/2023	
Lombardia	Continuous update, website, 23/05/2023	
Trentino-Alto Adige	Continuous update, website, 23/05/2023	
Veneto	Continuous update, website, 23/05/2023	
Friuli-Venezia Giulia	Continuous update, website, 23/05/2023	
Liguria	Continuous update, website, 23/05/2023	
Emilia-Romagna	Continuous update, website, 23/05/2023	
Toscana	Continuous update, website, 23/05/2023	

Umbria
  ASL Umbria 1
  ASL Umbria 2
    District of Terni
    District of Foligno
    District of Spoleto
    District of Narni e Amelia
    District of Orvieto
    District of Valnerina
	
	Continuous update, website, 23/05/2023
	Periodic update, Excel tables
	13/04/2023[1]
	23/05/2023[1]
	06/04/2023[1]
	02/05/2023[1]
	07/02/2023[1]
	03/04/2023[1]
		
		Continuous update, website, 23/05/2023
		Periodic update, Excel tables
		26/01/2023[1]
		14/03/2023[1]
		24/02/2021[1]
		04/01/2023[1]
		17/01/2022[1]
		03/02/2023[1]

Marche	Continuous update, website, 23/05/2023	
Lazio	Continuous update, website, 23/05/2023	
Abruzzo	Continuous update, website, 23/05/2023	

Molise
  District of Campobasso
  District of Isernia
  District of Termoli-Larino
	
	Periodic update, website, 11/2018[1]
	Periodic update, pdf table, 10/2018[1]
	Unknow (list requested to the Public Relations Office), pdf table, unknown[2]	

Campania	Periodic update, website, 20/12/2022	Periodic update, website, 20/12/2022
Puglia	Continuous update, website, 23/05/2023	

Basilicata
  Lagonegrese and Senisese
  Val D'Agri
  Potenza and Potentino
  Vulture, Melfese and Alto Bradano
	Continuous update, Word table
	15/12/2022[1]
	24/11/2022[1]
	16/01/2023[1]
	13/09/2022[1]
		Continuous update, Word table (12/12/2022)[1]

Calabria
  ASP Cosenza
  ASP Catanzaro
  ASP Crotone
  ASP Reggio Calabria
  ASP Vibo Valentia
	
	Periodic update, website, 23/05/2023
	Periodic update, website, 26/04/2023
	Periodic update, pdf table, unknown[2]
	Periodic update, pdf table, unknown[2]
	Periodic update, website, 19/05/2020
		
		Periodic update, website, 23/05/2023
		Periodic update, website, 26/04/2023
		Periodic update, pdf table, unknown[2]
		Periodic update, pdf table, unknown[2]
		Periodic update, website, unknown[2]

Region	Frequency of update, distribution method, date of the list used in the study (day/month/year)	
	GPs	PLSs
Sicilia		
ASP Agrigento	Periodic update, pdf tables	Periodic update, pdf tables
District of Agrigento	09/05/2023	22/09/2021
District of Bivona	29/05/2023	30/11/2022
District of Canicattì	03/01/2023	03/01/2023
District of Casteltermini	06/09/2021	27/03/2017
District of Licata	07/07/2022	27/03/2017
District of Ribera	20/02/2023	27/03/2017
District of Sciacca	14/02/2023	27/03/2017
ASP Caltanissetta	Periodic update, website, 22/09/2021	Periodic update, website, 01/10/2019
ASP Catania	Periodic update, pdf table, 13/04/2023	Periodic update, pdf table,13/04/2023
ASP Enna	Periodic update, Excel table, unknown[2]	Periodic update, Excel table, unknown[2]
ASP Messina	Periodic update, website, unknown[2]	Periodic update, website, unknown[2]
ASP Palermo	Periodic update, pdf table, 12/05/2021	Periodic update, pdf table, 12/05/2021
ASP Ragusa	Periodic update, website, unknown[2]	Periodic update, website, unknown[2]
ASP Siracusa	Periodic update, pdf table, 01/12/2018	Periodic update, pdf table, 01/12/2018
ASP Trapani	Periodic update, pdf table, unknown[2]	Periodic update, pdf table, unknown[2]
Sardegna		
ASL Sassari	Continuous update, website, 23/05/2023	
ASL Olbia	Continuous update, website, 23/05/2023	
ASL Nuoro	Continuous update, website, 23/05/2023	
ASL Lanusei	Continuous update, website, 23/05/2023	
ASL Oristano	Continuous update, website, 23/05/2023	
ASL Sanluri	Continuous update, website, 23/05/2023	
ASL Carbonia	Continuous update, website, 23/05/2023	
ASL Cagliari	Continuous update, website, 23/05/2023	

ASP: national health trust (Azienda Sanitaria Provinciale), ASL: national health trust (Azienda Sanitaria Locale), GP: general practitioner, PLS: primary care paediatrician (pediatra di libera scelta), 1: date of update deducted by the file name, 2: date of update not reported and not deductible.

Corresponding Author: Zeno Dalla Valle, Faculty of Medicine, University Vita-Salute San Raffaele, Via Olgettina 58, 20132 Milan, Italy
e-mail: dallavalle.zeno@hsr.it

Home care models dedicated to COVID-19 patients: the experience of a Local Health District of Veneto Region (Italy)

Silvia Manea[1], Marco Pinato[2], Laura Salmaso[3], Silvia Vittorii[1], Michela Biasio[1], Matteo Rigoni[4], Vinicio Manfrin[5], Elisabetta Bertocco[6], Mirko Zanatta[7], Mario Saia[3]

Abstract

Background. *During COVID-19 pandemic, health professionals have been working in an extreme uncertainty context. Affected patients needed to be cared at home as long as possible to avoid virus spreading and hospital resources saturation. The Veneto Regional Administration (North-east of Italy) released Regional guidelines about it. The Western Healthcare District of the Local Health Authority of the city of Vicenza (180,000 inhabitants) implemented a healthcare pathway following them. Aim of the study is to describe the results and outcomes of such implementation.*

Methods. *In the implemented health care pathway, a new service called "Special Unit of continuity of care" (USCA) with physicians and nurses has been dedicated to the prise en charge at home of patients suffering from Sars-CoV-2. They were referred to the USCA by general practitioners or by hospital specialists, and managed through a daily clinical monitoring by regular home visits and phone calls, specialist consultations and therapy management. In order to prevent hospital admission, an oxygen concentrator when possible has been employed and managed at home by the members of the USCA when the oxygen saturation was below 93%. An observational retrospective study has been conducted using anonymized data from different databases: the USCA activity database (from 12/01/20 to 21/31/21), the hospital and Emergency Department discharge databases, and the "healthcare co-payments exemptions database". The latter database refers to the people excluded - because of their chronicity - from the co-payment of a list of medical exams and services. Descriptive and multivariate logistic regression analyses have been implemented.*

Results. *1,419 patients suffering from Sars-CoV-2 have been cared and managed by the USCA in the considered period of time (mean 11.4 days), of whom 787 (55.5%) with at least one chronic condition (described in the above quoted "healthcare co-payments exemption database") and 261 provided with oxygen concentrator. 275 (19.4%) needed a hospital admission, 39 (2.8%) in intensive unit; 53 died during hospitalization (3.8%). Out of the 261 patients utilizing oxygen concentrator, 103 have been admitted to*

1 *Primary Care Unit, Western Healthcare District, Local Health Authority "8 Berica", Vicenza, Italy*
2 *Public Health Department, Local Health Authority "8 Berica", Vicenza, Italy*
3 *Clinical Governance Unit, Local Health Authority "Azienda Zero", Padua, Italy*
4 *Hospital Management Department, Local Health Authority "8 Berica", Vicenza, Italy*
5 *Infectious Diseases Unit, Local Health Authority "8 Berica", Vicenza, Italy*
6 *Pneumology Unit, Local Health Authority "8 Berica", Vicenza, Italy*
7 *Emergency Unit of Valdagno, Local Health Authority "8 Berica", Vicenza, Italy*

Legenda: ED = Emergency Department; GP = General Practitioner; HCED = Healthcare co-payment exemptions database; HCD = Healthcare District; HCP = Healthcare Professional; HDR = Hospital Discharge Record; HS = Hospital Specialist; ICU = Intensive Care Unit; IQR = Interquartile Range; LHA = Local Health Authority; NHS = National Healthcare Service; OR = Odds Ratio; SAS = Statistical Analysis System; SD = Standard Deviation; USCA = Special Units of Continuity of Care

hospital (39.5%), 7.3% in intensive unit and 8.0% died. In implemented multivariate analyses, the use of oxygen concentrator, proxy measure of the severity of the condition, is the major determinant for the risk of hospital admission (adj OR: 3.2, CI 2.3-4.3) and of dying within 30 days (adj OR: 2.8 CI 1.5-5.1). Among the 261 patients provided with oxygen concentrator, 158 (60,5%) have been managed at home without any admission to emergency department and/or hospitalization.

Conclusions. *In an uncertain context such as COVID-19 pandemic, the already-implemented home care model has been modified by integrating the USCA physicians and nurses and specialist care networks to prevent hospitalization and the sense of isolation and abandonment of people as much as possible. Almost 1,500 patients suffering from COVID-19 have been cared for at home over 13 months by such new service with complex and multidisciplinary activities. The risk of hospitalization and death appears determined by the severity of the pathology with high and significant OR 60% of patients with oxygen concentrators who, despite an initial high hyposaturation were not hospitalized, represent, partly, the group of patients who would have been requiring hospital care in the absence of a home care pathway in a standard situation.*

Introduction

20th February 2020 was the day when the first Italian case of Covid-19 was reported in the Lombardy Region. An integrated National Surveillance System has been created after that, monitoring the increase of the cases in the different areas of the country and the risk of saturation of hospital wards, and - above all - of the intensive care units.

The Italian National Healthcare Service (NHS) is based on a network of 20 Regional Services, where the central government defines the minimum healthcare provisions of services to be guaranteed to all citizens and financed through the general taxation. Meanwhile, the Regional Governments are responsible for the organization and delivery of healthcare to the citizens and can provide additional health services on their own funds. Basic decentralized medicine is organized on a primary care basis in Local Health Authorities (LHAs) which are, in turn, divided into healthcare districts (HCDs) on which, in addition to other services, even the general practitioners (GPs) functionally depend.

Healthcare professionals (HCPs), during the COVID-19 pandemic, had to operate in a context of uncertainty: the overwhelming surge of patients simultaneously seeking medical care caused Intensive Care Units (ICUs) overcrowding and hospital beds' saturation. Pre-existing pathways for homecare management had to be used and adapted, aiming to reduce as much as possible the access to ICUs and hospitals, while maintaining the quality of care provided (1). Homecare provision for non-severe cases and/or those discharged from the hospitals turned out to be a pivotal action of the regional public health response. It was based on the well-developed health-social care services that were diffusely delivered at home by the HCDs, even before the outbreak of COVID-19 (2).

The Italian central government instructed all Regional governments to create special medical units called Special Units of Continuity of Care (USCAs) for managing COVID-19 patients in the community and monitoring those in home-isolation, supporting the GPs (2), with the purpose of reducing the burden on hospitals and ICUs. USCAs, where operative, had a pivotal role in home-based care provision, through telephone consultations, home visits and support to local GPs. The Veneto Region (north-east of Italy, with nearly 5 million inhabitants) activated the USCAs by the end of March 2020, issuing regional guidelines (3, 4).

This paper aims to describe the implementation and the clinical outcomes of care pathways for home-care management of patients suffering from COVID-19 through the USCAs, who may otherwise have required inpatient hospital care, in the Western HCD (about 180,000 residents) of the LHA "8 Berica" in Vicenza, Veneto Region, north-east of Italy (5).

Materials and Methods

Study design

A retrospective medical record review of all COVID-19 patients who received medical care from the USCAs in the Western HCD of the LHA 8 "Berica", from 01/12/2020 to 31/12/2021, has been conducted.

Home care pathway for patients suffering from COVID-19

Patients with confirmed or suspected COVID-19, who needed monitoring and/or therapy, were referred to the USCA by their GPs, by the Emergency Department (ED) physicians or by Hospital Specialists
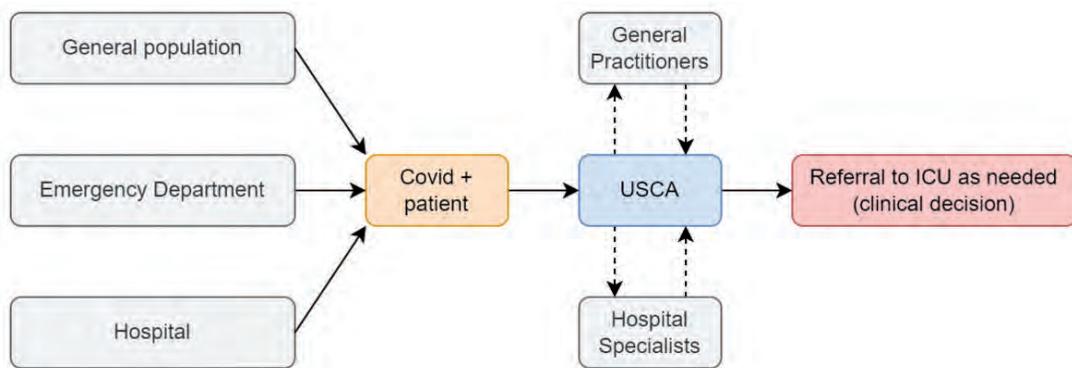
Fig. 1 - Referral pathway of patients suffering from COVID-19 to the USCA to be managed at home, Western HCD of LHA "8 Berica", Vicenza, Veneto Region (Italy)

(HSs), through email or direct telephone call at a dedicated mobile number, which was active 12 hours per day, 7 days per week (Figure 1).

Criteria for referral to USCA was mainly left on physicians' clinical decisions, considering patient's risk factors and clinical presentation. USCA physicians have been trained through remote courses by HSs (infectious diseases, lung and emergency department specialists) who became their referral specialists for cases cared at home.

Physicians of USCA units monitored patients through daily medical at-home evaluations (included, but not limited to, vital assessment: SpO2, heart and respiratory rates, blood pressure, body temperature), regular phone calls, management of therapy and frequent consulting with above-mentioned specialists, even remotely.

Patients with oxygen saturation levels below 93% were at high risk to be admitted to hospitals. Due to overcrowding of ED rooms and hospital wards, a home management approach, when possible, became necessary and had been implemented. If eligible, some of these patients were provided with an oxygen concentrator, with a maximum oxygen flow rate of 5 L/min. USCA physicians, supported by two pneumologists even by remote consultation, instructed the patients and/or their caregivers on how to use the device and monitored the utilization and the effectiveness both through home visits and remotely.

Sources of data

All diseased residents of the Western HCD of the LHA "8 Berica" who received USCA medical care had been identified through the USCA electronic archive which collected patients' demographic data and clinical data such as the start and end dates of USCA medical care, the date of assignment of the oxygen concentrator, the saturation levels at rest and under exertion.

Only records in the USCA electronic archive referred to residents suffering from Covid-19 were included in the study and linked with the hospital discharge records (HDRs) and with the healthcare co-payments exemptions database (HCED).

HDRs contain data on all inpatient episodes and were used to analyze hospital admissions and 30-day in hospital mortality.

The HCED was used to assess the presence of chronic conditions. It includes information on all individuals with a diagnosis performed by a medical specialist with specific conditions for which the NHS provides specific inpatient and outpatient free of charge services (i.e.: chronic obstructive pulmonary disease, diabetes, hypertension, cancer).

The study was conducted using anonymized records of data routinely collected by the healthcare services. All regional healthcare records undergo a standardized anonymization process that assigns a unique anonymous code to each individual, allowing record linkage between electronic healthcare records without any possibility of back retrieving the subject's identity. All data in the LHA registries are recorded with the patient's consent and can be used as aggregate data for scientific studies without further authorization. This study complies with the Declaration of Helsinki and the Italian Decree n.196/2003 on personal data protection.

Statistical analysis

Univariate and bivariate analyses were performed to summarize data with respect to the patient demographic characteristics. Continuous variables were reported with descriptive statistics [mean, S.D., median and interquartile range (IQR)]. For categorical variables, frequencies and percentages were calculated. The difference between groups was examined by Student's t-test or Mann–Whitney test for continuous variables, Pearson's χ^2 or Fisher's exact test for categorical variables, as appropriate. A P-value <0.05 was considered statistically significant.

We plotted Kaplan-Meier curves for hospitalization; curves were compared using the log-rank test. Follow-up started at the date of USCA taking charge until date of the first hospitalization or death or end of follow-up (30 days from the start of taking charge).

The OR 30-day hospital admissions and 30-day in-hospital mortality were estimated using logistic regression in both univariate and multivariate models, adjusting for age, sex, presence of chronic diseases, assignment of oxygen concentrator.

All statistical analyses were conducted using SAS (Statistical Analysis System) software V.9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Overall, in the considered time period, 1,419 patients who tested positive for COVID-19 were provided home-care by USCA physicians, for an average period of 11.4 days (std. dev.: 7.1) with a maximum of 69 days, through daily phone calls, at-home visits and management of therapy.

Patients were 714 males and 705 females; the mean age was 59.7 years (std. dev.: 18.9); 787 of them (55.5%) had already a registered chronic disease (Table 1).

Among the 1,419 patients, 275 (19.4%) required admission to hospital and 39 (2.8%) were referred to ICU, due to clinical instability and/or worsening of the symptoms; 53 (3.8%) died during hospitalization (Figure 2).

261 out of 1,419 (18,4%) were found with low levels of oxygen saturation (SpO2 < 93%), needing oxygen supplementation, and were provided with an oxygen concentrator and monitored at home by USCA. Among them, 158 (60,5%) have been managed completely at home without any admission to the emergency department and/or to hospital wards. We consider these patients to be the most vulnerable, with

Table 1 - Baseline characteristics of 1,419 patients with USCA home-care, by assignment of oxygen concentrator

	With portable oxygen concentrator n=261		Without portable oxygen concentrator n=1,158		Total n=1,419		p-value
	N	%	N	%	N	%	
Gender							
Male	124	47.51	590	50.95	714	50.32	0.3693
Female	137	52.49	568	49.05	705	49.68	
Age							<.0001
mean (SD)	67.1	(13.8)	58.0	(19.5)	59.7	(18.9)	
00-39	8	3.07	187	16.15	195	13.74	
40-49	22	8.43	184	15.89	206	14.52	
50-59	47	18.01	223	19.3	270	19.03	
60-69	62	23.75	197	17.01	259	18.25	
70-79	69	26.44	202	17.44	271	19.1	
80+	53	20.31	165	14.25	218	15.36	
Chronic conditions							
Yes	175	67.05	612	52.85	787	55.46	<.0001
No	86	32.95	546	47.15	632	44.54	
Duration of home care by USCA							
mean (SD)	13.6	(9.0)	10.9	(6.5)	11.4	(7.1)	<.0001

SD: standard deviation
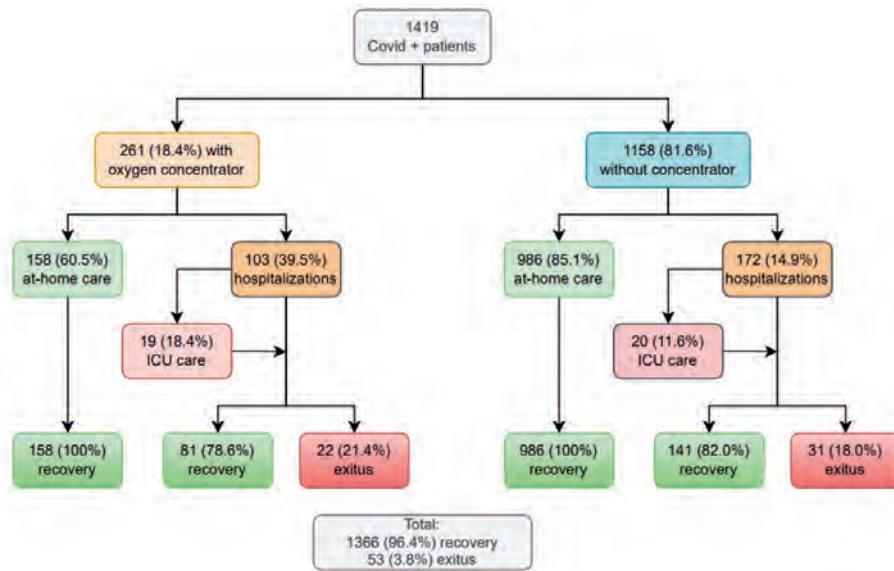
Fig. 2 - Outcomes of patients affected by COVID-19 managed at home by the USCA, Western HCD of LHA "8 Berica", Vicenza, Veneto Region (Italy).
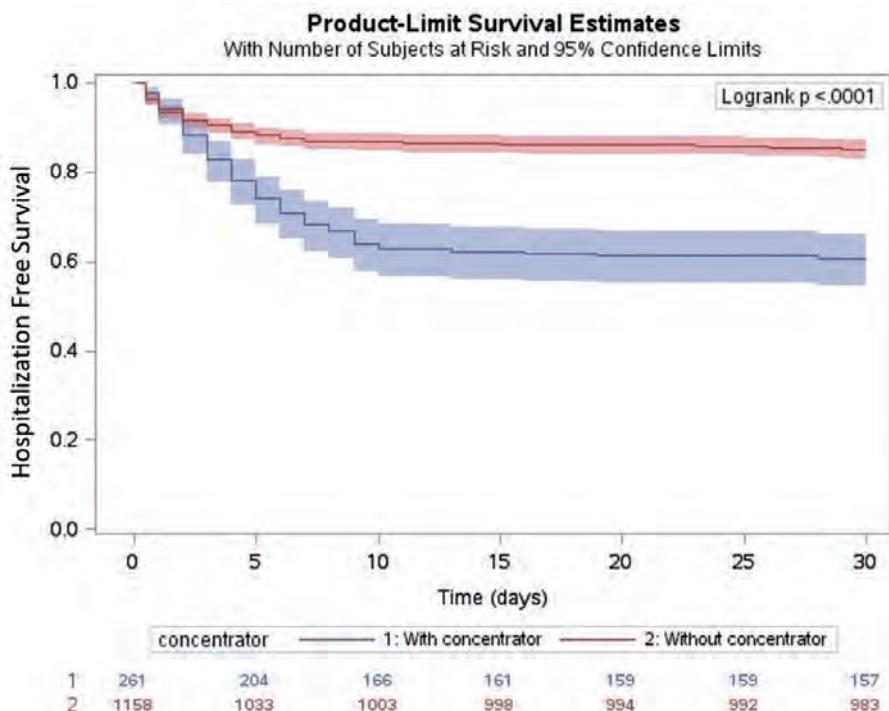
Fig. 3 - Kaplan–Meier 30-day hospitalization estimates by presence of concentrator

a high risk of complications due to their desaturation: part of these group of patients, under different circumstances, would have been cared in a hospital setting at first.

Figure 3 represents a Kaplan-Meier hospitalization-free survival curve according to presence of concentrator.

Patients with concentrator, as expected, show significant higher risk to be admitted to hospital (p<.0001), in particular the risk is higher in the first 10 days, after that the risk remain stable. At 5 days after the start of USCA home-care the hospitalization free survival was 74% for patients with concentrator and 88% for patients without concentrator, while at
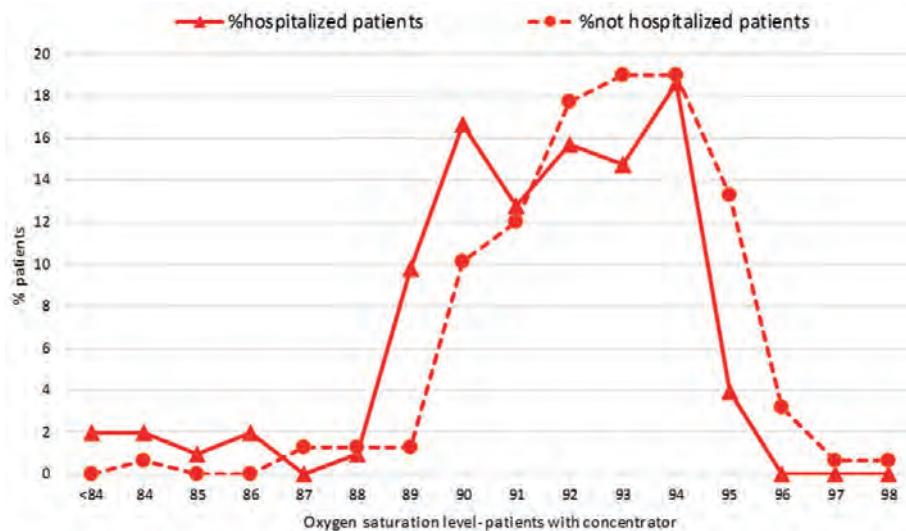
Fig. 4 - At-rest oxygen saturation level of patients suffering from COVID-19 managed by USCA at first home visit by them, differentiating the ones who have been hospitalized from the ones who have not.

10 days it was 63% vs 87%.

Figure 4 shows the at-rest oxygen saturation level of patients at home at the very first home visit by USCA possibly leading *to prise en charge* by them, differentiating the ones who have been hospitalised from the ones who have not.

Among the 261 patients who were provided with the oxygen concentrator, 3.8% had a saturation level lower then 88, 47.7% between 88 and 92 and the remaining 48.5% above 92. As expected, the percentage of hospitalization at 30 days is higher among those with saturation lower than 88 (70%) and decreases as saturation levels increase (respectively 46% and 30%).

Over the 30-day follow-up, 103 patients (39.5%) with concentrator needed an admission to hospital, 19 (7.3%) were referred to ICU and 21 (8.0%) died during hospitalization.

Multivariate logistic regression showed that patients with an oxygen concentrator (reserved to patients with SpO2 < 93%), had 3 times greater odds of 30-day hospitalization adjusted for pathology, age and sex, (adj OR: 3.2; CI 2.3 - 4.3), see Table 2, and of 30-day in-hospital mortality (adj OR: 2,8; CI 1.5 – 5.1) in Table 3.

Table 2 – Logistic regression analysis of 30-day hospital admission

	30 day-Hospital admission (n=275)				
	n (%)	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Gender			0.0126		0.0002
Male	157 (22.0%)	1.40 (1.08;1.83)		1.74 (1.3;2.32)	
Female	118 (16.7%)	*Rif.*		Rif.	
Age		1.04 (1.03;1.05)	<0.0001	1.04 (1.03;1.05)	<0.0001
Chronic conditions			<0.0001		0.4392
Yes	195 (24.8%)	2.27 (1.71;3.02)		1.14 (0.82;1.59)	
No	80 (12.7%)	*Rif.*		Rif.	
Oxygen concentrator			<0.0001		<0.0001
Yes	103 (39.5%)	3.74 (2.78;5.03)		3.16 (2.32;4.30)	
No	172 (14.9%)	*Rif.*		*Rif.*	

Table 3 – Logistic regression analysis of 30-day in-hospital mortality

	n(%)	Crude OR (95% CI)	p-value	Adjusted OR (95%CI)	p-value
		30 day-Hospital admission			
Gender			0.3521		0.0261
Male	30 (4.2%)	1.3 (0.75;2.26)		1.96 (1.08;3.56)	
Female	23 (3.3%)	*Rif.*		Rif.	
Age mean (SD)	59.7 (18.9)	1.1 (1.07;1.12)	<0.0001	1.1 (1.07;1.13)	<0.0001
Chronic conditions			0.0001		0.7398
Yes	44 (5.6%)	4.1 (1.99;8.46)		1.14 (0.52;2.5)	
No	9 (1.4%)	*Rif.*		Rif.	
Oxygen concentrator			<0.0001		0.0008
Yes	22 (8.4%)	3.35 (1.9;5.88)		2.78 (1.53;5.05)	
No	31 (2.7%)	*Rif.*		*Rif.*	

Discussion and conclusion

Thanks to the cooperation of professionals of different expertise (infectious diseases, lung and ED specialists and USCA), over a period of 13 months, nearly 1,500 patients suffering from COVID-19 have been constantly monitored through daily phone calls, home-visits and careful management of complex pharmacological therapy, aiming to support both the patients and the healthcare system sustainability, avoiding at the same time both the overcrowding of EDs, and the saturation of hospital wards.

The risk of hospitalization and of death correlates, as expected (6), with the clinical severity of the disease, represented by the proxy "use of oxygen concentrator", with high and significant OR, even adjusted for pre-existing pathology and age, risk factors for severe COVID-19 disease (7).

At the same time, out of the 261 patients who were provided with oxygen concentrator because of low saturation levels, 158 (60.5%) have been managed completely at home without any admission to ED and/or hospital wards. This group of patients, in a standard situation, would have likely been hospitalized or referred to the ED, as being considered high-risk at first (8).

In a situation of uncertainty and hospital saturation, such as during the COVID-19 pandemic, health care provided at home has shown effectiveness in taking care of patients, avoiding hospital care when possible and, eventually, mitigating the feeling of isolation and abandonment. Previous studies have shown that similar protocols are well accepted (9), with high patient satisfaction (10), and first analysis seems to indicate cost-effectiveness (10-12) and effectiveness with lower rates of hospitalization and mortality (13, 14).

As other studies reported (15), when home visiting is managed with the integration of specialists' healthcare network, as our model, hospitalization could be reduced. It is reasonable to expect that integrated solutions, even outside COVID-19 experience, with collaboration among different healthcare workers, even remotely, should result in an overall reduction in hospitalization rate (16). This is even more important focusing on the Italian demographic distribution, with 23,5% of the people being 65 or older, even more at risk than the general population, as shown by the Italian mortality rates from COVID-19 (17, 18).

In our experience the USCA has been a flexible option, capable of integrating with other healthcare professionals, both in the hospital and in the local communities, while mitigating patients' feeling of isolation and abandonment. This organisational model has allowed the management of nearly 1,500 patients, in a context of limited human resources and distress within the healthcare system and hopefully avoiding the seek of ED care and/or hospitalization of a subgroup of them, in particular for 158 patients provided with a special device to sustain lung functioning.

Our next aim is to analyze further our data to evaluate the economic impact of our model as alternative to conventional hospitalization during a pandemic.

Riassunto

I modelli di presa in carico domiciliare per le persone affette da COVID-19: l'esperienza di un Distretto socio-sanitario Veneto

Introduzione. Durante la pandemia da COVID-19, i professionisti sanitari hanno operato in un contesto di estrema incertezza. Si è reso necessario mantenere il più possibile i pazienti a domicilio per evitare il diffondersi del virus e la saturazione delle risorse ospedaliere: la Regione Veneto ha definito delle Linee Guida regionali in merito. Il distretto ovest dell'ULSS 8 Berica (180.000 residenti) ha implementato un percorso assistenziale per contestualizzarle nel territorio. Obiettivi dello studio sono la descrizione dell'applicazione e degli esiti di tale percorso assistenziale.

Metodi. Il percorso assistenziale definisce che le Unità Speciali di Continuità assistenziale (USCA) si prendano carico proattivamente dei pazienti affetti da COVID-19, segnalati dai medici territoriali o ospedalieri, su loro giudizio clinico, con monitoraggio quotidiano tramite visite domiciliari e contatti telefonici regolari, confronto con gli specialisti e gestione della terapia. Per evitare il ricovero, con saturazione di ossigeno inferiore a 93%, veniva consegnato e gestito un concentratore di ossigeno a domicilio. Tramite i dati anonimizzati del sistema informativo territoriale che descrive l'attività delle USCA dal 01/12/20 al 31/12/21, del flusso della Scheda di Dimissione Ospedaliera, del Pronto soccorso e delle esenzioni. Sono state effettuate analisi descrittive e multivariate di regressione logistica per analizzare l'attività svolta e gli esiti.

Risultati. Nel periodo considerato sono stati presi in carico a domicilio 1.419 pazienti affetti da COVID-19 (media di 11,4 giorni), dei quali 787 (55,5%) con almeno un'esenzione per patologia e 261 con concentratore di ossigeno. Per 275 (19,4%) si è reso necessario un ricovero ospedaliero, per il 2.8% (39) in terapia intensiva; 53 sono deceduti durante il ricovero (3,8%). Dei 261 pazienti in ossigenoterapia, 103 sono stati ricoverati (39,5%), il 7,3% in terapia intensiva e l'8,0% è deceduto. Nelle analisi multivariate l'uso di concentratore, proxy della gravità di patologia, è il maggiore determinante il rischio di ricovero (adj OR: 3,2, CI 2,3-4,3) e di decesso entro 30 giorni (adj OR: 2,8 CI 1,5-5,1). Dei 261 pazienti che hanno utilizzato un concentratore di ossigeno a casa, 158 (60,5%) sono stati assistiti completamente presso il loro domicilio senza ricorrere al Pronto Soccorso e/o a ospedalizzazioni.

Conclusioni. In una situazione di incertezza si è mutuato l'attuale modello di cure domiciliari integrandolo con la partecipazione di medici delle USCA e l'integrazione con le reti assistenziali specialistiche per evitare per quanto possibile l'ospedalizzazione e il senso di isolamento e abbandono delle persone. Quasi 1.500 pazienti affetti da SARS-CoV-2 sono stati presi in carico a domicilio nell'arco di 13 mesi con attività complesse e multidisciplinari. Il rischio di ricovero e di decesso appare legato alla gravità di patologia (con OR elevati. Il 60% dei pazienti con concentratore che, malgrado un'iniziale iposaturazione elevata, non sono stati ricoverati rappresentano, in parte, il gruppo di pazienti che in una situazione standard avrebbe necessitato di cure ospedaliere in mancanza di un percorso di presa in carico domiciliare.

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Corresponding Author: Dr. Silvia Manea, Director of Primary Care Unit, Western Healthcare District, Azienda ULSS 8 Berica, Viale Rodolfi 37, 36100 Vicenza, Italy
e-mail: silvia.manea@aulss8.veneto.it

Impact of COVID-19 pandemic on emergency and elective surgery. A retrospective observational analysis in Apulia, southern Italy

Francesco Paolo Bianchi[1,2], Antonio Daleno[2], Donato Rizzi[1], Giovanni Migliore[2], Silvio Tafuri[1,2]

Abstract

Introduction. *In Italy, at the beginning of the COVID19 pandemic, only emergency and life-saving elective surgical procedures were allowed with obvious limitations in terms of numbers of operable cases. The aim of our study is to evaluate the performance of surgical activities by Apulian healthcare facilities (Southern Italy) under the pandemic emergency pressure.*

Methods. *The surgical procedures in study were identified via the Apulian regional archive of hospital discharge forms. We used the ICD9 codes in order to define the elective and urgency surgeries in analysis, and we extended our search to all procedures performed from 2019 to 2021.*

Results. *The number of all procedures decreased from 2019 to 2020; the reduction was higher for elective surgery (-43.7%) than urgency surgery (-15.5%). In 2021, an increase compared to 2020 was recorded for all procedures; nevertheless, elective surgeries registered a further slightly decrease compared to 2019 (-12.4%), while a slightly increase was observed for urgency surgeries (+3.5%). No particular variation was observed considering sex and age at surgery of the patients, and days of hospitalization from 2019 to 2021.*

Conclusions. *The impact of COVID19 on Apulian regional health system has been extremely shocked and has required the implementation of strategies aimed at containing the infection and guaranteeing health services as far as possible. A new paradigm of hospital care for SARS-COV-2 patients in the post-emergency phase in Italy is needed, in order to optimize the resources available and to guarantee high standards of quality and efficiency for citizens.*

[1] *Department of Interdisciplinary Medicine, Aldo Moro University of Bari, Italy*
[2] *Health Direction, Bari Policlinico General-University Hospital, Bari, Italy*

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first identified in late 2019 in the city of Wuhan (Hubei province of China). Subsequently, the World Health Organization (WHO) declared that the SARS-CoV-2 disease (COVID-19) had reached a pandemic state on March 11th, 2020 (1).

In Italy, at the beginning of the pandemic, hospital facilities were strengthened by applying the Italian Ministry of Health recommendations for COVID-19 patients, to assist the increasing numbers of affected patients who needed intensive support therapy (2). Nonurgent procedures were stopped and delayed to reallocate the healthcare personnel (especially nurses and anesthesiologists) to deal with the COVID-19 emergency situation. This measure freed ventilators and other instruments and converted surgical theatres into additional intensive care unit beds as needed; several surgical departments were closed and converted into COVID-19 medical wards. Moreover, surgeons were requested to help medical personnel in the COVID-19 elective and emergency wards. In this setting, only emergency and life-saving elective surgical procedures were allowed with obvious limitations in terms of numbers of operable cases (2). A 2020 survey (3) investigated the current practice of emergency surgery in Italy during the first weeks of the pandemic; 71 Italian general surgery units practicing emergency surgery were interviewed, showing that 74% of surgeons operated only on urgent cases, and the number of interventions significantly dropped, with over 40% of non-traumatic abdominal emergency cases that had an unusual delayed treatment.

Apulia (Southern Italy, 4,000,000 inhabitants) is the second biggest Region in Southern Italy. At the start of the pandemic, the hospitals' framework was rearranged and some "Covid Hospitals", entirely dedicated to SARS-CoV-2-positive patients, were designed. In particular, the total number of beds dedicated to COVID patients was 3,062, with 263 beds in COVID intensive care units. In other hospitals, the wards were separated into areas dedicated to SARS-CoV-2-positive patients and areas reserved for SARS-CoV-2-negative subjects. These sectors were separated from one another either functionally or physically. Most anesthesiologists and surgeons were reallocated in support of clinical and intensive-care activities, and several surgical wards and surgical equipment were used in support of COVID19 patients' treatment. Therefore, surgical activities were greatly reduced, guaranteeing only emergency operations and life-saving elective surgical procedures. In 2021, additional COVID-dedicated settings were obtained in the form of emergency facilities, often located in fair centers, such as the so-called Large Emergency Unit in Bari's Eastern Fair exhibition space (4). The hiring of new staff, the reorganization of spaces and healthcare personnel, and the start of the vaccination campaign have allowed for a normalization of surgical activities, with the aim of a return to pre-pandemic performances.

In this context, our study aims to evaluate the performance of surgical activities of Apulian hospital facilities under the pandemic emergency pressure. We compared four elective and four emergency surgeries during three years (2019, 2020, and 2021), to define the trend of procedures and the characteristics of the patients in the pre- and post-pandemic period.

Material and Methods

This is a retrospective observational study.

The surgical procedures in study were identified via the procedures analyzed by the Italian National Program Outcomes 2022 (5). The Apulian regional archive of hospital discharge forms, an online database containing all information regarding hospital and inpatient procedures carried out in Apulian hospital facilities, was used to define the procedures; we used the ICD9 codes (6) in order to describe four elective and four emergency surgeries as follow:

• Elective surgery
- Prostatectomy (ICD9 codes: 60.21, 60.29, 60.62, 60.69, 60.99, 60.5)
- Thyroidectomy (ICD9 codes: 06.2, 06.31, 06.39, 06.4, 06.50, 06.51, 06.52, 06.98)
- Cardiac valvuloplasty (ICD9 codes: 35.11, 35.12, 35.14, 35.21, 35.22, 35.23, 35.24, 35.26, 35.28, 96)
- Laparoscopic cholecystectomy (ICD9 codes: 51.22, 51.23)
• Emergency surgery
- Appendicectomy (ICD9 code: 47.01)
- Crude reduction of fracture of the femur (ICD9 codes: 79.25, 79.35)
- Percutaneous transluminal coronary angioplasty (ICD9 code: 00.66)
- Endovascular removal of obstruction from head and neck vessels (ICD9 code: 39.74).

We extended our search to all procedures performed from 2019 to 2021. The selection of these surgical interventions is not random; rather, it stems from a

preliminary analysis of the pre-pandemic years, where they emerged as the most numerous and representative procedures within their respective categories.

The final dataset was created as an Excel spreadsheet that included information on sex, age at surgery, and days of hospitalization of patients. An anonymized data analysis was performed using STATA MP17 software.

Continuous variables are reported as the mean ± standard deviation and range, and categorical variables as proportions. The hospitalization rate was defined as the number of hospitalizations divided by the Apulian population, extracted (only the male population was considered for prostatectomy) from the archives of the National Institute of Statistics (ISTAT). The t-student's test for independent data was used to compare continuous variables between the years under analysis, while the chi-square test was employed to compare categorical variables across the same time frame. A p-value < 0.05 was considered statistically significant for all tests.

Results

Table 1 describes the trend of elective and emergency procedures from 2019 to 2021; for all procedures, a decrease from 2019 to 2020 was observed, more marked for elective surgery (on average - 43.7%) than emergency surgery (on average - 15.5%). In 2021, an increase compared to 2020 was recorded for all procedures; nevertheless, elective surgeries registered a further slightly decrease compared to 2019 (-12.4%), while a slightly increase was observed for emergency surgeries (+3.5%).

Figures 1 and 2 describe the hospitalization rates per semester; the greatest rate fluctuations are observed in the second semester for elective procedures, while the first semesters seem to impact more on emergency surgery. The statistical comparison of the hospitalization rates between years under analysis is described in Table 2.

The characteristics of the patients undergoing surgery are described in Table 3. No statistically

Table 1 - Number of procedures and percentage change between the years under analysis.

Procedure	2019	2020	2021	Δ% 2020-2019	Δ% 2021-2020	Δ% 2021-2019
Elective surgery						
Prostatectomy	3,723	2,057	3,227	-44.7%	56.9%	-13.3%
Thyroidectomy	1,885	1,255	1,637	-33.4%	30.4%	-13.2%
Cardiac valvuloplasty	1,711	794	1,636	-53.6%	106.0%	-4.4%
Laparoscopic cholecystectomy	5,213	2,972	4,243	-43.0%	42.8%	-18.6%
Emergency surgery						
Appendicectomy	1,373	1,060	1,303	-22.8%	22.9%	-5.1%
Crude reduction of fracture of the femur	3,923	3,477	3,970	-11.4%	14.2%	1.2%
Percutaneous transluminal coronary angioplasty	5,475	3,980	5,044	-27.3%	26.7%	-7.9%
Endovascular removal of obstruction from head and neck vessels	162	161	204	-0.6%	26.7%	25.9%

Table 2 - Statistical comparison of hospitalization rates between years.

Procedure	2019 vs. 2020	2019 vs. 2021	2020 vs. 2021
Elective surgery			
Prostatectomy	<0.0001	<0.0001	0.526
Thyroidectomy	0.001	0.890	0.007
Cardiac valvuloplasty	<0.0001	<0.0001	0.107
Laparoscopic cholecystectomy	<0.0001	<0.0001	0.962
Emergency surgery			
Appendicectomy	0.007	0.207	0.156
Crude reduction of fracture of the femur	0.008	0.021	0.737
Percutaneous transluminal coronary angioplasty	0.062	0.012	0.521
Endovascular removal of obstruction from head and neck vessels	<0.0001	0.510	0.224
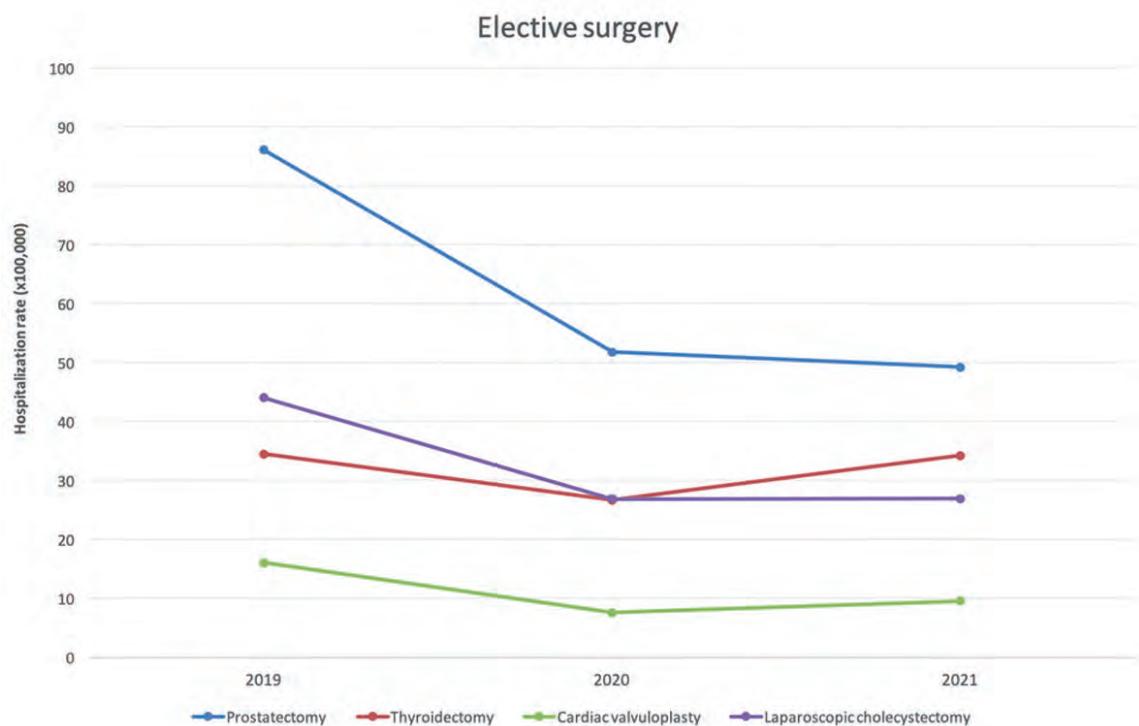
Figure 1 - Hospitalization rates for elective surgery. Years 2019-2021.
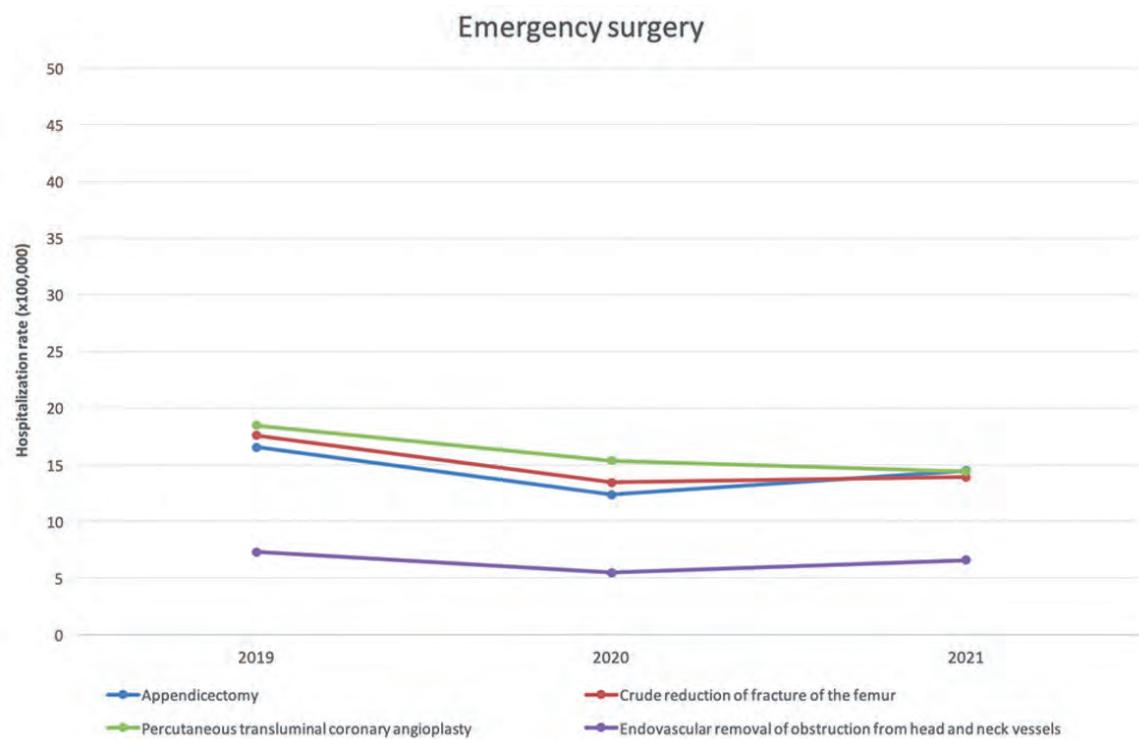
Figure 2 - Hospitalization rates for emergency surgery. Years 2019-2021.

Table 3 - Characteristics of the patients undergoing surgery. Years 2019-2021.

Procedure		Male sex; n (%)			Age at surgery mean±SD			Days of hospitalization mean±SD		
		2019	2020	2021	2019	2020	2021	2019	2020	2021
Emergency	Appendicectomy	750 (54.6)	627 (59.2)	651 (53.6)	30.6±19.4 (3-94)	28.5±19.8 (2-89)	33.7±20.0 (2-98)	5.7±3.1 (0-36)	6.3±4.0 (1-40)	5.0±3.2 (0-50)
	Crude reduction of fracture of the femur	1,037 (26.4)	912 (26.2)	1,019 (26.1)	79.4±14.0 (0-106)	79.5±15.0 (4-103)	79.3±15.0 (5-106)	9.7±5.8 (1-69)	8.5±5.1 (1-52)	9.3±5.9 (0-115)
	Percutaneous transluminal coronary angioplasty	4,117 (75.2)	2,998 (75.3)	3,861 (76.6)	68.6±12.3 (34-94)	68.3±12.0 (16-101)	67.8±12.2 (26-99)	8.1±7.0 (0-122)	7.6±6.0 (0-54)	7.9±6.5 (0-102)
	Endovascular removal of obstruction from head and neck vessels	60 (37.0)	72 (44.7)	89 (43.6)	74.2±13.0 (37-93)	72.2±10.9 (47-88)	74.3±12.0 (24-96)	12.1±8.5 (1-37)	16.3±11.7 (0-65)	13.6±24.8 (0-339)
Elective	Prostatectomy	3,723 (100.0)	2,057 (100.0)	3,227 (100.0)	67.7±8.2 (40-94)	68.3±7.8 (25-87)	68.1±8.1 (24-95)	4.9±2.2 (1-28)	4.7±3.0 (1-43)	5.6±3.3 (0-58)
	Thyroidectomy	450 (23.9)	304 (24.2)	396 (24.4)	52.6±14.2 (12-84)	51.6±13.7 (18-90)	53.1±14.1 (12-87)	3.5±6.4 (0-146)	3.4±3.0 (0-38)	3.6±3.6 (0-92)
	Cardiac valvuloplasty	946 (55.3)	415 (52.3)	926 (56.6)	70.1±12.1 (14-92)	68.2±11.5 (24-88)	71.0±12.3 (17-97)	14.8±11.7 (1-124)	13.3±6.9 (3-43)	14.4±11.3 (1-160)
	Laparoscopic cholecystectomy	1,968 (37.8)	1,147 (38.6)	1,649 (38.9)	56.7±15.0 (6-93)	57.6±13.9 (5-92)	56.2±14.6 (12-94)	4.0±5.3 (1-70)	4.1±5.3 (1-44)	3.5±3.6 (0-57)

significant variations were observed considering sex, age at surgery, and days of hospitalization from 2019 to 2021 ($p > 0.05$).

Conclusions

The results of our survey show how the measures implemented by Apulian Health Government to deal with COVID19 were able to guarantee urgent surgical procedures even in the most critical phases of the pandemic. This evidence is confirmed by other experiences in Italy, as reported in the literature. Bonalumi et al. (7) described the re-organization of cardiovascular surgery activities in Lombardy (Northern Italy, 10,000,000 inhabitants); a hub-and-spoke system was introduced that efficiently safeguarded access to the heart and vascular surgical services for patients who required non-deferrable, urgent and emergency treatments. Nevertheless, a slight decrease was observed in 2021 for appendicectomy and percutaneous transluminal coronary angioplasty; the various population lockdowns required to restrain the virus may have reduced the injuries and traumatic accidents, as well as the excess of mortality due to COVID19 may have reduced the number of at-risk subjects for cardiac and neurology stroke.

As expected, a decrease in the elective procedures was observed; this has also been described by a 2020 Italian survey (2), that was designed to elucidate the impact of the first 5 weeks of COVID-19 emergency on elective surgery for oncological disease in Italy; the questionnaire was sent to 54 oncological surgical Units from 36 Italian hospitals, showing that these Units reduced their hospital beds, surgical activities, had less availability of intensive care unit beds, and had a reduction of outpatient clinics. The number of surgical procedures decreased, ranging from a median number of 3.8 per week before COVID-19 to 2.6 later on. Similar evidence was observed in a 2022 retrospective study (8); the Authors investigated the monthly number of hospitalizations for colorectal and breast cancers in Abruzzo in the year 2020, comparing them with the admissions that occurred in the years 2018-2019. A reduction of elective oncological surgery for colorectal cancer by 35.71% and for breast cancer by 10.36% was found. In 2021 we observed an increase in elective procedures, but a return to pre-pandemic levels was observed only for valvuloplasty surgery; the reason could have been that, in addition, the pandemic has also led to the reduction of other services, including instrumental examinations and

investigations for early diagnosis. Indeed, several experiences in the literature reported a decrease in oncological activities (9), and diagnostic procedures (10). Therefore, an underdiagnosis of prostate, thyroid, and gallbladder diseases could explain the decrease in related surgical procedures. On the other hand, Valnieri et al. (11) reported prostatectomies and cholecystectomies among the elective procedures more likely to be inappropriate; in this light, their decrease may be also interpreted as a reorganization by surgical wards to manage procedures with high potential for inappropriateness. Specific investigations are needed to clarify this point.

The strength of our study is the analysis of three years and the comparison between the pre- and post-pandemic period; moreover, the comparison between emergency and elective procedures allows us to evaluate the response of the Regional Health Service to the adaptation of the services and resources available due to the pandemic situation. The main limitation is the restricted choice of the surgical interventions selected, although other studies in the literature investigated our topic for comparable procedures (5, 11-13). Moreover, the results of Apulia are not generalizable to all Italian Regions; nevertheless, Apulia is the second most populated region in southern Italy, and therefore its management impacts a large portion of the population of southern Italy, including at least the territories of Basilicata (Southern Italy, 560,000 inhabitants), Molise (Southern Italy, 300,000 inhabitants), and part of Campania (Southern Italy, 5,800,000 inhabitants) and Calabria (Southern Italy, 2,000,000 inhabitants). Future studies will evaluate the trend of surgical procedures also in 2022 and the years to come, to evaluate the strategies implemented to guarantee surgical services in the context of circulation of SARS-CoV-2.

Currently, a new paradigm of hospital care for SARS-COV-2 patients in the post-emergency phase in Italy has been proposed, with the distinction of COVID19 patients into: (i) hospitalized *because of* COVID19 (patients with clinical, laboratory, and radiographic signs of lower airway involvement); and: (ii) hospitalized *with* COVID19 (patients without clinical, radiographic and laboratory signs of lung involvement, whose hospitalization was determined by other causes); a new organizational model that approaches hospitalized patients according to their COVID status is required, guaranteeing the best possible functioning of the hospital supply (4). Its implementation at the Bari Policlinico General-University hospital, the biggest hospital in Apulia,

allowed more rational management of COVID19 patients and available resources.

One of the next challenges for public health institutions will be to manage one of the consequences of the decreased number of services offered during the pandemic emergency phase, i.e. the recovery of the waiting lists that have arisen. In this light, the Apulian Region Government in July 2022 provided for a budget change to allocate a waiting list disposal plan through the funding of shifts in additional performance to the health personnel of public and private hospital facilities (14). The results of this regulation will be seen in 2023 and the following years, but the real challenge will be to reorganize the services to optimize the resources available and to guarantee high standards of quality and efficiency for the citizens.

Riassunto

Impatto della pandemia COVID-19 sulla chirurgia d'urgenza e programmata. Un'analisi osservazionale retrospettiva in Puglia, Italia meridionale

Introduzione. In Italia, all'inizio della pandemia di COVID-19, sono state consentite solo procedure chirurgiche di emergenza e salvavita, con ovvie limitazioni in termini di numeri di casi operabili. L'obiettivo del nostro studio è valutare le prestazioni chirurgiche nelle strutture sanitarie pugliesi (Italia meridionale) sotto la pressione dell'emergenza pandemica.

Metodi. Le procedure chirurgiche in studio sono state identificate tramite l'archivio regionale pugliese delle schede di dimissione ospedaliera (SDO). Sono stati utilizzati i codici ICD9 per definire le chirurgie programmate e d'urgenza in analisi, estendendo la nostra ricerca a tutte le procedure effettuate dal 2019 al 2021.

Risultati. Il numero delle procedure in analisi è diminuito dal 2019 al 2020; la riduzione è stata maggiore per la chirurgia programmata (-43,7%) rispetto a quella d'urgenza (-15,5%). Nel 2021 è stato registrato un aumento rispetto al 2020 per tutte le procedure; tuttavia, gli interventi programmati hanno registrato un ulteriore lieve calo rispetto al 2019 (-12,4%), mentre si è osservato un leggero aumento per gli interventi in urgenza (+3,5%). Non è stata osservata alcuna variazione significativa considerando sesso e età al momento dell'intervento dei pazienti e i giorni di degenza dal 2019 al 2021.

Conclusioni. L'impatto del COVID-19 sul sistema sanitario regionale pugliese è stato estremamente rilevante e ha richiesto l'attuazione di strategie finalizzate a contenere l'infezione e garantire i servizi sanitari. È necessario un nuovo paradigma di assistenza ospedaliera per i pazienti con SARS-COV-2 nella fase post-emergenza in Italia, al fine di ottimizzare le risorse disponibili e garantire elevati standard di qualità ed efficienza per i cittadini.

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Corresponding author: Silvio Tafuri, MD, PhD, Department of Interdisciplinary Medicine, Aldo Moro University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy
e-mail: silvio.tafuri@uniba.it

Influenza and Covid-19 Vaccination in 2023: a descriptive analysis in two Italian Research and Teaching Hospitals. Is the On-Site strategy effective?

Pier Mario Perrone[1,2], Simone Villa[1], Giuseppina Maria Raciti[1], Laura Clementoni[1], Valentina Vegro[1], Francesco Scovenna[1], Augusto Altavilla[1], Adriana Monica Tomoiaga[1], Valentina Beltrami[1], Ilaria Bruno[1], Marcello Vaccargiu[1], Elisa Astorri[1], Navpreet Tiwana[3], Matteo Letzgus[3], Peter Johannes Schulz[4], Fabrizio Ernesto Pregliasco[1,5], Silvana Castaldi[1,3]

Abstract

Introduction. *Vaccinations represent an extremely effective tool for the prevention of certain infectious diseases - such as influenza and COVID-19 -, particularly for those categories at risk due to both their frail condition or professional exposure, such as healthcare workers. The aim of this study is to describe the course of the anti-influenza and anti-COVID-19 vaccination campaign at two Research Hospitals in Milan, Italy.*
Study design. *Multicentre, cross-sectional study.*
Methods. *For the 2023-24 vaccination campaign, the two facilities opted for two different approaches. At the Hospital A, two different strategies for vaccinating healthcare workers were implemented: a fixed-site vaccination clinic and two mobile vaccination groups run by Public Health residents of the University of Milan. At the Hospital B, on the other hand, a single fixed-site outpatient clinic run by Public Health residents of the University of Milan was used. On the occasion of the campaign, a survey was also carried out using anonymous online questionnaires to investigate healthcare workers attitudes towards vaccination.*
Results. *A total of 1,937 healthcare workers were vaccinated: 756 were immunized against influenza only, 99 against COVID-19 only, and 1,082 against both. The results show a substantial difference in vaccination adherence among medical and nursing staff compared to other professional categories. In particular, the category with the highest vaccination adhesion turned out to be that of medical doctors with 55.7% adhesion while, on the contrary, the category with the lowest adhesion turned out to be that of auxiliary personnel characterized by 7.4% adhesion. At the same time, the comparison between the two hospital facilities showed a double adherence rate by the staff of Hospital A as regards both the flu vaccine (40.6% and 20.1%) and the anti-COVID-19*

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[1] *Department Biomedical Sciences for Health, University of Milan, Milan, Italy*

[2] *Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy*

[3] *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

[4] *Faculty of Communication Sciences, Institute of Communication and Health, Università della Svizzera italiana, Lugano, Switzerland*

[5] *IRCCS Ospedale Galeazzi-Sant'Ambrogio, Milan, Italy*

vaccine (26.4% and 12.3%). Finally, the survey showed that the attitude towards influenza vaccination is lower among auxiliary staff in terms of both knowledge and vaccination attitude.

Conclusions. *The results of the study show a vaccination adherence in line with that of previous years, although lower than the values recommended by the principal national and international Organizations. The analysis of the differences between the two facilities and the surveys carried out will allow for the implementation of targeted interventions to increase adherence in future campaigns.*

Introduction

Influenza is an acute viral respiratory disease caused by influenza viruses, a group of RNA viruses of the family Orthomyxoviridae. Among these, influenza B and C viruses circulate primarily among humans, while influenza A viruses infect mainly aquatic birds although they are widespread among mammals, humans included (1). Every year, the World Health Organization (WHO) estimates that seasonal influenza epidemics among humans – caused by two types of influenza viruses (i.e., seasonal influenza A and B viruses) – affect 1 billion people worldwide. Severe forms of influenza occur in 3-5 million people every year, resulting in on average on 300-600,000 deaths (2,3). In Europe, influenza is responsible for up to 50 million symptomatic cases and for about 15,000-70,000 influenza-related deaths (4). In Italy, during the last influenza season (i.e., 2022-2023), about 14 million people were diagnosed with influenza based on the Epidemiological Report by the RespiVirNet – a national Italian surveillance system based on influenza cases notification by General Practitioners and Paediatricians (5).

Among the influenza viruses, influenza A viruses have the potential to cause pandemics – the rapid spread of a new human influenza around the world – such as the one occurred on 2009 caused by the A(H1N1) pdm09 strain (6). Thus, seasonal influenza can represent a major public health issue, especially when large parts of the population are affected at the same time overwhelming national health systems.

Furthermore, seasonal influenza can heavily impact countries' economic systems because of a direct impact on countries' health systems as well as losses in productivity across sectors due to absenteeism from work and by staff functioning at reduced capacity even after they have returned to work (7). Among the direct impacts on health systems, seasonal influenza epidemics increase the demand for medicines, laboratory reagents, and personal protective equipment as well as increase costs for hospitalization and workload on healthcare workers (HCWs) (8–10).

Although influenza can affect virtually everyone, regardless of their age and sex, people at risk the most to suffer from its severe forms and eventually die because of it are the elderly, children under the age of 5 years, pregnant women, and people affected by non-communicable diseases (e.g., heart and pulmonary diseases (11–15). Therefore, a common prevention strategy is to offer vaccination against influenza to those most at risk as well as those working directly in contact with them, such as HCWs (16,17). Indeed, due to its intrinsic characteristics, vaccination is one of the most effective tools of preventive medicine (18). Influenza infection among HCWs, as a matter of fact, can rapidly spread among colleagues and to hospitalized patients suffering from other health conditions, such as non-communicable diseases, leading eventually to severe forms of influenza in vulnerable populations (19).

In Europe, among HCWs, the median VC in 2020-21 was 52% (range 16-71%), compared to 33% of the 2018-19 season (20). A similar increase in VC among HCWs was observed in all EU/EEA countries for the 2020-21 (21). In Italy, the influenza vaccination is recommended to all HCWs, irrespective of whether they have contact with patients, and influenza VC should be at least 75% (22). However, VC among HCWs was about 15-20% in the past few years, near to the one of general population (20.2 % in 2022) (23,24).

In the winter season 2020-21, during the coronavirus disease 2019 (COVID-19) pandemic, influenza VC among HCWs increased in different Italian hospital settings (25,26) also due to the new campaign organization models (27–30) sometimes mediated by the organizational experience of the anti-COVID vaccination campaign (31,32). However, in the following winter seasons, influenza VC dropped. Because of changes in VC trends among HCWs, it is important to identify and describe the determinants affecting influenza vaccination adherence so that prevention strategies focused on HCWs are strengthened.

We developed a study that aims to explore the reasons for influenza vaccine adherence among HCWs

working in two research and teaching hospitals (IRCCS) in Milan, Italy, during the winter season 2023-24 as well as to assess the influenza VC among different subsets of HCWs of these two hospital settings.

Methods

Our study focuses on the winter vaccination campaign against seasonal influenza implemented from October 1 to November 30, 2023, of HCWs of two IRCCSs in Milan. In both hospital with the influenza vaccination the possibility has been offered to be vaccinated also against COVID 19.

Hospital A's approach

At Hospital A, a pavilion hospital, two different strategies were implemented for HCWs vaccination: a fixed-site vaccination ambulatory and two mobile vaccination teams.

The fixed-site vaccination ambulatory was open every working day from 9:00 a.m. to 3:00 p.m. as it was very well-known by all HCWs to be the place where influenza vaccination is administered each year. While the mobile vaccination teams, composed by Public Health residents, were deployed to different pavilions of the hospital in order to be the closest possible to HCWs to increase the VC. Mobile vaccination teams went in each pavilion twice, between November 8 and 27 2023, from 9:00 a.m. to 2:00 p.m.

HCWs were informed about vaccination campaign against influenza and COVID-19 through the hospital's intranet, where information about times and locations of both the fixed-site vaccination ambulatory and the mobile vaccination team were available. HCWs were encouraged to book an appointment but were also let the chance to show up without a previous reservation.

Hospital B's approach

At Hospital B, a single-building hospital, HCWs were informed about the vaccination campaign via email to express their interest via a request form to be immunized either against flu, COVID-19, or both – either together or in different days. From November 6, 2023, all HCWs that filled the request form were contacted via phone calls to schedule the appointments.

The vaccine ambulatory was open all mornings from 9:00 a.m. to 2:00 p.m.

HCWs were encouraged to book an appointment for influenza vaccination but had also the chance to show up without a reservation, while this was not possible for vaccination against COVID-19.

Survey administration

From November 7 to 29, 2023, all HCWs were invited to fill an online, anonymous survey, after being immunized, to provide information on their date of birth, sex, hospital, professional category, and area of activity as well as their knowledge around influenza (i.e., three questions) and their attitudes regarding seasonal influenza vaccination (i.e., two questions).

The questionnaire was developed by a multidisciplinary team made by public health experts and sociologists of the Institute of health communication at the University of Italian Switzerland (Lugano) and included several elements of vaccination knowledge and misconception.

Respondents could select their professional category among the following: physician in staff, resident physician, nurse, technician, auxiliary staff, administrative staff, and others (e.g., social workers, nutritionists). Similarly, they could choose among these areas of activity: general medicine, general surgery, surgical specialty, medical specialty, intensive care unit (ICU), administration, and other (e.g., technical services).

HCWs were asked to rank their level of disagreement/agreement on five statements on knowledge about influenza and attitude toward influenza vaccination, from one (i.e., complete disagreement) to seven (i.e., complete agreement).

Data management and analysis

Data from self-administered questionnaires were collected through Google Form on November 30, 2023. Immunization records were retrieved from the online, regional immunization information system (SII) managed by the Milan's public health authority; while corresponding professional category was asked during the immunization sessions and collected on a separate Microsoft Excel file.

Aggregated data as of November 1, 2023, on hospital's staff by age (i.e., 18-29, 30-39, 40-49, 50-59, and 60+ years), sex, and professional category were retrieved from hospitals' human resources unit.

A new variable (i.e., age) was created from data extracted from the regional SII by considering the date of birth and the date of vaccination.

Categorical variables were summarized using the number of individuals and corresponding percentages,

while continuous variables were summarized, based on their distribution, either with mean and standard deviation (SD) or median and interquartile range (with first and third quartiles). Survey's scores were summarized with mean and SD.

Total and stratum-specific VC were computed using the total of the vaccine administered based on SII data divided by the total staff as of November 1, 2023, as per human resources databases. Furthermore, for Hospital A, HCWs' attributes of those immunized in the fixed-site vaccination ambulatory and those vaccinated by mobile immunization teams were summarized and compared.

All the statistical analyses were conducted with STATA v.18 (Stata Statistical Software: College Station, TX: Stata Corp LP).

No ethical approval was required for this study, according to the Italian Law (33).

Results

In the current influenza vaccination campaign held in both Hospital A (total staff of 3730 HCWs) and Hospital B (total staff of 1599 HCWs) 1937 HCWs were vaccinated: 756 were immunized only against influenza, 99 only against COVID-19, and 1082 against both.

The total number of HCWs immunized against influenza was 1838/5329 (VC=34.49%), while total of immunized against COVID-19 was 1181/5329 (VC=22.16%).

Baseline characteristics

The majority of HCWs immunized were female (1,256/1,937, 64.84%), physicians (775/1,937, 40.01%), were working in the Hospital A (1,597/1,937, 82.45%), and about half (898/1937, 46.36%) were aged below 40 years as described in Table 1. Among

Table 1 - Baseline description of the healthcare workers immunized in the 2023-2024 winter season in two research and teaching hospital in Milan, Italy (n=1937).

	Total (n = 1937)		Anti-COVID-19 (n = 1181)		Anti-influenza (n = 1838)	
	N1	%1	N1	%1,2	N1	%1,2
Sex						
Female	1256	64.84	735	58.52	1188	94.59
Male	681	35.16	446	65.49	650	95.45
Age (median, IQR)3	**42**	**32,55**	**41**	**31,56**	**42**	**32,55**
Age groups						
18-29 years	398	20.55	255	64.07	386	96.98
30-39 years	500	25.81	318	63.60	482	96.40
40-49 years	356	18.38	200	56.18	340	95.51
50-59 years	420	21.68	234	55.71	399	95.00
60+ years	263	13.58	174	66.16	231	87.83
Pregnancy status						
Pregnant	34	2.71	16	47.06	29	85.29
Non pregnant	1071	85.27	625	58.36	1028	95.99
Unknown	151	12.02	94	62.25	127	84.11
Role						
Physician	775	40.01	538	69.42	742	95.74
Resident	187	9.65	134	71.66	180	96.26
Nurse	253	13.06	145	57.31	238	94.07
Auxiliary staff	56	2.89	22	39.29	50	89.29
Technician	89	4.59	54	60.67	82	92.13
Administration	170	8.78	63	37.06	162	95.29
Others	400	20.64	219	54.75	377	94.25
Unknown	7	0.36	7	-	6	-
Hospital						
Hospital A	1597	82.45	985	61.68	1516	94.93
Hospital B	340	17.55	196	57.64	322	94.71

[1] Frequency (N) and percentage (%) are used when not otherwise stated. [2] Percentages, when not otherwise stated, are computed using the corresponding frequency divided by the total. [3] Median and first and third interquartile were used as the age distribution was not normal. Acronyms: COVID-19, coronavirus disease 2019; IQR, interquartile range.

those immunized, male HCWs were more frequently vaccinated against COVID-19 (446/681, 65.49%) compared to female HCWs (735/1,256, 58.52%).

Vaccine coverages

As summarized in Table 2, Hospital A had the highest VCs against influenza with 1,516/3,730 HCWs (VC=40.64%) vaccinated against it versus 322/1,599 (VC=20.14%) of Hospital B. Similar figures could be observed for anti-COVID-19 vaccinations, with 985/3,730 HCWs (VC=26.41%) of Hospital A against the 196/1,599 (VC=12.26%) ones of Hospital B.

By stratifying VCs for influenza by HCWs' role, physicians had the highest VC compared to other categories (i.e., 742/1,331, VC=55.75%), while auxiliary staff ranked as the lowest ones, with only 50/676 (VC=7.40%). Difference between hospitals were evident with 599/799 (VC=75.00%) physicians immunized against influenza at Hospital A against 143/532 (VC=26.88%) at Hospital B. Despite this, nurses and auxiliary staff had similar VCs in both hospitals, with 188/1,529 (VC=12.30%) vs. 50/392 (VC=12.76%) nurses immunized and 30/433 (VC=6.93%) vs. 20/243 (VC=8.23%) auxiliary staff vaccinated in Hospital A and Hospital B, respectively. It is interesting to note that in both hospitals the flu vaccination coverage has always been higher when compared to COVID vaccination in almost every professional category except the administration staff in hospital A ,where COVID vaccination coverage is three times higher than influenza vaccination, VC 8.25% and 2.75% respectively.

Fixed-site ambulatory vs. mobile teams

At Hospital A, 207/1,597 (12.96%) HCWs were vaccinated by mobile vaccination teams. Those most frequently immunized by such teams were younger than those vaccinated by the fixed-site ambulatory (41.50 vs. 43.66), irrespective of their sex with 146/1,081 (13.51%) females vs. 61/516 (11.82%) males. Among HCW categories by role, residents immunized by mobile teams had the highest proportion (50/175, 28.57%) followed by technicians (15/65, 23.08%), while the proportion of other categories ranged between 6.15 and 15.62%.

Survey responses

Overall, during the current campaign, 401 HCWs responded to the online, self-administered survey, as described in Table 3, corresponding to 33.95% of all HCWs immunized against influenza (n=1,181). Most frequently the respondents were female HCWs (270/401, 67.33%), aged between 30-59 years (274/401, 68.32%), physicians (131/401, 32.67%), working on medical specialties (87/401, 21.70%), and from Hospital A (271/401, 67.58%).

Looking at the mean scores on questions on knowledge about influenza and attitude toward influenza vaccination, four HCWs categories ranked below the total average as displayed in Table 4. Namely,

Table 2 - Total vaccination coverage and specific to influenza and COVID-19 by hospital and stratified by healthcare workers.

	Hospital A (n = 3730)					Hospital B (n = 1599)				
	Total	Anti-influenza		Anti-COVID-19		Total	Anti-influenza		Anti-COVID-19	
	N	N	%	N	%	N	N	%1	N	%1
Total	3730	1516	40.64	985	26.41	1599	322	20.14	196	12.26
Role										
Physician	799	599	75.00	439	54.96	532	143	26.88	99	18.61
Resident	-	168	-	127	-	40	12	30.00	7	17.50
Nurse	1529	188	12.30	122	7.98	392	50	12.76	23	5.87
Auxiliary staff	433	30	6.93	12	2.77	243	20	8.23	10	4.12
Technician	440	60	13.64	40	9.09	90	22	24.44	14	15.56
Administration	509	14	2.75	42	8.25	195	48	24.62	21	10.77
Others	-	357	-	203	-	107	20	18.69	16	14.95
Unknown	-	-	-	-	-	7	7	-	6	-

[1] Percentages are computed using the corresponding frequency divided by the total. Acronyms: COVID-19, coronavirus disease 2019.

Table 3 - Baseline characteristics of healthcare workers who responded to the online, self-administered survey (n=401).

	Total (n = 401)	
	N	%
Sex		
Female	270	67.33
Male	131	32.67
Age (median, IQR)3	**44**	**33,55**
Age groups		
18-29 years	79	19.70
30-39 years	90	22.44
40-49 years	95	23.69
50-59 years	89	22.19
60+ years	48	11.97
Role		
Physician	131	32.67
Resident	39	9.73
Nurse	60	14.96
Auxiliary staff	18	4.49
Technician	35	8.73
Administration	55	13.72
Others	63	15.71
Hospital area		
Administration	58	14.46
General Medicine	37	9.23
Specialized Medicine	87	21.70
ICU	10	2.49
General Surgery	12	2.99
Specialized Surgery	50	12.47
Neonatal and paediatrics	52	12.97
Radiology	28	6.98
Other	67	12.97
Hospital		
Hospital A	271	67.58
Hospital B	130	32.42

Acronyms: ICU, intensive care unit; IQR, interquartile range.

auxiliary staff (18/50, 36.00% of those immunized against influenza) ranked with the lowest scores in every item, especially for those on knowledge about influenza, followed by nurses (60/238, 25.21%) and technicians (60/82, 73.17%).

Discussion

Our study shows the relatively low adherence (~34%) among HCWs working in two major research and teaching hospitals in Milan, Italy, to the current vaccination campaign. Adherence was not uniform across the two hospital settings, with Hospital A having double the proportion of HCWs vaccinated than Hospital B (41% vs. 20%). A similar figure can be observed when looking at vaccine-specific figures for whom influenza had, generally, a higher VC compared to COVID-19. This may be due in part to fear of side effects from COVID vaccination despite extensive literature demonstrating the safety and effectiveness of this preventive tool (34–38).

Among HCWs, in both hospital, physicians were the ones with the highest VC, especially for influenza. This is aligned with the current body of knowledge (17,39,40). The reasons behind such a discrepancy might be explained by the differences in their social and formative backgrounds (e.g., different courses of study, lack of refresher courses).

Although observing that physicians have, in general, higher VC among HCWs these are far from being optimal and effective according to a public health perspective, also as highlighted by the Italian Ministry of Health (22). The importance of having HCWs vaccinated against influenza is, actually, its impact on their patients as those cured by unvaccinated physicians are more likely to not adhering to influenza vaccine campaign, as demonstrated by Godoy in 2015 (41).

Table 4 - Survey score means and standard deviations of all who responded to the on-line survey (n=400) and those self-reported roles that had average scores below in at least four of the survey items presented below.

	Total (n = 401)	Nurse (n = 60)	Auxiliary staff (n = 18)	Technician (n = 35)	Other (n = 60)
Knowledge questions					
Importance of vaccination	5.49 (1.48)	5.28 (1.68)	4.56 (1.95)	5.20 (1.37)	5.10 (1.65)
HCWs are the one most exposed	6.11 (1.31)	5.68 (1.81)	5.50 (2.07)	5.91 (1.25)	6.08 (1.09)
Severity of complications	5.75 (1.36)	5.62 (1.51)	4.61 (1.85)	5.74 (1.29)	5.53 (1.26)
Attitude questions					
Vaccinate next year	6.42 (1.26)	6.23 (1.56)	6.06 (2.01)	6.46 (0.98)	6.23 (1.38)
Recommend to other HCWs	6.39 (1.07)	6.17 (1.42)	6.17 (1.30)	6.31 (0.99)	6.27 (1.30)

Acronyms: HCWs, healthcare workers.

Conversely, in both hospitals, nurses and auxiliary staff had one of the lowest VC ever recorded. This, coupled with the survey score results – for which both HCWs categories ranked below the average – raises major concerns, especially for the nature of their job which requires close contacts with hospitalized and vulnerable people as frontline workers (42).

Similar poor levels of influenza VC among nurses and auxiliary staff were observed in another study in Italy (43), although elsewhere VCs seem to be much higher. Some studies attributed influenza vaccine hesitancy among nurses to the idea that other prevention measures (e.g., hand washing and wearing face masks) are more effective than influenza vaccine. Other researchers analyzed the personal decision-making process among nurses who consider influenza vaccination as a personal matter rather than a evidence-based measure (30,44), thus encouraging the employment of personal motivators (45). What we have seen can be associated in general with the reduced knowledge of the importance of vaccination as a preventive tool that is observed in many populations (46–51)

Comparing current influenza VC with past trends – only possible for Hospital A, a decreasing adherence back to pre- and early-COVID-19 figures (52,53) can be perceived with the 2020-2021 influenza season ranking as the one reaching the highest VC (i.e., 52%) (52). Similar trends can be seen in the general Italian population, whose influenza VC increased from ~17% in the 2019-20 influenza season to ~24% in 2020-21, and later plateauing at about 20% in recent years (54). Likewise, other studies have recorded, among different populations including HCWs, higher influenza vaccine rates (pooled rate 49%) compared to other influenza seasons (pooled rate 34%), including the 2009 pandemic (pooled rate 39%) sustained by the A(H1N1) pdm09 strain (55). The comprehensive VC of the influenza was about 34 %, and showed us a different data when we compared the two hospitals: 40.6% at Hospital A and 20.1% at Hospital B. At Hospital A results are lower than the 2021–22 influenza vaccination campaign, when VC was 52%. However, influenza VC among HCWs increased during the COVID-19 pandemic in Italy, consistent with a general increase in VC in the general population (over 20% in 2020-21) (54). Likewise, other studies have recorded among different populations, including HCWs, higher influenza vaccine rates (pooled rate 49%) compared to other influenza seasons (pooled rate 34%), including the 2009 pandemic (pooled rate 39%) sustained by the A(H1N1) pdm09 strain (21). The results show a relevant and pervasive difference

in adhesion to campaign between physicians and other HCWs, as seen by Latorre et al in 2011 and Paoli et al in 2019 (43,56). Indeed in both the hospitals the physicians had the higher VC while the worst was registered by administrative and auxiliary staff.

Discrepancies in COVID-19 and influenza VCs between the two hospitals can be explained by the new strategy for vaccination administration implemented in Hospital B. Conversely, Hospital A has a relatively longer history of influenza vaccination campaigns, also employing different health promotion activities (39,52,53), that might explain the higher coverages observed.

Conclusions

Although important aspects are covered by this article, several limitations are present and need to be considered. Firstly, by being a relatively new facility, Hospital B has not adopted any health promotion activity to sensitize its HCWs in the past compared to Hospital A, which performed several immunization campaigns in the past. Secondly, data used in this study is limited to the vaccines administered in the two hospitals and does not include vaccination administered elsewhere e.g., in other vaccination centers and/or by general practitioners, or vaccine purchased in pharmacy. Thirdly, regarding the filling out of the online questionnaire, Hospital B displayed a very poor internet connection that prevented many potential respondents to complete it. Fourthly, the survey questionnaire was accessible to all individuals within Hospital A via the hospital's intranet, potentially leading to inadvertent completion by HCWs who were not compliant with the vaccination campaign. In contrast, at Hospital B, the survey QR code was exclusively provided to individuals who had been vaccinated. A limitation of the questionnaire study was the low number of responses due to participation in the survey on a voluntary basis. This combined with the wide range of responses based on a series of likert scales regarding knowledge related to vaccinations and interest in influenza vaccination, as well as the large subdivision of the responding population in a wide range of professional groups makes the inferential analysis and the achievement of statistical significance extremely complex. All of this then provides the basis for possible new studies to specifically investigate this area through different modalities or a different mode of operator involvement, such as a survey performed throught paper form offered in each

hospital ward presented by the research team to each health worker.

To our knowledge, this is one of the first studies presenting results from the current 2023-24 seasonal influenza vaccination campaign. Our results further stress the lack of adherence to influenza and COVID-19 vaccination and their respective VCs among HCWs in hospital settings, especially among nurses and auxiliary staff. Making use of the results of this study, we encourage healthcare planners to deliver more effective health education and promotion activities to draw attention on the relevance of the vaccination against seasonal influenza vaccination – as well as against COVID-19 – to the whole hospital population and with particular interest for the hard-to-reach subsets (57).

Riassunto

Vaccinazione antinfluenzale ed anti-Covid nel 2023: un'analisi descrittiva in due Ospedali di Ricerca e Didattici italiani. La strategia On-Site è efficace?

Introduzione. Le vaccinazioni rappresentano uno strumento estremamente efficace per la prevenzione di alcune malattie infettive – quali influenza e COVID-19 –, in particolare per quelle categorie a rischio sia per le proprie condizioni di fragilità che per esposizione professionale come gli operatori sanitari. Scopo di questo studio è descrivere lo svolgimento della campagna vaccinale antiinfluenzale e anti-COVID-19 presso due ospedali di ricerca e di insegnamento milanesi.

Disegno dello Studio. Studio multicentrico, trasversale.

Metodi. In occasione della campagna vaccinale 2023-24 le due strutture hanno optato per due approcci diversi. Presso l'Ospedale A sono state implementate due diverse strategie per la vaccinazione degli operatori sanitari: un ambulatorio di vaccinazione in sede fissa e due gruppi di vaccinazione mobili gestiti da specializzandi di Igiene e Medicina Preventiva dell'Università degli Studi di Milano. Presso l'Ospedale B, invece, è stato utilizzato un unico ambulatorio in sede fissa gestito da specializzandi di Igiene e Medicina Preventiva dell'Università degli Studi di Milano. In occasione della campagna è stata, inoltre, svolta un'indagine tramite questionari anonimi online per indagare l'attitudine verso la vaccinazione del personale.

Risultati. Sono stati vaccinati un totale di 1937 operatori sanitari: 756 sono stati immunizzati solo contro l'influenza, 99 solo contro il COVID-19, e 1082 contro entrambi. Dai risultati emerge una differenza sostanziale di adesione alle vaccinazioni tra personale medico-infermieristico rispetto alle altre categorie professionali. In particolare, la categoria con la più alta adesione vaccinale è risultata essere quella dei medici con il 55.7% di adesione mentre al contrario la categoria a più bassa adesione è risultata essere quella del personale ausiliario caratterizzato dal 7.4% di adesione. Allo stesso tempo il confronto tra le due strutture ospedaliere ha mostrato una percentuale di adesione doppia da parte del personale dell'Ospedale A sia per quanto riguarda il vaccino antinfluenzale (40.6% e 20.1%) sia per quanto riguarda il vaccino anti-COVID-19 (26.4% e 12.3%). L'indagine, infine, ha mostrato come l'attitudine nei confronti della vaccinazione antiinfluenzale risulti più bassa tra il personale ausiliario sia per quanto concerne conoscenza che attitudine vaccinale.

Conclusioni. I risultati dello studio mostrano un'adesione vaccinale in linea con quella degli anni precedenti, sebbene inferiore ai valori consigliati dalle principali organizzazioni nazionali e internazionali. L'analisi delle differenze tra le due strutture e delle survey svolte permetteranno di implementare interventi mirati per aumentare l'adesione nelle prossime campagne.

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Corresponding author: Pier Mario Perrone, Department Biomedical Sciences for Health, University of Milan, Via Mangiagalli 31, 20133 Milan, Italy
email: piermario.perrone@unimi.it

COVID-19 Immunity in the Cohort of IRCCS San Raffaele Hospital Employees after BNT162b2 Vaccination: A Retrospective Observational Study

Manuel Stocchi[1], Pietro Melodia[1], Alessandra Lucini[2], Rebecca De Lorenzo[2,3], Carola Pozzi[4], Patrizia Rovere-Querini[2,3], Anna Odone[5], Cristina Renzi[1,6], Carlo Signorelli[1]

Abstract

Introduction. The COVID-19 pandemic represents the most severe health and socioeconomic crisis of our century. It began with the first reports in China, in the Wuhan region in December 2019, and quickly spread worldwide, causing a new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Among the population most at risk of infection and developing severe forms of the disease are the elderly and healthcare workers, who are more exposed to infected individuals. On December 11, 2020, the Food and Drug Administration approved the emergency use of the BNT162b2 vaccine, the first mRNA vaccine in history. Since then, the total number of vaccine doses administered has exceeded 12 billion. Italy was the first European country to be affected by the pandemic, recording the highest number of total COVID-19 cases (25,695,311) and, after the first 70 days, had the highest crude mortality rate (141.0 per 100,000). In this study, we analyze the rate of SARS-CoV-2 infection among healthcare workers at the San Raffaele Scientific Institute in Milan before and after receiving the BNT162b2 vaccine.
Study design. Retrospective observational cohort study.
Methods. The study analyzed the immunization status of 858 employees of the San Raffaele Scientific Institute in Milan, including doctors, healthcare workers, and administrative staff. The analysis is based on previous studies on the same cohort and is integrated with extrapolation and additional analysis of data from the Preventive Medicine Service's Biobank dataset of the same hospital to estimate the infection rate, duration of the disease, and antibody levels recorded in the personnel before and after receiving the double BNT162b2 vaccination.
Results. The analysis confirms the positive impact achieved by the introduction of mRNA vaccination in reducing the SARS-CoV-2 infection rate and increasing antibody levels in healthcare workers. Although the BNT162b2 vaccination may not provide

complete protection against SARS-CoV-2, it appears to be able to reduce the number of infections, particularly the more severe and symptomatic forms often detected in individuals with various risk factors and comorbidities, making them more vulnerable. Healthcare workers, who have extensive contact with patients and record the greatest decrease in the infection rates, represent the population that receives the most benefit from vaccination.

Conclusions. *The evidence suggests that vaccinations are essential in protecting high-risk groups, such as healthcare workers, from SARS-CoV-2 infection. Providing adequate vaccination coverage to healthcare workers limits the spread of infections and decreases the severity of disease manifestations, while also reducing their duration.*

Introduction

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 infection as a pandemic (1). Italy was among the first countries in the European region to experience the detrimental effects of the pandemic, partly due to its high proportion of people aged 70 years or older (2, 3). Lombardy region reported the highest crude COVID-19 mortality rate (141.0 per 100,000) 70 days after the beginning of the epidemic, out of all European metropolitan areas with similar socio-demographic characteristics (4, 5).

This situation led the Italian government to promptly implement public health measures, such as limiting travel and avoiding behaviors at risk of encouraging the transmission of the infection (6). The efficacy of implementing fundamental public health principles such as personal hygiene, the utilization of personal protective equipment, was reestablished (7).

Italy also adopted rapid antigen tests, which were quickly implemented and regulated in sectors like healthcare and education, where the patient facing staff personnel were at higher risk of infection (8). Healthcare personnel have been at the forefront of the battle against COVID-19, facing an elevated risk of infection due to their continuous exposure to infected patients and colleagues (9-11). To protect these essential workers and ensure the uninterrupted delivery of healthcare services, mRNA-based vaccines for COVID-19 were introduced globally from late 2020 (12).

On 22 December 2020, the Italian Medicines Agency (AIFA) authorizes the marketing of the new anti-COVID-19 vaccine from Pfizer/BioNTech, BNT162b2 in Italy for all those aged 16 or over (13-15). The primary aim of vaccination has been to reduce the risk of infection and reduce the severity of symptoms in case of positive swab tests (16).

This study is built on the previous longitudinal observational study conducted by the Internal Medicine Operating Unit at San Raffaele Scientific Institute in Milan, which assessed the kinetics of immune response of B and T cells using serological tests and ELISpot IFN-γ in healthcare workers and non-healthcare personnel. Demographic and clinical data were collected through an anonymous survey (17, 18).

The San Raffaele Scientific Institute can be considered a particularly relevant center for selecting the study population, due to the following reasons. The Hospital is located in the geographical area where the first two European outbreaks of COVID-19 were found (19). The first case in the metropolitan city of Milan was diagnosed at the San Raffaele Scientific Institute (20). The large tertiary hospital enables to include a substantial sample size. The laboratory and epidemiological data collected during the epidemic (also with the collaboration of members of the CORONADX research group) were deemed sufficiently complete.

The aim of the study was to evaluate the impact of mRNA vaccination on SARS-CoV-2 infection rates, antibody levels and duration of illness among employees of the San Raffaele Scientific Institute.

Specific objectives were to determine the incidence of SARS-CoV-2 infections among healthcare workers using PCR swabs (both before the first dose of mRNA vaccine and up to 10 months after vaccination), to evaluate the antibody levels of individual employees, with particular attention to IgM and IgG values, before the first vaccination and at 10-month intervals after the first, second and third dose (booster), the determination of the COVID-19 disease average duration in workers with at least one mRNA vaccination, considering the time elapsed between the day of onset of the disease and the day of return to work, and the determine changes in Covid-19 symptoms, in relation to comorbidities and pre-existing risk factors, in infections that occurred before and after vaccination with BNT162b2.

Methods

This retrospective cohort study included a dataset with 858 records of employees of the San Raffaele

Scientific Institute in Milan, encompassing patient-facing staff, such as doctors and other healthcare professionals, and non-patient-facing administrative staff. The inclusion criteria considered a population of individuals over the age of 18, who received at least one dose of BNT162b2 mRNA COVID-19 vaccine, starting January 2021 to June 2021, up to a maximum of three doses, limited to the period of time when the Internal Medicine Operations Unit administered the questionnaires 10 months after the first dose.

The data are extrapolated from the anonymized database of the Internal Medicine Operating Unit, containing information on sex, age, profession, anthropometric measurements, medical history, drug therapy and symptoms in case of infection or post-vaccination. This data was collected through questionnaires administered to HSR employees, 10 months after vaccination. The survey aimed to collect demographic and anthropometric data, as well as medical history and adverse effects following the administration of two doses of the vaccine. Data on pre-existing comorbidities were collected, classified as follows: (a) current or previous cancer; (b) allergic conditions; (c) diabetes mellitus (type 1 or type 2); d) blood diseases (anaemia, coagulopathies); (e) history of immunosuppression/transplants; f) cardiovascular diseases; g) neurological conditions; h) autoimmune diseases; i) infectious diseases; (l) history of smoking; m) pharmacological treatment; The questionnaire also included information on medical events related to COVID-19, with a focus on COVID-19 viral infections contracted up to 6 months before and up to ten months after vaccination. COVID-19 symptoms were studied through a series of questions, covering various symptoms and effects. Questions about vaccination side effects included localized reactions (pain, swelling, redness at the injection site), systemic reactions (fever, fatigue/malaise, chills, headache, vomiting/nausea, diarrhea, muscle pain, swollen lymph nodes, dizziness /confusion), allergic reactions (widespread itching, rash unrelated to the injection, asthma, throat tightness, anaphylaxis) and other reactions (altered sleep quality, memory loss, anxiety, psychological distress, feelings of gratitude/relief/ joy, attention deficit, palpitations, pain, loss of appetite, increased thirst, intolerance to heat/cold, menstrual cycle disorders, difficulty carrying out daily activities). Finally, employees were asked to identify themselves as either patient-facing staff (physicians, nurses, physiotherapists, psychologists, social health workers (OSS), technical assistance workers (OTA), technical assistance workers, speech therapists, obstetricians, orthoptics), or nonpatient-facing staff (Administrative Employees).

This first dataset was integrated with the data contained in a second anonymized Database of the Hospital Biobank, created on the basis of the analyzes carried out by the Preventive Medicine Service on the disease status of HSR employees. All data was collected over time after anonymization. Health checks and employee health surveys have evolved over time. In October 2020, only RT-PCR was being performed. From November 2020 to January 2022, RT-PCR was used for the diagnosis of symptoms compatible with Covid, and upon return to hospital activity after Covid infection/quarantine due to close contact, as well as upon return from abroad, and upon return after illness with symptoms compatible with Covid in subjects negative to the swab carried out at the onset of symptoms, and as screening of contacts in healthcare workers. A second type of test using Rapid Antigenic was carried out as screening for access to the departments.

Since January 2022 the procedures have been updated again and RT-PCR was only necessary for the diagnosis of symptoms compatible with Covid, while Rapid Antigen was used in case of return to hospital activity after illness/quarantine, and screening of close contacts in healthcare workers.

A maximum of 3 doses of BNT162b2 vaccine are taken into consideration in the study, as they fall within the complete cycle as referred to in decree No. 172/2021. The booster dose was intended for the prevention of SARS-CoV-2 infection and made mandatory from 15 December 2021, at least 5 months after the administration of the second dose, for all categories of workers at greater infectious risk, such as healthcare workers, and also extended to non patient-facing staff.

Antibody titers were tested by the Elecsys Anti-SARS-CoV-2 assay (Roche, Basel, Switzerland) specific for the viral SARS-CoV-2 1 Nucleocapsid protein (N) at T0 and by the Elecsys SARS-CoV-2-S (Roche, Basel, Switzerland) against the RBD of the viral Spike (S) protein at T1, T2, T3, and T4. The Roche Elecsys Anti-SARS-CoV-2 is an electrochemiluminescence immunoassay (ECLIA) targeted on total immunoglobulins (IgTot: IgA, IgG, and IgM) against the N-protein. The result is given as a cut-off index (COI) and qualitative results: for COI 1.0, the sample is reactive and positive (manufacture datasheet: 09289267501V0.6). The manufacturer indicated a specificity of 99.80% and a sensitivity of 99.50% 14 days post-PCR confirmation. The Roche

anti-SARS-CoV-2-S is an ECLIA detecting total immunoglobulins (IgTot: IgA, IgG, and IgM) against the RBD of the viral S-protein. The quantification range is between 0.4 and 250.0 U/mL, which is further extended to 2500.0 U/mL by a 1:10 dilution of the sample automatically performed by the instrument. Specificity and sensitivity (≥14 days after diagnosis) are 174 99.98% and 98.8%, respectively, when the manufacturer's suggested COI for positivity 0.8 U/mL is 175 used (21).

Peripheral blood samples were collected at five crucial time points. T0, the Day 0 shortly before the first vaccine administration. T1, 21 days after the first dose (shortly before the second dose) to assess the response to the initial vaccination. T2, 21 days after the second dose, reflecting the immune response upon completing the vaccination regimen. T3, 6 months after the first dose. T4, Prior to the booster dose (10 months after the first dose).

Results

The study highlighted a reduction in the incidence of SARS-CoV-2 infections in the different categories of workers at the San Raffaele Hospital, following vaccination with mRNA. Out of a total of 858 healthcare worker records (856 after duplicates removed) the incidence of SARS-CoV-2 Infections were 7.7% (66) in HSR Employees pre-BNT162b2 vaccination population, and decreased up to 4.6% (39) in HSR Employees post-BNT162b2 vaccination (Fig. 1.A).

The incidence of SARS-CoV-2 infections by gender affected 7.6% of men and 7.8% of women pre-vaccination, decreasing to 4% and 4.9% in the post-vaccination phase. (Fig. 1.B). The study recorded a drop in the infection rate from 9.2% to 4.1% (from 51 to 23 employees) for patient-facing staff. On the contrary, among non patient-facing staff, the number of infections remained stable in the two phases, affecting 5% and 5.3% of employees (from 15 to 16 employees) (Fig. 2.A).

A decrease in the number of SARS-CoV-2 infections was observed in medical personnel from 3.1% to 2.7% (from 17 to 7 employees), but even more significant in healthcare workers in close contact with patients (Nurses, Social-Health Operators(OSS), Technical-Assistance Operators(OTA), Psychologists, Physiotherapists, Obstetricians, Orthoptics) from 11.5% to 5.4% (34 to 16 employees) (Fig. 2.B).

The incidence of SARS-CoV-2 infections was then analyzed, before and after vaccination, in subgroups of workers, divided on the basis of the number of pre-existing risk factors: workers who did not present comorbidities, employees who had at least one, and those with 2 or more comorbidities. The analysis shows a significant decrease in the incidence of post-vaccination infections in each group of patients. In the group without comorbidities, the incidence dropped

Tab. 1 - Characteristics of the study sample

	Total	Females	Males
HSR Employees	856	553 (64.60%)	303 (35.40%)
AGE (years), median (IQR)	53.75 (25.17-79.01)	52.69 (25.17-78.86)	56.06 (26.04-79.01)
BMI (kg/m²), median (IQR)	23.60 (12.21-44.27)	22.32 (12.21-44.27)	25.26 (12.21-44.27)
	Pre-vaccine infections		
Occupation		INFECTED	NOT INFECTED
Patient facing staff		51 (9.19%)	504 (90.81)
Doctors		17 (6.61%)	242 (93.39%)
Health care professions*		34 (11.49%)	262 (88.51%)
Non patient facing staff		15 (14.85%)	286 (85.15%)
	Post-vaccine infections		
Occupation		INFECTED	NOT INFECTED
Patient facing staff		23 (4.0%)	532 (96%)
Doctors		7 (2.70%)	252 (97.28%)
Health care professions*		16 (5.40%)	280 (94.6%)
Non patient facing staff		16 (5.31%)	285 (94,69%)

(*): The group includes Nurses, OSS, OTA, Psychologists, Physiotherapist, Obstetrics, Oral Hygienist and Ortoptics

Tab. 2 - Characteristics of Comorbidities in HSR Employees

Comorbidities	HSR Employeers with Comorbidities (%)
Current Neoplastic Disease or Under Treatment in the previous year	14 (1.63%)
Respiratory Pathology	40 (4.67%)
Obesity (BMI>30)	41 (4.79%)
Cardiovascular Disease	38 (4.44%)
Neurological Disease	20 (2.33%)
Diabetes Mellitus	16 (1.87%)
Chronic Renal Failure	5 (0.58%)
Coagulopathies	8 (0.93%)
History of Immunosuppression/Organ Transplant	8 (0.93%)
Hypertension	161 (18.81%)
Liver Disease	3 (0.35%)
Sickle Cell Anemia or Thalassemia	6 (0.70%)
Autoimmune Disease	71 (8.29%)
Gastrointestinal Disease	17 (1.96%)
Infectious Disease	6 (0.70%)
Previous Smoking History	92 (10.75%)
Current Smoking History	99 (11.57%)

from 9.3% to 4.8%. In the second group, workers with at least one comorbidity, showed a decrease from 6.9% to 4.3%. Even in the third group, among the most vulnerable workers, there is modest drop from 5.3% to 4.6% (Fig. 3).

From the analysis of health coverage offered through BNT162b2 vaccination, in terms of incidence, cases of SARS-CoV-2 infection decreased from 66 to 17 after a full course, and the median period of time without infection in vaccinated employees was 47 days (p.max: 93 days. p.min: 5 days) (Fig. 4).

Among the different forms of SARS-CoV-2 infection (asymptomatic, monosymptomatic, polysymptomatic - with two symptoms - and multisymptomatic - with three or more symptoms -), there has been a general decline in the incidence of COVID-19 post-vaccination, with a reduction from 2.7% to 0.7% in the asymptomatic form, from 0.8% to 0.5% in the monosymptomatic form, from 0.8% to 0.1% in the polysymptomatic form, up to a decrease from 3.4% to 0.7% in the multi-symptomatic one (Fig. 5).

From the analysis of symptoms, a general decline in symptoms is observed in post-vaccination

Tab. 3. Symptoms Distribution in Covid-Infected HSR Employees

Symptoms	Pre-Vaccine Coronavirus Infected HSR Employees (%)	Post-Vaccine Coronavirus Infected HSR Employees (%)
Fever ≥ 37.5 °C & Chills	25 (2.91%)	2 (0.23%)
Cough	11 (1.28%)	1 (0.12%)
SoreThroat	18 (2.10%)	2 (0.23%)
Rhinorrea	12 (1.40%)	4 (0.46%)
Dyspnea	9 (1.05%)	0 (0.0%)
Chest Pain	5 (0.58%)	1 (0.12%)
Anosmia/Ageusia	15 (1.75%)	6 (0.70%)
Myalgia/Arthralgia	15 (1.75%)	1 (0.12%)
Asthenia	27 (3.15%)	3 (0.35%)
Headache	17 (1.98%)	5 (0.58%)
Nausea/Vomiting	7 (0.82%)	7 (0.82%)
Diarrhea/Abdominal Pain	4 (0.47%)	4 (0.47%)
Conjunctivits	6 (0.70%)	3 (0.35%)
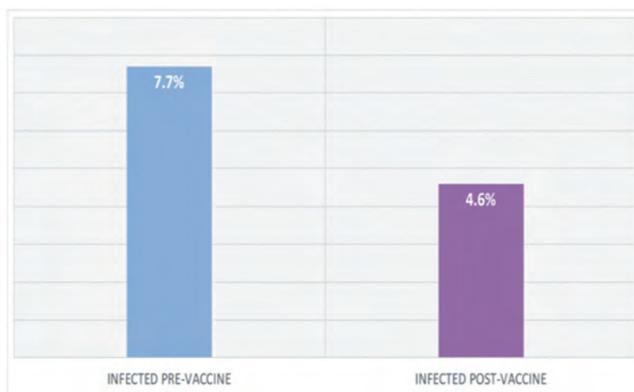
Figure 1.A - Incidence of Coronavirus Infections in HSR Employees pre-and-post BNT162b2 vaccination
Figure 1.B - Incidence of Coronavirus Infections by gender in HSR Employees pre-and-post BNT162b2 vaccination

infections.

In the subgroup of employees without risk factors, and in employees with at least one risk factor, they were associated with milder forms with reduction of symptoms, compared to their counterparts before vaccination (Fig.6.B) (Fig.6. C).

However, SARS-CoV-2 infection in employees who had 2 or more risk factors remains associated with a more symptomatic condition compared to employees without comorbidities. (Fig.6.D).

From the analysis of the blood samples, (collected at 5 time points: the day before the first vaccine administration (T0); 21 days after the first dose and shortly before the second dose (T1); 21 days after the second dose (T2), 6 months after first dose (T3), 10 months after first dose (T4)). IgG antibody levels have demonstrated substantial increases after each vaccine dose enhancing immune responses. The antibody median levels found among employees in the different pre- and post-vaccination phases were summarized, specifically reporting the levels of 2 different types of antibodies: Anti-S (Anti-RBD) and Anti-N. (Fig. 7.A).
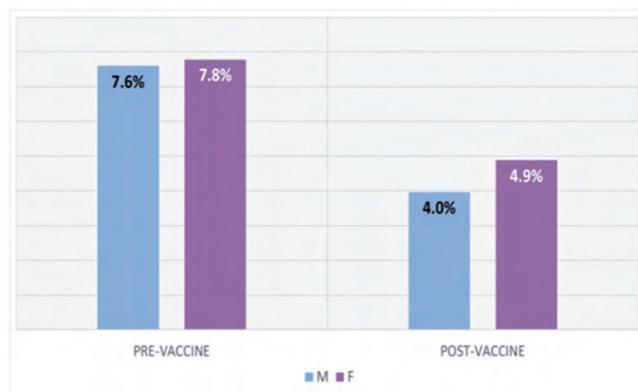
The population of HSR employees showing an
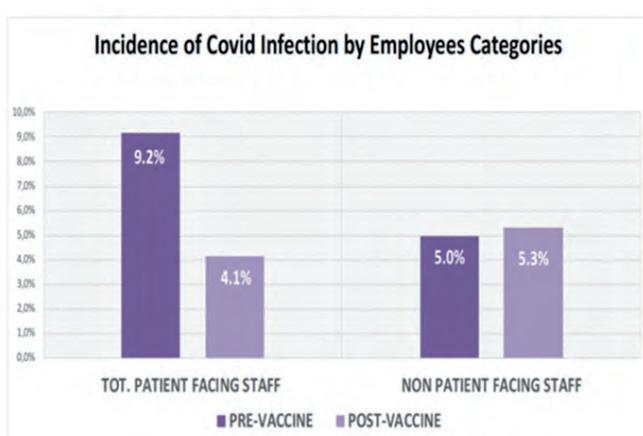
Figure 2.A - Incidence of Coronavirus Infections by HSR Employees Categories pre-and-post BNT162b2 Vaccination
Figure 2.B - Incidence of Coronavirus Infections by HSR Employees Subgroup pre-and-post BNT162b2 Vaccination
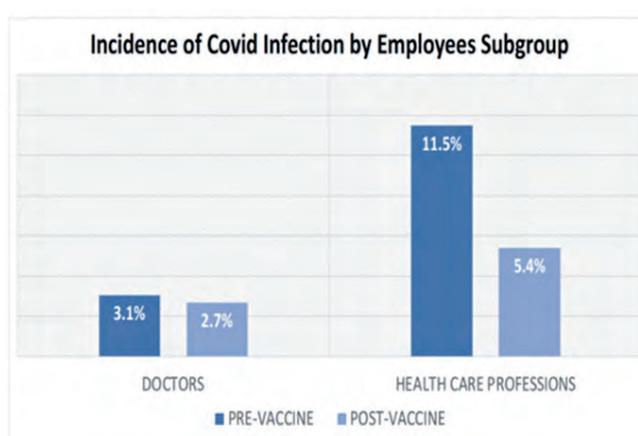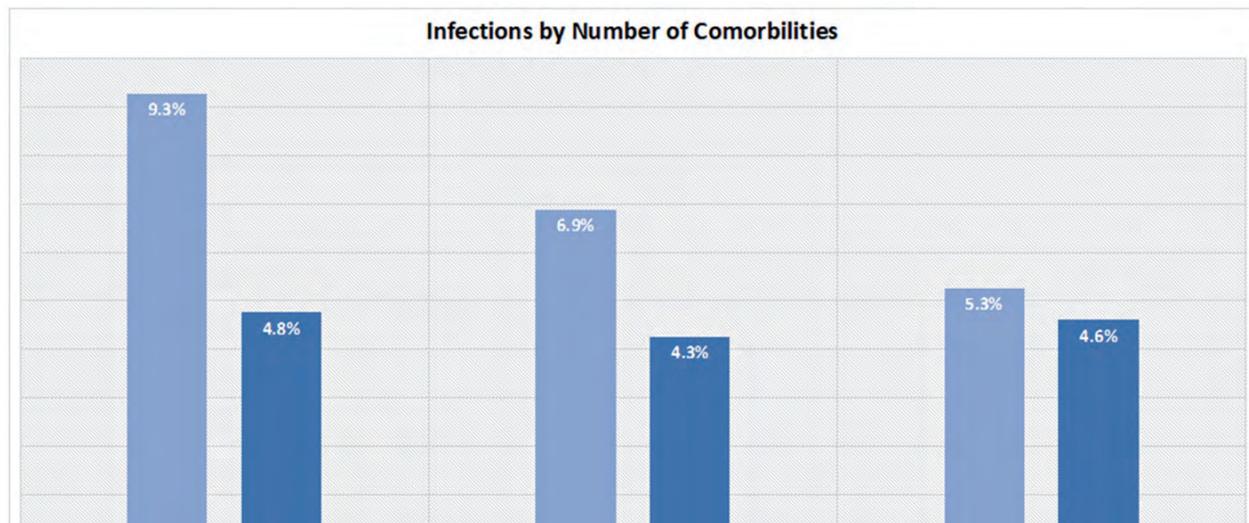
Figure 3 - Incidence of Coronavirus infections in HSR Employees by number of comorbidities pre-and-post BNT162b2 Vaccination

anti-N-specific antibody titer >1 U/ml at baseline (T0) was considered naturally seropositive (with a history of SARS-CoV-2 infection prior to vaccination. Pre-vaccination levels were around 5.03 U/ml, tripled in the pre-booster dose phase, reaching average values of 15.71 U/ml, with a median value 6 months after the first vaccination of 10.37 U /ml. (Fig. 7.B).

The levels of anti-S antibodies at T1, T2, T3 and T4 showed how a second administration of the mRNA vaccine, added to the first, 21 days later, produced a significant stimulation of the immune system with a significant increase from 96.32 to 1678.74 U/ ml. While after 6 months a halving of the antibody values was observed, reaching a value of 867.88 U/ml, further decreased in T4, 758.13 U/ml (Fig. 7.C-E).
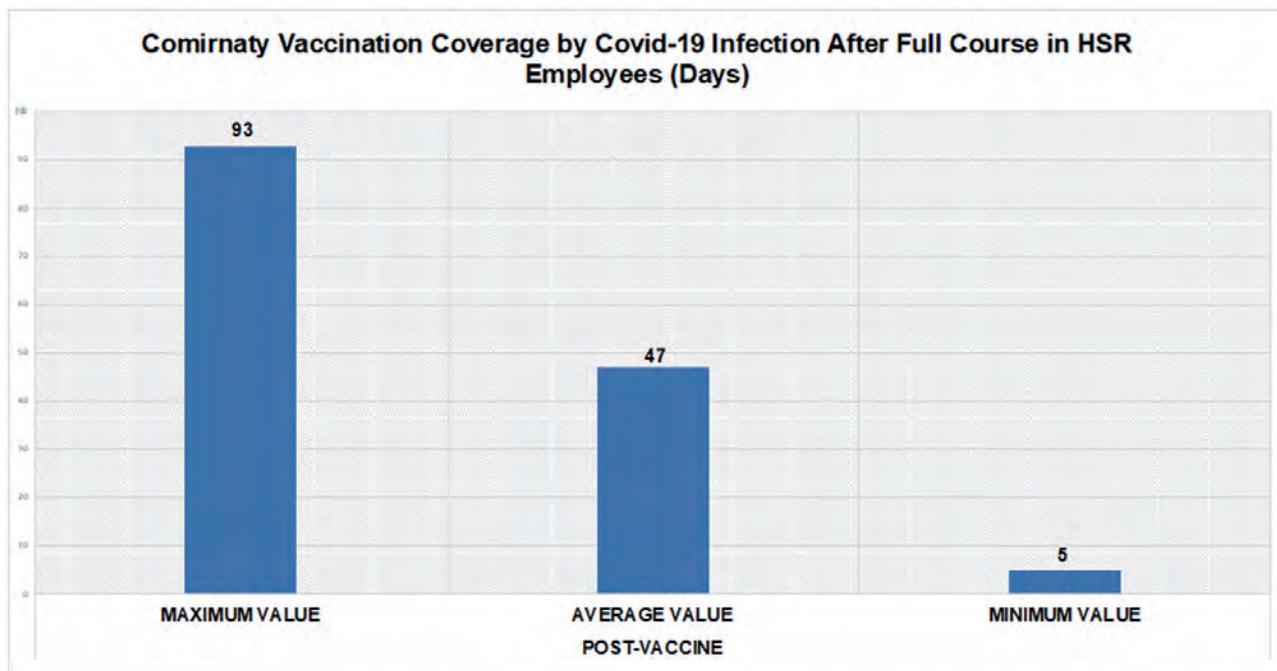
Figure 4 - Representation of the Duration of BNT162b2 Vaccination Coverage Before Reinfection in HSR Employees
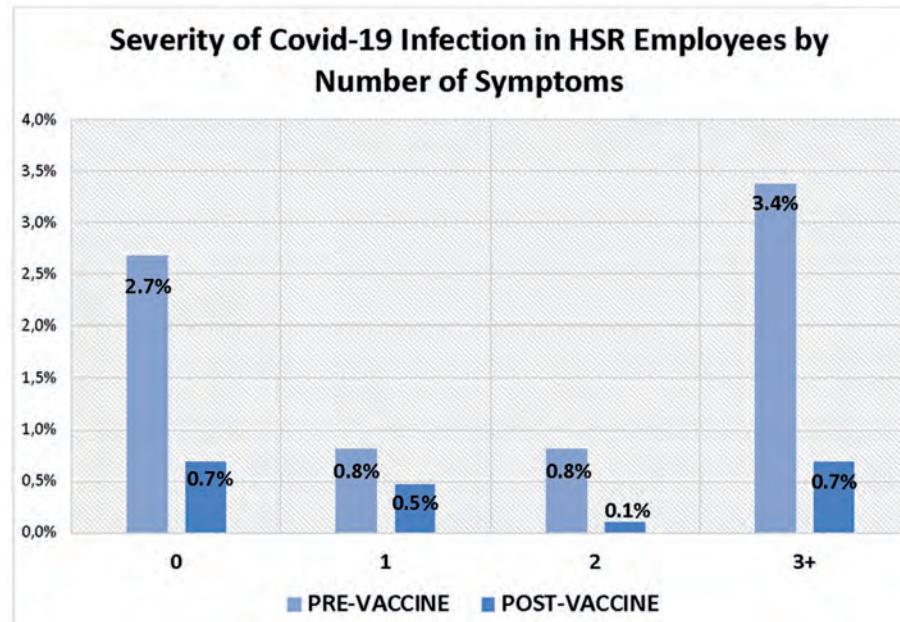
Figure 5 - Incidence of different forms of Coronavirus disease (asymptomatic, mono-symptomatic, poly-symptomatic, pluri-symptomatic) in HSR Employees pre-and-post BNT162b2 Vaccination

A reduction in the days of absence from work due to COVID-19 illness was also ascertained, with an average absence time that dropped from 16.3 days in the 6 months before the first vaccination to 14.25 days in the 10 months after vaccination (Fig. 8).

Discussion

Our study considered a cohort of 856 (858 without 2 duplicate records) employees of the IRCCS San Raffaele Hospital, including both professional figures in close contact with the patient (facing-patient staff) and administrative figures, not in close contact with
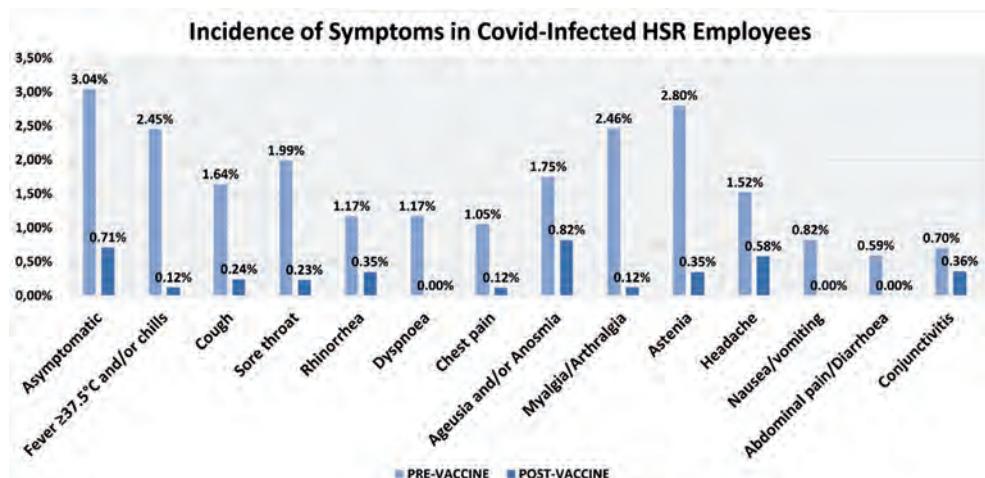
Figure 6.A - Incidence of Symptoms in Coronavirus-Infected HSR Employees pre-and-post BNT162b2 vaccination
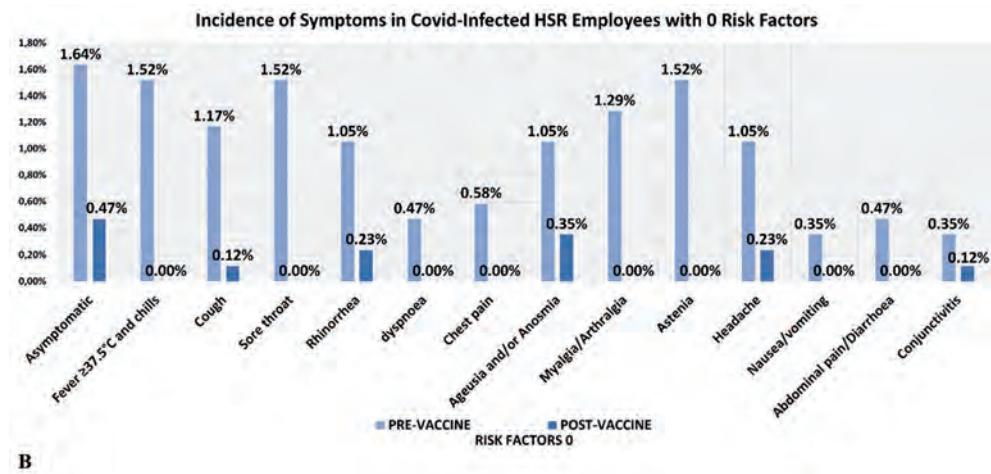
Figure 6.B - Incidence of Symptoms in Coronavirus-Infected HSR Employees with 0 Comorbidities pre-and-post BNT162b2 vaccination
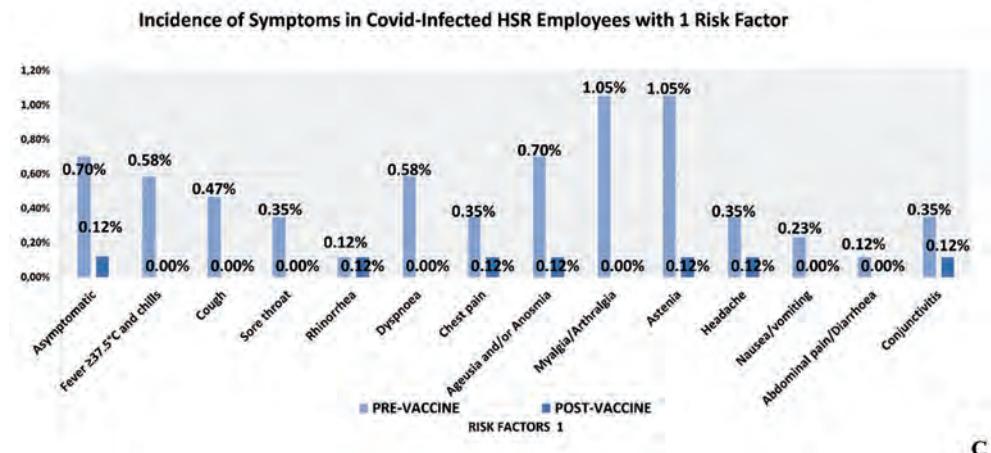
Figure 6.C - Incidence of Symptoms in Coronavirus-Infected HSR Employees with 1 Comorbidities pre-and-post BNT162b2 vaccination
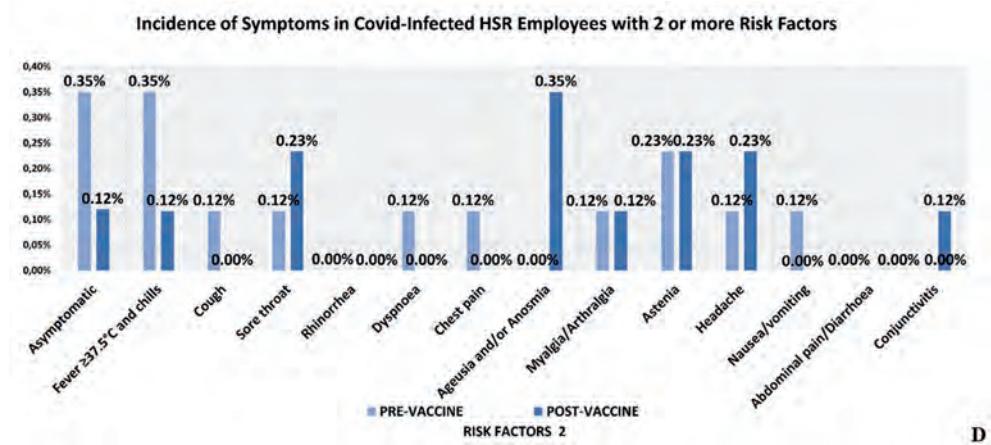
Figure 6.D - Incidence of Symptoms in Coronavirus-infected HSR Employees with 2 or more Comorbidities pre-and-post BNT162b2 vaccination

the patient (non patient-facing staff). The common inclusion criteria were age over 18 years and having received at least one dose of the BNT162b2 mRNA COVID-19 vaccine (BNT162b2). The study demonstrates the effectiveness of the BNT162b2 vaccination (VE) and therefore the usefulness and priority of use in one of the professions most at risk of contracting SARS-CoV-2 infection, such as the category of Healthcare Workers. From the NEJM clinical trial on which the EMA's evaluation was based, we know that the safety and efficacy of the BNT162b2 vaccine against laboratory-confirmed SARS-CoV-2 infection is equal to 95% (22).

As demonstrated in our study, even among the different categories of workers at San Raffaele Hospital, the incidence of SARS-CoV-2 infection in a cohort of 856 HSR employees decreased from 7.7% before vaccination to 4.6%.

Specifically, for the category of patient-facing staff, we recorded a decrease in the infection rate from 9.2% to 4.1%, compared to a more stable rate (from 5% to 5.3%) in the subgroup of administrators who are exposed to a lower risk, as found in the English study (SIREN), Israeli, and Italian studies. However, the greatest effectiveness is observed in the categories of patient-facing staff, and in fact, we found the highest effectiveness after vaccination in the subgroup of healthcare workers (nurses, OSS, OTA, psychologists, physiotherapists, obstetricians) which decreased from 11.5% to 5.4% (from 34 to 16) compared to medical personnel who recorded only a minimal decrease from 3.1% to 2.7% (from 17 to 7 employees) (23-25).

From the analysis of this German article, as well as this second publication from the United Kingdom, a link is shown between pre-existing comorbidities and more severe manifestations of Covid-19, which may lead to a higher likelihood of hospitalization within 90 days. In both cases, vaccination provides greater protection for the most at-risk personnel, resulting in a general decrease in infections and limiting the occurrence of severe forms of the disease. Additionally, our subdivision of HSR personnel based on the number of comorbidities reveals a general decreasing trend in infections and in the subsequent development of illness and serious complications, with a reduction of 4.5% in the group without comorbidities and a more modest reduction of 0.7% in the most vulnerable patients (26, 27).

Furthermore, the BNT162b2 vaccine does not guarantee complete protection against SARS-CoV-2 infection, and these studies also demonstrates the possibility of becoming infected after one or both
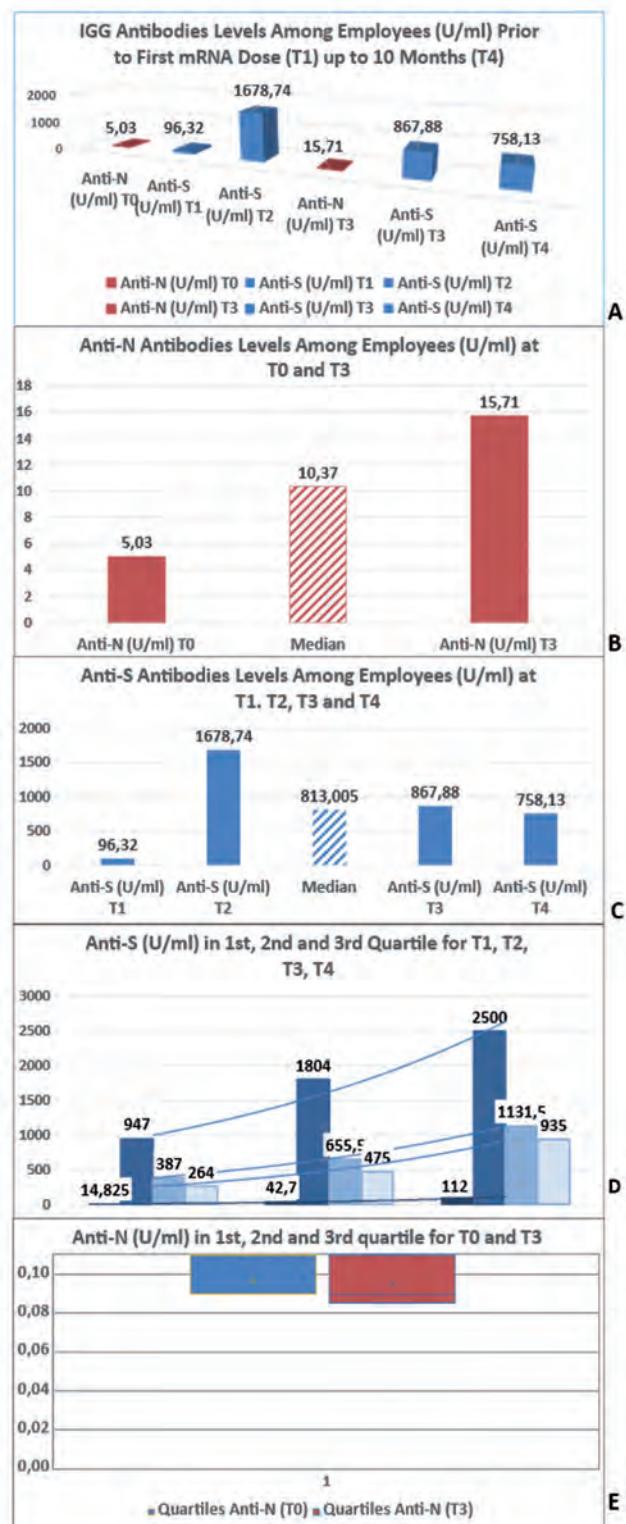
Figure 7.A; IgG Antibodies Levels Among Employees (U/ml) prior to First mRNA Dose (T1) up to 10 Months

Figure 7.B; Anti-N Antibodies Levels Among Employees (U/ml) at T0 and T3

Figure 7.C; Anti-S Antibodies Levels Among Employees (U/ml) at T1, T2, T3 and T4

Figure 7.D; Anti-S (U/ml) in 1st, 2nd and 3rd Quartile for T1, T2, T3, T4

Figure 7.E; Anti-N (U/ml) in 1st, 2nd and 3rdQuartile for T0 and T3
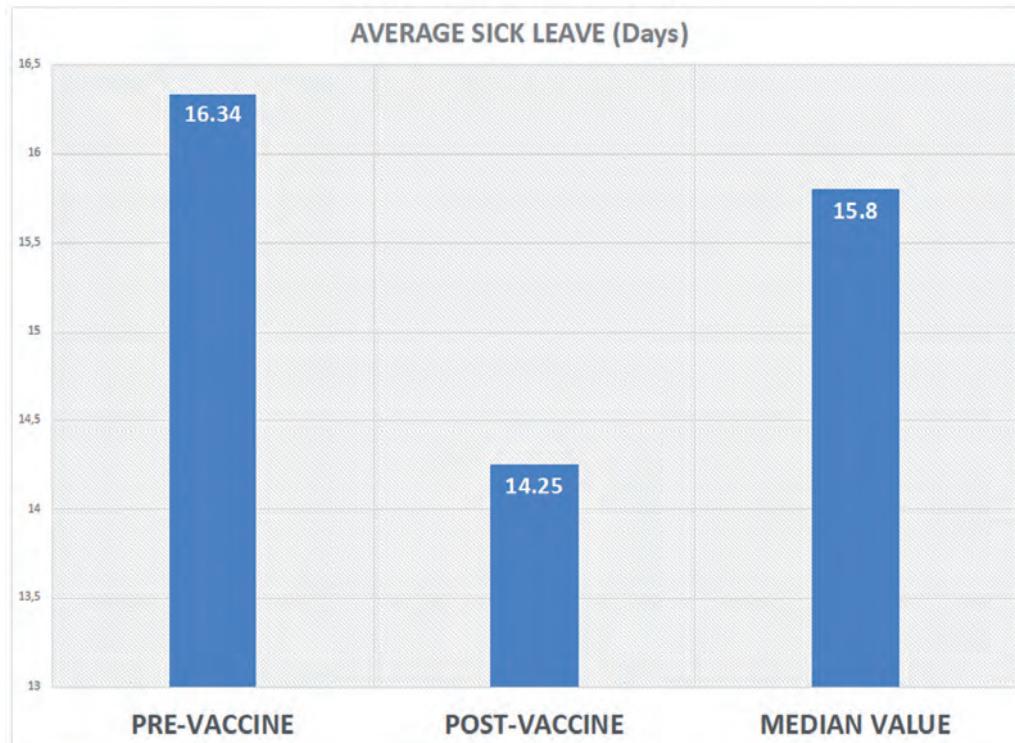
Figure 8 - Representation of the Average Sick-Leave (Days) in HSR Employees pre-and-post BNT162b2 Vaccination

doses of BNT162b2. Our study also identifies cases of infection occurring a few days after the second dose (as early as 5 days) and even after reaching the maximum efficacy of 95% coverage 7 days after the second dose (28-30).

From our analysis COVID-19 symptoms, we have observed a clear and overall decrease in symptoms in post-vaccination cases. However, it is important to note that SARS-CoV-2 infections with two or more risk factors remains associated with a more symptomatic disease, which can worsen already complex conditions, highlighting greater fragility and propensity for more clinically serious diseases in this category. As known in the literature, those who experienced symptoms were more likely to report adverse events. Vaccination is highly recommended for the most vulnerable individuals, as it helps reduce the incidence of severe forms and provides better protection for those with complicated medical histories, resulting in a general reduction in symptoms (31-35).

The results overall highlight the benefits of mRNA vaccination in mitigating the risk of SARS-CoV-2 infection among healthcare workers.

The kinetics of antibodies show that a single dose following an infection leads to a greater production of immunoglobulins compared to two doses of BNT162b2 given 3 weeks apart (36-38). The robust antibody responses observed after vaccination suggest increased protection against the virus, which is critical for maintaining a safe and uninterrupted healthcare environment.

Antibody titers increase rapidly after the first dose and remain more stable over time, especially in HIV-positive subjects. On the other hand, antibody titers in individuals who have never been infected show a gradual growth that increases exponentially after the second dose. Both groups, as demonstrated in the literature, experienced a decrease in Ig levels already 6 months after completing vaccination (39-42).

From a health surveillance perspective, it would be interesting to be able to investigate the effectiveness of a new vaccination cycle with booster doses in the population of HSR employees. The systematic collection of data relating to adverse effects and local resilience would in fact benefit from the specific skills of the population under study and would thus contribute to monitoring the safety of COVID-19 vaccines (43).

Conclusions

This cohort study conducted at the IRCCS San Raffaele Hospital in Milan confirms the positive impact obtained from the introduction of mRNA vaccination on reducing SARS-CoV-2 infection rates and increasing antibody levels in the healthcare worker population. In particular, the effectiveness of mRNA vaccination in reducing severe forms of COVID-19 infection is demonstrated, as is the poor ability to prevent reinfections, also given the high rate of SARS-CoV-2 variants. Exposure to patients proves to be an important risk factor for SARS-CoV-2 infection, so the population of healthcare workers turns out to be a population at greater risk of infection than the general population. Healthcare workers (nurses, social health workers, etc.) benefit most from mRNA vaccination, with a greater reduction in the infection rate after vaccination. Furthermore, the presence of comorbidities in the population infected with COVID-19 is associated with more symptomatic forms of the disease. These findings highlight the critical role of vaccination in offering adequate coverage to healthcare workers and limiting disruptions in healthcare delivery during the pandemic.

Riassunto

Immunità da COVID-19 nella coorte di dipendenti dell'IRCCS Ospedale San Raffaele dopo Vaccinazione BNT162b2: Uno Studio Osservazionale Retrospettivo

Introduzione. La pandemia da COVID-19 rappresenta la più grave crisi sanitaria e socioeconomica del nostro secolo. È iniziata con le prime segnalazioni in Cina, nella regione di Wuhan nel dicembre 2019, per poi diffondersi rapidamente in tutto il mondo, provocando una nuova Sindrome da Malattia Respiratoria Acuta Grave Coronavirus 2 (SARS-CoV-2). Tra la popolazione più a rischio di infezione e di sviluppo di forme gravi della malattia vi sono gli anziani e gli operatori sanitari, che sono più esposti ai soggetti infetti. L'11 dicembre 2020 la Food and Drug Administration ha approvato in emergenza l'uso del vaccino BNT162b2, il primo vaccino a mRNA della storia. Da allora il numero totale di dosi di vaccino somministrate ha superato i 12 miliardi. L'Italia è stato il primo Paese europeo ad essere colpito dalla pandemia, registrando il maggior numero di casi totali di SARS-CoV-2 (25.695.311) e, dopo i primi 70 giorni, ha avuto il tasso grezzo di mortalità più alto (141,0 per 100.000). In questo lavoro, analizziamo il tasso di infezione da COVID-19 nei dipendenti ospedalieri dell'Istituto di Ricovero e Cura a Carattere Scientifico Ospedale San Raffaele prima e dopo aver ricevuto il vaccino BNT162b2.

Disegno dello studio. Studio osservazionale di coorte retrospettivo.

Metodi. Lo studio ha analizzato lo stato di immunizzazione di 858 dipendenti dell'Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele di Milano, tra medici, operatori sanitari e personale amministrativo. È basato sulle analisi condotte nel precedente studio relativo alla stessa coorte, integrandole con l'estrapolazione e l'analisi aggiuntiva dei dati provenienti dal dataset della Biobanca del Servizio di Medicina Preventiva dello stesso ospedale per stimare il tasso di infezione, la durata della malattia e i livelli anticorpali registrati nel personale prima e dopo la doppia vaccinazione BNT162b2.

Risultati. L'analisi conferma l'impatto positivo ottenuto dall'introduzione della vaccinazione con mRNA nel ridurre i tassi di infezione da COVID-19 e nell'aumentare i livelli di anticorpi negli operatori sanitari. Sebbene la vaccinazione BNT162b2 possa non fornire una protezione completa da SARS-CoV-2, sembra in grado di ridurre il numero di infezioni, in particolare le forme più gravi e sintomatiche, spesso rilevate in soggetti con diversi fattori di rischio e comorbilità, e per questo più fragili. Gli operatori sanitari, dato il loro ampio contatto con i pazienti, sono la popolazione che trae maggiori benefici dalla vaccinazione, ottenendo il maggior calo nel tasso di infezione.

Conclusioni. I risultati dello studio rafforzano il ruolo cruciale delle vaccinazioni nella protezione dei gruppi a più alto rischio di infezione da COVID-19 da, come quello degli operatori sanitari. Fornire un'adeguata copertura vaccinale agli operatori sanitari limita le infezioni e le manifestazioni più gravi di malattia, riducendone al tempo stesso la durata.

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Corresponding author: Manuel Stocchi, Faculty of Medicine, University Vita-Salute San Raffaele, IRCCS San Raffaele Scientific Institute, Via Olgettina, 60, 20132 Milan, Italy
e-mail: stocchi.manuel@hsr.it

Exploring future perspectives and pipeline progression in vaccine research and development

Riccardo Vecchio[1,2], Leandro Gentile[3,4], Silvio Tafuri[5], Claudio Costantino[6], Anna Odone[3,4]

Abstract

Introduction. *The COVID-19 pandemic had a profound impact on vaccines' Research and Development, on vaccines' market, and on immunization programmes and policies. The need to promptly respond to the health emergency boostered resources' allocation and innovation, while new technologies were made available. Regulatory procedures were revised and expedited, and global production and distribution capacities significantly increased. Aim of this review is to outline the trajectory of research in vaccinology and vaccines' pipeline, highlighting major challenges and opportunities, and projecting future perspectives in vaccine preventables diseases' prevention and control.*

Study Design. *Narrative review.*

Methods. *We comprehensively consulted key biomedical databases including "Medline" and "Embase", preprint platforms, including "MedRxiv" and "BioRxiv", clinical trial registries, selected grey literature sources and scientific reports. Further data and insights were collected from experts in the field. We first reflect on the impact that the COVID-19 had on vaccines' Research and Development, regulatory frameworks, and market, we then present updated figures of vaccines pipeline, by different technologies, comparatively highlighting advantages and disadvantages. We conclude summarizing future perspectives in vaccines' development and immunizations strategies, outlining key challenges, knowledge gaps and opportunities for prevention strategies.*

Results. *COVID-19 vaccines' development has been largely supported by public funding. New technologies and expedited authorization and distribution processes allowed to control the pandemic, leading vaccines' market to grow exponentially. In the post-pandemic era investments in prevention are projected to decrease but advancements in technology offer great potential to future immunization strategies. As of 2023, the vaccine pipeline include almost 1,000 candidates, at different Research and Development phase, including innovative recombinant protein vaccines, nucleic acid vaccines and viral vector vaccines. Vaccines' technology platforms development varies by disease. Overall, vaccinology is progressing towards increasingly safe and effective products that are easily manufacturable and swiftly convertible.*

[1] PhD National Programme in One Health approaches to infectious diseases and life science research, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy

[2] Collegio Ca' della Paglia, Fondazione Ghislieri, Pavia, Italy

[3] Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy

[4] Medical Direction, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

[5] Interdisciplinary Department of Medicine, Aldo Moro University of Bari, Bari, Italy

[6] Department of Health Promotion, Maternal and Infant Care, Internal Medicine and Excellence Specialties (PROMISE) "G. DAlessandro", University of Palermo, Palermo, Italy

Conclusions. Vaccine research is rapidly evolving, emerging technologies and new immunization models offer public health new tools and large potential to fight vaccines preventables diseases, with promising new platforms and broadened target populations. Real-life data analysis and operational research is needed to evaluate how such potential is exploited in public health practice to improve population health.

Introduction

The COVID-19 pandemic has propelled vaccine research into an unprecedented era of challenges and opportunities, sparking a global initiative to swiftly develop, produce, and distribute effective vaccines. The health emergency underscored the critical need to expedite advancements in scientific frontiers, accelerating efforts to find innovative preventive solutions. The emergence of SARS-CoV-2 has triggered a race against time within the scientific community, driving the development and manufacturing of new vaccine platforms. The substantial increase in both public and private investments in vaccine research has reshaped the scientific landscape, resulting in a significant overhaul of processes and authorization procedures. Notably, the adoption of practices like the rolling reviews contributed to expedite vaccine approval while upholding stringent safety and efficacy standards (1). Engagement from various stakeholders, including governments, academic institutions, pharmaceutical companies, and international organizations, has fostered extensive collaboration in Research and Development (R&D), together with an unprecedented sharing of knowledge. Regulatory authorities have intensified their involvement and interaction with sponsors, governments had to re-evaluate the importance of their preparedness for pandemics, leading them to prioritize investments and seek ways to accelerate the development of new medicines. Companies have also reconsidered the structure of their R&D initiatives, focusing on primary outcomes rather than burdening trials with secondary endpoints and evaluations. Additionally, they have re-assessed the approaches used in conducting clinical trials, including the application of predictive modeling for the selection of trial sites (2).

Regulatory frameworks

The global pandemic triggered a paradigm shift in international regulatory mechanisms, notably through the implementation of innovative approaches. In Europe, the use of rolling reviews enabled researchers to continuously submit data throughout multiple review cycles as it became accessible, preceding the formal application submission. This approach actually departed from the traditional approval pathway, where all data undergoes assessment at the conclusion of clinical trials. Adopted by several health authorities worldwide during the pandemic (3), rolling reviews allowed regulators to continuously evaluate emerging data, expediting the assessment and potential approval of vaccines by expediting the review process (4). In the United States, this approach was not an independent procedure, but rather considered a facet linked to the "Fast Track Designation" under the Food and Drug Administration (FDA) guidance (5). Furthermore, the urgency to address the pandemic prompted regulatory agencies to implement expedited Marketing Authorizations (MAs), such as the EMA's Conditional Marketing Authorization (CMA) and the FDA's Accelerated Approval (6). MAs facilitated the provisional endorsement of vaccines using interim data, conditional upon meeting specific criteria to ensure their safety, effectiveness, and ongoing monitoring. Innovative pragmatic approaches swept vaccine deployment while ensuring continuous evaluation and data gathering post-endorsement to address an unmet medical need (1).

The impact of the COVID-19 pandemic on vaccine global market: manufacturing, volumes, Research and Development

With the introduction of COVID-19 vaccines, the global production of vaccine doses experienced a significant surge, rising from 5.8 billion doses in 2019 to 16 billion doses in 2021 (7). COVID-19 vaccine doses alone accounted for 67% of the global volume in 2021 (7). This unprecedented increase in production had a substantial economic impact. The costs associated with manufacturing and distributing vaccines soared alongside global distribution, prompting a pivotal shift in R&D expenditure. In 2021, the estimated global investments dedicated

to vaccine development saw a substantial increase, rising from approximately 1 billion to 13 billion dollars (8). Furthermore, the production timelines significantly changed: before COVID-19, the average duration from initial Phase I clinical testing to final product approval spanned over nearly a decade. This sharply contrasted with the development timelines of COVID-19 vaccines, completed in less than a year (3). For instance, certain clinical development phases were initiated before the preceding phases had been entirely concluded (2).

Who provides funding?

In pandemic times, substantial investments were facilitated by various funding sources. Before the pandemic, basic vaccine research and early-stage development often received support from the public sector (9). Throughout the pandemic, an unparalleled amount of resources was allocated to finance clinical trials, expand manufacturing capabilities, and establish Advance Purchase Agreements (APAs). A study requested by the European Parliament's Policy Department for Economic, Scientific and Quality of Life Policies reported that governments, primarily the US (with some not-for-profit entities), massively supported corporate investments, either for R&D, manufacturing, or both, by nearly EUR 9 billion. Governments and other public entities constituted more than 80% of the overall external funds identified. Their support was provided through grants and loans (10). The substantial investments from the public sector, combined with remarkable collaborative initiatives by regulatory bodies, enabled manufacturers to develop vaccines within a 10-month period and simultaneously expand manufacturing capabilities.

Progress and sustainability

Enterprising companies ventured into risk-based investments to support the development of COVID-19 vaccines, a conventional approach in drug development that was unprecedentedly expanded during the crisis (2). Despite the substantial growth in the global vaccine market size due to COVID-19, it is expected that this impact will wane by 2024, with the projected vaccine market size returning to pre-pandemic estimates (11). The resolution of the pandemic crisis and the subsequent departure from emergency regulatory measures and significant public funding will require a more cautious approach to vaccine R&D within companies. This transition calls for a recalibration towards sustainable financial practices. While the extraordinary public funding during the pandemic

facilitated swift progress in vaccine development and other medical interventions, companies are now faced with the imperative of establishing a sustainable financial framework for future R&D initiatives. The conclusion of emergency regulatory mechanisms indicates a need for companies to exercise caution and prudence in their R&D pursuits, giving priority to long-term financial sustainability over rapid, resource-intensive breakthroughs. This transition emphasizes the importance of striking a strategic balance between innovation and fiscal responsibility, promoting a renewed focus on cost-effectiveness, efficient resource allocation, and the pursuit of R&D projects that ensure sustained viability and societal benefit in the post-pandemic landscape.

Aim

Within a realm characterized by the rapid pace of scientific advancements and collaborative endeavors, this article explores the evolving perspectives of vaccine R&D. It carefully examines technological progress and assesses the transformative impact of COVID-19 on the trajectory of vaccinology. Our review aims to capture the current landscape of vaccine R&D; this entails mapping its pathways and delineating the current vaccine pipeline, which integrates both established and emerging technologies, while forecasting their present and potential future applications.

Methods

The review integrates research articles and literature reviews, retrieving information from different sources. Searches were conducted in Medline and Embase up to January 2024 using key words and MeSH terms (i.e. vaccines, immunization), and we also referred to the BioRxiv and MedRxiv platforms for unpublished data and supplementary details. In addition, we consulted selected clinical trial registries, publicly available documents, and reports from technical committees at both national and international health level. Further data and insights were collected interviewing experts in the field. We first embark on reconstructing the trajectory of vaccine research, elucidating the overarching direction and the array of tools currently available: this involved delineating the general path of progression and highlighting the available resources. Subsequently, we provide detailed insights into the platforms currently prominent in the vaccine pipeline: our exploration encompass understanding their

functionalities, strengths and limitations, current fields of experimentation, and, whenever feasible, prospects for future applications. Finally, we synthesize the literature findings, consolidating them into a dedicated summary table. The content of this paper was presented during the advanced course "Vaccination in high-risk individuals" organized by the International School of Epidemiology and Preventive Medicine "Giuseppe d'Alessandro" at the "Ettore Majorana" Foundation and International Centre for Scientific Culture on 2023 November 22-25 (12).

Results

Vaccine R&D trajectory

A well-known barrier in vaccine development since its early stages has been the decreasing effectiveness of immunostimulation as antigens are simplified and purified. Earlier attenuated or inactivated whole-organism vaccines provided a significant immunogenicity but were poorly tolerated due to frequent side effects (13,14). As shown in Figure 1, to reduce reactogenicity, vaccines have progressively shifted towards formulations comprising only sections of the microorganism, subunits, or purified antigens (15). However, while vaccines containing a limited set of purified antigens typically demonstrate superior safety profiles compared to live-attenuated and whole-pathogen vaccines, a decrease in their immunogenicity often occurs (13). For instance, purified protein antigen vaccines without adjuvants elicit a modest antibody response with minimal or no T cell response. The incorporation of adjuvants or other enhancers facilitated the reinstatement of immunogenicity in these vaccines, often showcasing significantly enhanced tolerability profiles, compared to conventional whole inactivated organism vaccines. These adjunctive components serve to amplify and fine-tune the body's immune reaction, compensating for the lower immunogenicity of certain novel vaccine technologies. Thus, the strategic use of these enhancers becomes essential in maximizing vaccines' effectiveness, ensuring resilient and comprehensive immune protection.

Adjuvants for Vaccine Platforms

The role of adjuvants in vaccine formulations has long been recognized. Alum-adjuvanted vaccines were approved over 70 years ago during the development of vaccines for diphtheria, tetanus, pertussis, and poliomyelitis. This type of adjuvant preferentially stimulates CD4 cells. Since then, adjuvants have evolved over time, progressing towards formulations that are less reactive, while still capable of stimulating both the humoral and cellular arms of the immune system. More recent vaccines, such as those for human papillomavirus and hepatitis B, have benefited from similar but updated adjuvants, like AS04, which is more selective in activating TLR4 and ensuing cellular component of the immune response. Oil-in-water emulsion adjuvants (as well as those constituted by liposomes) such as MF59 and AS03, have been used in the past and reintroduced more recently in innovative forms. For instance, AS02 has been deployed in experimental vaccines for malaria (16). In general, novel adjuvants' formulations comprising emulsions or liposomes involve the incorporation of monophosphoryl lipid A (MPLA). This compound maintains its capacity to trigger the innate immune response through its interaction with TLR-4 (17): liposomes with the addition of MPLA have been tested in malaria vaccines as seen in the instances of AS01 (18) and ALF formulations (19). New adjuvants have evolved to ensure concurrent stimulation of both CD4 and CD8 cells. The enhancement of CD8+ T-cell responses can be further augmented by exogenous components such as saponins. Specifically, the saponin QS21, derived from the bark of the Chilean native tree Quillaja Saponaria, can significantly boost these responses. For instance, the AS01B adjuvant combines MPL with QS21 saponin and has been employed in the Herpes zoster recombinant vaccine. Among recent advancements in adjuvant development, the AS01E stands out. It serves as an adjuvant for recombinant protein vaccines, which have already been employed against COVID-19 (20). This platform effectively merges various principles used in its precursors. Specifically, this compound constitutes a complex where saponin combines with specific fatty acids, namely cholesterol and phospholipids (20). It is already incorporated into several vaccines currently under development, including the R21/Matrix-M malaria vaccine (21) and selected influenza vaccines (22).

Where to next after the pandemic?

As of 2023, the global vaccine pipeline include almost 1000 candidates, the majority being recombinant protein vaccines (22%), mRNA vaccines (18%), inactivated vaccines (14%), viral vector vaccines (14%), and conjugate vaccines (11%) (23). Below, we provide an overview of the vaccine R&D pipeline and its innovative aspects, organized by technology
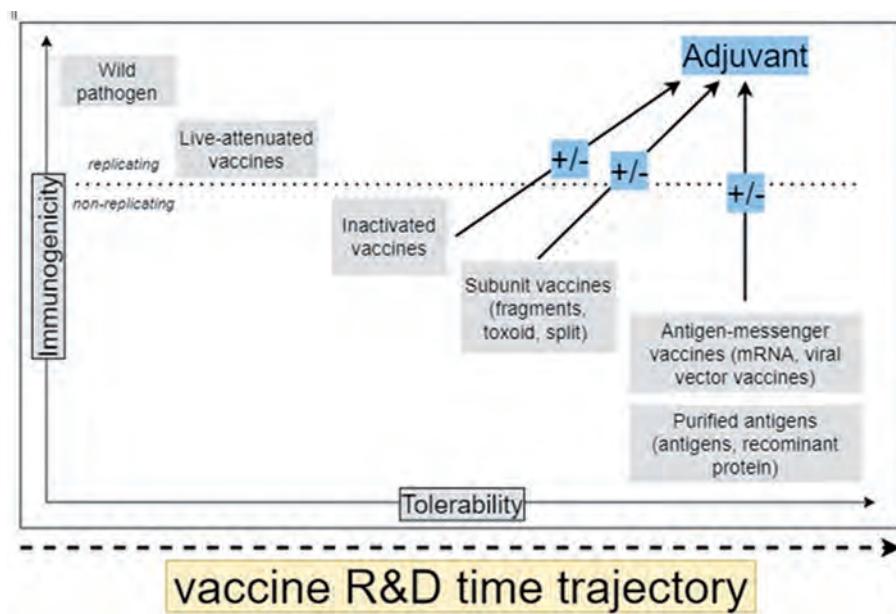
Figure 1 - Vaccine R&D time trajectory

type. We outline the immunological mechanisms, applications, and the preventive areas currently being tested. A summary is reported in table 1.

Recombinant protein vaccines

Recombinant proteins have been used as drugs for decades (24). They are often produced using bacteria, yeast, mammalian, or insect cells as factories for antigens (25). Recent advancements in recombinant protein technology have significantly enhanced efficiency and accessibility, enabling cost-effective production across various microbial and expression host systems (26,27). Despite their advantages, the immune-stimulating potential of subunit vaccines tends to be lower compared to those containing the entire virus. As a result, the administration of

Table 1 - Vaccine platforms, advantages and disadvantages

Vaccine platform	Advantages	Disadvantages
Recombinant protein	Safe and well-tolerated Stable at higher temperatures (2-8°C)	Low immunogenicity Requirement of adjuvant or conjugate to increase immunogenicity
mRNA	Safe and well-tolerated Highly adaptable to new pathogens No need for adjuvants	Immunological instability (over time and depending on new emerging variants) Requirement of complicated cold chain management (-15 to -80°C)
Viral vector	Stronger immune response (preservation of native antigen) Mimicking natural infection Stable at higher temperatures (2-8°C)	Complicated manufacturing process
Inactivated	Safe and well-tolerated Stable at higher temperatures (2-8°C)	Complicated manufacturing process Moderate immune response Requirement of high-dose formulations or adjuvants (under investigation for mucosal vaccines) Less adaptable to new pathogen
Conjugate (polysaccharide)	Longer duration of protection compared to polysaccharide vaccine Stable at higher temperatures (2-8°C)	Complicated manufacturing process

multiple doses and the inclusion of adjuvants are often necessary. During the COVID-19 pandemic, the spotlight has shifted towards recombinant protein vaccines, marking a pivotal moment in vaccination strategies. NVX-CoV2373 is a recombinant vaccine against SARS-CoV-2 in which nanoparticles are mixed with AS01E adjuvant. It requires a standard cold storage (2-8°C) (28,29). Data from phase 3 clinical trials, which led to their commercialization, highlighted an efficacy of NVX-CoV2373 of around 90% against the B.1.1.7 (Alpha) SARS-CoV-2 variant (30,31). Furthermore, as real-world data is accumulating, in a prospective observational study, NVX-CoV2373 protein-adjuvanted vaccine demonstrated less reactogenicity (77.6%) than mRNA vaccines (95.9%) (32). Italian real-world data collected on 21000 subjects showed an estimated effectiveness of a NVX-CoV2373 primary cycle higher than BNT162b2 and similar to mRNA-1273 (around 45%) (33). A decrease in effectiveness based on the circulating variant has also been documented in post-market observational studies of both mRNA COVID-19 vaccines (34). While recombinant technology may still exhibit limitations in terms of long-term efficacy, its advantages in terms of reactogenicity and a high safety profile make such technology extremely advantageous. In March 2023, EMA recommended the approval of PHH-1V as a booster vaccine for COVID-19 (35). PHH-1V is an adjuvanted recombinant protein vaccine that applies recombinant DNA technology to combine two distinct receptor binding domains (RBDs) from the Beta and Alpha variants of SARS-CoV-2. A booster dose of PHH-1V administered at 6 months demonstrated significantly higher neutralizing antibody titers, compared to individuals who received the BNT162b2 mRNA vaccine, showing efficacy against different variants (36,37). The DNA recombinant protein vaccine PHH-1V exhibited also low reactogenicity and achieved significantly superior neutralizing antibody responses, compared to BNT162b2 (38). Notably, PHH-1V does not require deep-freezing for distribution or onsite storage (36): this characteristic facilitates storage and distribution across diverse logistical and healthcare settings. A saponin-adjuvanted recombinant DNA vaccine (RZV), specifically designed for preventing herpes zoster (HZ), has already received approvals from both the FDA and EMA, showing greater effectiveness than the zoster live attenuated vaccine (ZVL) (39,40). Differently from ZVL, its low reactogenicity enables administration to high-risk immunocompromised patients aged 18 and older, expanding vaccine's target

population; this expansion positively impacts on preventive strategies aimed at vulnerable individuals, providing an improved tool in the planning phase of public health policies. Additional examples include recombinant protein vaccines against malaria: in October 2023, the World Health Organization (WHO) recommended the R21/Matrix-M malaria vaccine as it was shown to reduce symptomatic cases of malaria by 75% during the 12 months following a 3-dose series in areas with highly seasonal transmission (41). Two recombinant vaccines have already been approved by the FDA and EMA for respiratory syncytial virus (RSV) prevention among elders (42,43), one of which has also been approved for vaccination during pregnancy and for preventing the disease in newborns (44,45). Its characteristics make the recombinant platform attractive for the future: several vaccines using this technology are currently being studied in clinical research, including a quadrivalent seasonal influenza vaccine (46).

mRNA vaccines

The pioneering technology of messenger RNA (mRNA) vaccines has garnered immense recognition, notably highlighted by the 2023 Nobel Prize in Physiology or Medicine awarded to the scientists behind its development. mRNA, encoding a specific protein capable of mimicking the antigen, is delivered through lipid nanoparticles (LNPs) vaccine vehicles and enters cells solely via endocytosis. mRNA vaccines exhibit a self-adjuvant effect as the single-stranded RNA (ssRNA) can be identified by Toll-Like Receptor 7 (TLR7) and TLR8 within endosomes (47), subsequently triggering a cellular immune response in addition to the humoral response activated by the post-translational antigen presentation (48,49), without the need for an adjuvant. Furthermore, the lipids present in the nanoparticle, where the mRNA is carried, can stimulate the production of IL-6, thereby amplifying the CD4+ follicular helper T cell and B cell response (50). Due to their intrinsic ability to activate cellular immunity, this type of vaccine was first tested in an oncological setting, specifically in patients with advanced-stage melanoma, in an initial trial back in 2008 (51). As for recombinant protein vaccines, the advantages of mRNA-based vaccines stem from their proven effectiveness and safety records. Within the fight against SARS-CoV-2, mRNA vaccines have emerged as frontrunners, with BNT162b2 and mRNA-1273 receiving global emergency use authorization. The pandemic context has been a valuable testing ground for this type of vaccines

to assess their resilience. From this perspective, as mentioned earlier, mRNA vaccines share similar results in terms of effectiveness and reactogenicity with recombinant protein vaccines. They also face comparable challenges concerning the duration of effectiveness and efficacy against newly emerging variants: from an observational study in England, effectiveness of a BNT162b2 or mRNA-1273 booster against COVID-19 symptoms declined consistently under 50% at 10 or more weeks (52). In the case of mRNA vaccines, the challenge of immunological stability compounds the logistical issue of storage. It has been demonstrated that the lipid nanoparticle composition of these vaccines is influenced by certain elements, such as pH and temperature. Specifically, very low temperatures are associated with a higher particle concentration and better functionality, whereas exposure to excessively high temperatures compromises the nature of the nanoparticles, causing them to aggregate (53). This necessitates a cold-chain storage for these vaccines, posing organizational challenges both in terms of storage and transportation. For instance, ultra-cold storage requirements slowed down the distribution of COVID-19 mRNA vaccines in low income countries (54). The similar effectiveness of mRNA and recombinant vaccines is biologically proportional to the immune response prompted by both technologies: initial real-world data showed a similar response in both spike-specific CD4+ T cell response and acute and memory CD8+ T cell frequencies (55). Interestingly, observational studies have consistently indicated distinctions between the two mRNA COVID-19 vaccines concerning immune response (56,57) and clinical effectiveness (58,59) in immunocompromised populations with mRNA-1273 associated to better outcomes than BNT162b2. mRNA-1273 and BNT162b2 vaccines were associated with a very low risk of adverse events (60); mRNA-1273 was also found to be correlated to a lower risk of selected adverse events, such as pulmonary embolism, thromboembolic events, myocarditis, pericarditis and acute myocardial infarction, compared with BNT162b2 (61,62). While the incidence of myocarditis and pericarditis appears slightly elevated following mRNA vaccine administration compared to the general population, it remains considerably lower than the risk associated with a SARS-CoV-2 infection (63,64). When considering the broader spectrum of cardiovascular risks posed by COVID-19, the overall benefit-risk assessment strongly advocates for vaccination across all age and gender demographics (65). Overall, mRNA vaccine technology has demonstrated significant reliability. Initially, it provided a tool capable of addressing the pandemic threat, and over time, it has shown excellent efficacy in the medium term (though not entirely in the long term), along with an outstanding safety profile: effectiveness against severe diseases varied between 75% and 90% depending on the predominant variants (34). Not surprisingly, the vaccine pipeline using this technology is rich and extremely promising: a new vaccine (mRNA-1345) for preventing RSV disease in individuals over 60 has shown an 80% efficacy in a phase 3 trial (66). In the near future, a new pan-respiratory vaccine could combine three mRNA vaccines in the same formulation (mRNA-1230): COVID, influenza, and RSV (67). A Phase 1 Study has been started to evaluate the safety and immunogenicity of a mRNA Vaccine (mRNA-1644) against HIV. Furthermore, mRNA vaccines research for cancer treatment experienced a significant acceleration with the implementation of this technology during the pandemic period: the underlying mechanism involves antigen-presenting cells displaying tumour-associated antigens on both MHC class I and MHC class II to activate CD8+ and CD4+ T cells (68). Some trials showed sustained positive responses in cancer patients post mRNA-based vaccine treatment, without encountering uncontrollable toxic effects (69). mRNA vaccines exhibited potential as valuable therapeutic options for upcoming cancer treatments, particularly when used alongside supplementary immunotherapies (70). Administration of mRNA-4157/V940 vaccine as an adjuvant therapy during a 2b phase trial, in conjunction with a monoclonal antibody, decreased the risk of recurrence or death by 44% in individuals with completely removed stage III/IV melanoma (71).

Viral Vector Vaccines

The technology of recombinant vectors used to deliver antigens from a specific microorganism has been employed for a long time (72). Viral vectors are harmless and serve as vehicles to transport genetic information into host cells, prompting the synthesis of antigens that activate the immune response (73): they undergo genetic engineering to incorporate specific genes that encode crucial antigens of pathogens (74). Various viruses, including retrovirus, lentivirus, cytomegalovirus, and adenovirus, have been used as carriers. Among these, adenovirus stands out as the most commonly employed viral vector owing to its extensively documented safety profile and its ability to effectively stimulate the inflammatory

and immune systems (75). Indeed, one advantage of replicating vectors is their mimicry of a natural infection, resulting in the induction of cytokines and co-stimulatory molecules that provide a potent enhancing effect; viral vector vaccines can induce high immunogenicity without the use of an adjuvant, along with enduring immune responses (76). ChAdOx1-S and Ad26.COV2.S, two viral vector vaccines, were among the initial resources employed in the fight against COVID-19 (77). In the case of the ChAdOx1 nCoV-19 vaccine, the genetically modified chimpanzee adenovirus carries the gene responsible for the SARS-CoV-2 spike protein into the nucleus, where it is transcribed into mRNA by DNA polymerase (74). Despite their effectiveness in reducing SARS-CoV-2 complications, this type of vaccine has demonstrated lower immunogenicity compared to its mRNA counterparts. In a prospective cohort study conducted in the Netherlands, four weeks after the completion of the initial vaccination series, individuals who received mRNA-1273 vaccines exhibited the highest levels of neutralizing antibodies against the SARS-CoV-2 wild-type; this was followed by recipients of the BNT162b2 vaccine, whereas considerably lower antibody titres were observed in individuals vaccinated with the adenovirus vector-based vaccines ChAdOx1-S and Ad26.COV2.S (78). In a longitudinal analysis of immune response to four different COVID-19 vaccines, neutralizing antibody titres were also observed to be lower compared to NVX-CoV2373 (55). These findings are consistent with the distinct cellular dynamics triggered by different types of vaccines, showing a lower spike-specific CD4+ T cell response at 6 weeks post-immunization for viral vector vaccines, compared to mRNA vaccines and recombinant protein vaccines (55). Furthermore, viral vector vaccines demonstrated the capability to trigger Th1 cell responses, thereby eliciting strong protective effects (79). Viral vector-based vaccines are associated with more frequent systemic side effects, compared to mRNA-based vaccines (80,81,82). A systematic review reported a higher number of cardiovascular and hemorrhagic events following viral vector-based vaccine administration compared to mRNA-based vaccines, based on data collected from 98 studies (83). Furthermore, vaccine-induced immune thrombotic thrombocytopenia (VITT) has been reported after adenoviral vaccines administration (84,85) and a strong association was found between VITT and adenoviral vector-based vaccines (86,87,88) compared with mRNA-based vaccines (89), mostly among females aged below 60 (90). Nevertheless, viral vector

vaccines use is associated with significant logistical advantages, as demonstrated during the pandemic: this type of vaccine is challenging to manufacture but the enhanced molecular stability allows for storage at less extreme temperatures compared to mRNA platforms, facilitating also easier transportation (91,92). Viral vector vaccines represent a large share of the current vaccine pipeline, with over 130 candidates (23). Among these, approximately 80 are composed of adenoviral vectors and are being tested for vaccines against influenza, Ebola and HIV (93).

Inactivated vaccines

Inactivated vaccines, along with live attenuated vaccines, belong to a more traditional type of vaccines and have been widely used in clinical practice for a long time. Inactivated vaccines comprise all pathogen's components but in an inactivated state, making it unable to cause illness in humans. These vaccines are crafted using methods like heat, radiation, or chemical agents such as formaldehyde or β-propiolactone, that disassemble the viral structure and genetic material (94). Notably, inactivated vaccines are widely regarded as safe. However, they typically exhibit relatively lower immunogenicity, potentially resulting in a weaker immune response (95,96). To enhance vaccines' effectiveness high-dose formulations are required (97). Alternatively, adjuvants are often included to elicit a stronger immune response (98,99): influenza adjuvant trivalent inactivated vaccine was more effective in averting influenza-related outcomes compared to high-dose inactivated vaccine (100). VLA2001 (inactivated whole-virus, adjuvanted SARS-CoV-2 vaccine) was the first COVID-19 vaccine to receive a standard marketing authorization in Europe. In a phase 3 trial VLA2001 showed lower reactogenicity and exhibited higher immunogenicity compared to ChAdOx1-S (101). The safety and comprehensive knowledge of these vaccines still make them viable candidates for various platforms: currently, inactivated vaccines for influenza, Zika, and rabies are undergoing trials (102). Storage is permitted at standard temperatures (2-8°C) (28,29). In recent years, inactivated formulations have been employed for the production of mucosal vaccines (e.g., influenza, cholera), and others are currently under experimentation (e.g. against SARS-CoV-2) (103): in this context as well, the use of adjuvants emerges as a potential solution to enhance the efficacy of inactivated vaccines (104). However, uncertainties persist regarding the potential reactogenicity of current adjuvants for mucosal delivery (105).

Conjugate vaccines

Conjugate vaccines are a category within the domain of subunit vaccines, largely used for pneumococcal immunization. They are characterized by a specific composition where a polysaccharide chain is attached to a immunogenic carrier protein (106) in order to enhance immunogenicity and stability (23). This unique configuration allows conjugate vaccines to offer prolonged protection compared to raw polysaccharide vaccines (107,108). They require standard storage (2-8°C) (109), but their manufacturing is a complex process (110). Conjugate pneumococcal vaccines have evolved, progressively targeting a greater number of bacterial serotypes. Recently, PCV15 and then PCV20 have been added to the pool of available conjugate vaccines. In a phase 1/2 trial, V116, an experimental 21-valent pneumococcal conjugate vaccine (PCV), exhibited good tolerance with a safety profile largely similar to PPSV23. Furthermore, it was non-inferior to PPSV23 for the common 12 serotypes and superior for the 9 unique serotypes in V116 (111). Innovative conjugation methods are currently undergoing experimentation: site-specific covalent conjugation could lead to a more reliable conjugation process, allowing the incorporation of a greater variety of serotypes while reducing carrier-mediated immunological interference: VAX-24 exhibited a superior immunological response compared to PPV23 (112,113). Moreover, new Multiple Antigen Presenting System (MAPS) platform, harnessing a high-affinity noncovalent binding technology, showed a robust B-cell and T-cell immune response in animal models (114): a 24-valent pneumococcal MAPS vaccine has completed a Phase 2 trial in older adults (115) demonstrating a stronger antibody response compared to vaccinations with PCV13 and PPSV23 while maintaining a similar safety profile (116), and is currently undergoing a Phase 2 trial in infants (117).

Discussion

Ongoing efforts in vaccine R&D are prominently focused on innovative technologies designed to enhance the effectiveness and resilience of evolving vaccine platforms. These advancements not only show potential in strengthening vaccine efficacy, but also hold promise for addressing organizational challenges that emerged during the pandemic (118-120). The introduction of novel technologies may provide solutions to logistical complexities, particularly in the management of the cold chain, while simultaneously enabling more efficient and widespread immunization campaigns. Moreover, these advancements may set the stage for proactive initiatives targeting various potentially emerging diseases, especially within vulnerable populations, thereby enabling timely and comprehensive preventive approaches.

During the COVID-19 pandemic, technologies such as recombinant protein vaccines and mRNA vaccines have experienced remarkable success. These platforms have undergone extensive development and constitute the cornerstone of the current vaccine pipeline. While recombinant vaccines entered the market later, holding large potential, they have yet to undergo long-term evaluation compared to mRNA vaccines. Despite demonstrating highly reassuring levels of effectiveness and safety, mRNA vaccines present two main challenges to address: the first relates to their high immunological instability, requiring periodic booster doses; the second is an organizational concern regarding the storage of formulations at sufficiently low temperatures to prevent denaturation (121). The forthcoming generation of mRNA vaccines, using self-amplifying mRNA (saRNA), or replicon RNA, holds the potential to overcome these challenges. Replicons share the same mechanism of action as current mRNA vaccines but, additionally, they are linked to a self-amplifying gene that enables them to replicate within the cell: in this way, each replicon can transcribe for proteins, allowing the translation of a greater number of them. Another cutting-edge possibility involves the utilization of circular RNAs (circRNAs), a recent advancement in the mRNA vaccine domain: due to the absence of free ends susceptible to exonuclease degradation, they exhibit enhanced stability compared to linear mRNA vectors (122).

The challenge associated with the stability of newly manufactured vaccines is not only tied to their effectiveness, but also to the organizational aspects of their administration. Currently, innovative technologies ensure the production of safe vaccines but require periodic boosters. Thanks to their robust safety profile, they will facilitate administration to increasingly larger segments of the population, allowing for the prioritization of high-risk patients, regardless of age. The need to vaccinate more people and more frequently is propelling R&D to explore new combined formulations: as mentioned earlier, experimentation is underway for a pan-respiratory vaccine (mRNA-1230), while additional combinations are currently being explored. Notably, a vaccine candidate targeting influenza and COVID-19 (mRNA-1083) has already entered Phase 3 evaluation after

achieving antibody titres similar to, or greater than licensed quadrivalent influenza vaccines and the mRNA-1273 COVID-19 vaccine (123).

The substantial surge in vaccine research driven by the COVID-19 pandemic is set to decelerate. Given the extraordinary historical context and the unprecedented volume of funding, largely supplied from public and governmental sources, the vaccine pipeline has seen significant enrichment in recent years, both in terms of quantity and technological diversity. Platforms like mRNA, originally explored in other fields of medicine such as oncology, have shifted focus to infectious disease prevention, yielding remarkable outcomes within relatively short timeframes. As we transition from an emergency context, innovative technologies will face challenges: it is likely that only the most promising or those with a well-established track record of reliability will persist in use, contributing to a sustainable perspective. New technologies have far exceeded the challenges posed by the pandemic, with recombinant protein and mRNA platforms emerging as dominant players in the vaccine pipeline: they are currently undergoing trials for broader applications across various diseases and domains. However, certain limitations have undeniably emerged: historically, vaccine R&D developed from safer and less reactive platforms, but enhanced safety profiles often correlate with reduced immunogenicity. Especially in highly variable pandemic contexts, where exposure to rapidly evolving viral agents is prevalent, such vaccines have demonstrated limited long-term immunological stability. This highlighted the need for booster administrations and a decline in efficacy against emerging variants. Nonetheless, ongoing advancements are directed towards bolstering the stability and reliability of these tools: emerging technologies, such as experimental self-amplifying mRNA (saRNA) or circRNAs, aim to enhance the stability of mRNA vaccines, prolonging their efficacy over time and enabling more convenient and less resource-demanding transportation and storage methods. Overall, vaccine research is also progressing towards technologies that facilitate highly effective and large-scale public health strategies. In this context, improved safety profiles are poised to broaden the pool of eligible candidates, preventing potential complications from dangerous disease in high-risk individuals across all age groups (124). Additionally, biologically more stable technologies will streamline storage and transportation systems, thereby simplifying organizational and logistical processes. This study presents certain limitations related to the narrative

approach of our review. Its objective is to provide context to the current landscape of vaccine research, a field that has undergone significant acceleration amid the ongoing pandemic. Just as pathogens constantly evolve, vaccines necessitate adaptation to enhance effectiveness while upholding safety standards. Our data and reasoning provide insights to public health policymakers, tasked with enhancing the development of preventive strategies targeting broader populations, and ultimately maximizing efficiency in the utilization of both time and resources.

Riassunto

Opportunità e prospettive future della pipeline vaccinale e dell'innovazione in vaccinologia

Introduzione. La pandemia da COVID-19 ha avuto un profondo impatto sulla ricerca in ambito vaccinale, sul mercato globale, sui programmi e le politiche di immunizzazione. La necessità di far fronte in tempi rapidi all'emergenza sanitaria ha reso necessarie diverse innovazioni: a livello regolatorio le procedure di immissione in commercio sono state riviste e rese più rapide e la capacità di produzione e distribuzione ha visto un incremento significativo. Lo scopo di questa revisione è quello di ricostruire la traiettoria della ricerca in ambito vaccinale, evidenziandone le attuali sfide e le principali criticità.

Disegno dello studio. Lo studio è una revisione narrativa della letteratura.

Metodi. Le evidenze disponibili sono state selezionate consultando i principali database biomedici, preprint server, registri di trial clinici, selezionate fonti di letteratura grigia e rapporti scientifici. Ulteriori dati e approfondimenti sono stati raccolti attraverso la consultazione di esperti nel settore. Abbiamo analizzato l'impatto complessivo della pandemia sulla ricerca e sviluppo in ambito vaccinale, sui quadri normativi e sul mercato. Siamo passati poi ad analizzare l'attuale pipeline vaccinale e le tecnologie ad oggi impiegate. Infine, sono state riassunte le prospettive future nello sviluppo dei vaccini e nelle strategie di immunizzazione, delineandone le principali sfide e opportunità.

Risultati. Lo sviluppo dei vaccini COVID-19 è stato supportato da ingenti finanziamenti pubblici. Lo sviluppo di nuove tecnologie, insieme a processi di autorizzazione ed immissione in commercio più rapidi, hanno permesso di controllare la pandemia, generando una crescita esponenziale del mercato vaccinale globale. Nell'era post-pandemica, gli investimenti in prevenzione sono destinati a decrescere, ma i progressi tecnologici in atto hanno il potenziale per supportare le future strategie di immunizzazione. Nel 2023 la pipeline vaccinale include circa 1000 candidati, tra cui vaccini a proteine ricombinanti, vaccini a base di acidi nucleici e vettori virali, vaccini

inattivati e coniugati. Nella trattazione dettagliamo lo sviluppo delle piattaforme tecnologiche, differenziando malattia infettiva prevenibile e popolazioni target. In generale, la ricerca in ambito vaccinale progredisce verso prodotti sempre più sicuri ed efficaci, di facile produzione e stoccaggio e di agevole conversione.

Conclusioni. La ricerca in ambito vaccinale evolve rapidamente: le nuove tecnologie mettono a disposizione della sanità pubblica nuovi strumenti utili ad estendere la protezione vaccinale. Nuove ricerche basate su real-life data sono necessarie per valutare l'impatto di tale potenziale come strumento di prevenzione per la tutela della salute collettiva.

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Corresponding author: Anna Odone MD MSc MPH PhD, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Via Forlanini 2, 27100 Pavia, Italy
anna.odone@unipv.it

Language barriers during vaccination practice, the point of view of healthcare providers

Alessandro Bianconi[1], Giorgia Zanutto[1], Gisele Castagna[1], Angela Andrea Coa[1], Esther Rita De Gioia[1], Giulia Longo[1], Gaia Sicari[1], Giulia Tomaiuolo[1], Renato Todeschini[2], Paolo Pandolfi[2], Davide Gori[1]

Abstract

Background. *Language barriers are one of the main obstacles faced by migrants in accessing healthcare services. A compromised communication between migrants and Healthcare Providers in vaccination setting can result in increased vaccine hesitancy and decreased vaccine uptake. The objective of the current study is to investigate Healthcare Providers' perceptions about linguistic barriers faced during both routinary vaccination practice and the extraordinary vaccination program for Ukrainian refugees in the Local Health Authorities of Bologna and Romagna (Italy).*

Methods. *A cross-sectional study was conducted through the administration of a questionnaire examining Healthcare Providers' perceptions. A descriptive analysis and a multiple logistic regression model were adopted to analyze the collected data.*

Results. *Language barriers resulted as an obstacle to informed consent and to doctor-patient relationship. The strategies adopted were perceived as helpful in increasing vaccination adherence, despite communication difficulties were still experienced during refugees' vaccinations. Results suggest that the implementation of translated material and the use of professional interpreters may represent important strategies to overcome linguistic barriers, along with Healthcare Providers' training. Healthcare Providers' opinions could assist the implementation of new tools capable of countering language barriers.*

Conclusions. *The current study represents an example of providers' involvement in understanding the complexities behind the issue of language barriers in vaccination practice.*

[1] *Department of Biomedical and Neuromotor Sciences, University of Bologna, 40126 Bologna, Italy*
[2] *Department of Public Health, AUSL di Bologna, 40124 Bologna, Italy*

Introduction

Language barriers are recognized as one of the critical issues in migrant or refugee populations' access to healthcare services (1). Specifically, healthcare providers (HCPs) and patients not sharing the same language represent an important obstacle in offering adequate medical care (2). Individuals with limited context-specific linguistic proficiency are considered to be at higher risk of receiving substandard care due to the inability to effectively communicate with HCPs (3). Linguistic barriers may lead to decreased patient satisfaction and trust

in the healthcare system (4). In particular, language barriers and the inherent difficulties related to an unfamiliar setting may lead to the lack of effective communication between migrants and HCPs, increasing the rate of significant misunderstanding (4). These individuals may also be more likely to receive less important medical information, leading to consent problems and non-compliance with treatment plans (5,6).

Language barriers have been addressed as obstacles to reaching the highest standards of care, thus increasing the risk of liability, and affecting providers' effectiveness and satisfaction (4). HCPs facing linguistic barriers experience difficulties in obtaining informed consent and establishing a trustful relationship with patients, experiencing frustration and stress, which may negatively impact the quality of care (7). Furthermore, the presence of linguistic barriers has been associated with increased utilization of healthcare services, causing higher healthcare expenditure and decreased resource availability (8).

Linguistic barriers have been shown to interfere with vaccination practice and contribute to vaccine hesitancy (9). Referring to the 5C model of vaccine hesitancy, language difficulties may represent an obstacle to users' ability to understand, representing an example of constraint to vaccination uptake (10). A systematic review analyzing the determinants of vaccine uptake and under-vaccination in migrant populations in Europe found that language differences significantly compromise the communication between migrants and HCPs, leading to lack of information and decreased vaccine uptake (11,12).

To address this issue, healthcare organizations have implemented various strategies, including the presence of professional interpreters in healthcare settings, bilingual staff, and translated informative materials (13).

During complex emergencies, the risk of the occurrence of language barriers drastically increases, representing an obstacle in delivering care to displaced people (14). In early 2022, the escalation of the conflict between Russia and Ukraine led to the displacement of more than 8 million Ukrainians (15), urging the authorities of countries involved in hosting refugees to face linguistic barriers. In line with international agreements, national and local authorities of host countries established timely reception programs to ensure health and psychological care, housing, school and university attendance, and to facilitate the use of public transportation for displaced people (16). To face the ongoing COVID-19 pandemic, in accordance with the public health best practice on refugees' reception (17), vaccinations have been offered as part of these programs (18–20). In Italy, the refugees' reception strategies and their access to healthcare services were coordinated by Civil Protection at the national level and by the the Local Health Authorities (LHAs), the Municipalities and the Non Governmental Organzations (NGOs) at the local level. The adopted strategies were suited according to the specific context and included preferential routes in accessing health services for refugees, assisted by the presence of professional interpreters and the use of translated written materials (21).

The main objective of this study is to investigate the perceptions of HCPs about the issues related to linguistic barriers encountered during their routinary vaccination practice and those experienced during the extraordinary vaccination program implemented for the Ukrainian refugees in the LHA of Bologna and the District of Cesena of the LHA of Romagna (Italy). Furthermore, the study aims to analyze which tools and strategies are used to contrast language barriers and how those strategies could be strengthened according to HCPs' perceptions.

Materials and Methods

1. Study design

This cross-sectional study investigated HCPs perceptions about language barriers through the analysis of a questionnaire administered to those working as vaccinators in the LHAs of Bologna and the District of Cesena of the LHA of Romagna.

The data collection process took place in the period between October 20 and December 09, 2022. The selection process involved actively proposing the survey to all the HCPs that worked as vaccinators for the COVID-19 vaccination campaign. The total

number of eligible participants was 64 HCPs for the LHA of Bologna and 23 for the District of Cesena of the LHA of Romagna.

All participants were HCPs involved in the medical history collection and vaccine administration in vaccination centers in the LHA of Bologna and the LHA of Romagna. Participants were recruited in-site at the vaccination centers at the end of their shifts and asked to voluntarily participate in the study. Where in-person management of the survey was not possible, participants were actively recruited through alternative methods (e-mail, WhatsApp). The participants responded to the questionnaire autonomously through electronic devices (tablets, notebooks) provided by the authors. The survey was generated using Google Forms. Data were collected anonymously by the research team members. All enrolled individuals provided informed consent for data processing. The study protocol was reviewed and approved by the Ethics Committee for Research and Experimentation of the University of Bologna on 29 September 2022, protocol number: 0245767.

A search of the current literature showed the lack of validated tools that could effectively fit the context of the study. For this reason, the questionnaire was produced by a group of authors and reviewed by a group of public health experts, internal and external to the study. No intelligibility issues occurred during the data collection process.

The survey was composed of two sections. The first one aimed to analyze the experience of HCPs during their business-as-usual (BAU) work, and it was administered to every participant. The second one aimed to investigate specifically the experience of those participants who worked for the Ukrainian refugees' reception.

The first part of the survey collected participants' socio-demographic information, including age, gender, country of origin, spoken languages and professional qualifications. Next, data regarding the frequency of resorting to different strategies to overcome language barriers at the BAU level were asked. In addition, the perceived grade of interference of language barriers in the doctor-patient relationship and in obtaining informed consent, and the perceived usefulness of strategies adopted in adherence to additional vaccinations or doses were indagated through a "Likert-type Scale" level of agreement.

The second part of the survey investigated the use of strategies for overcoming language barriers other than translated materials and interpreters, prior experiences in working with interpreters, and

perceptions about the recent experience.

The English version of the survey questions can be found in the Results section (Tables 1-3).

2. Study setting during the Ukrainian crisis

Starting from 24 February 2022, a reception point for Ukrainian refugees was established nearby train and bus stations in the city center of the Metropolitan Area of Bologna. An individual code permitting access to the National Health Service was issued to all refugees. According to National COVID-19 restrictions for international travelers which were valid at the time, a mandatory COVID-19 test was requested within 48 hours from the arrival. When performing the tests, COVID-19 vaccination status was investigated, and voluntary vaccinations were proposed to those with incomplete immunization status. When needed and requested by the refugees, other vaccinations, such as Tetanus, Diphtheria, Pertussis, and Polio (Tdap-IPV), Measles, Mumps, and Rubella (MMR), or Varicella (V), were also offered.

To facilitate the communication between HCPs and refugees, the LHA of Bologna provided translated materials and ensured the presence of linguistic interpreters in the vaccination center. The translated materials consisted in general and COVID-19-specific informative material about healthcare services dedicated to refugees and how to reach them. Moreover, the necessary anamnestic forms for COVID-19 and other vaccinations were translated. All documents were available on a dedicated webpage (21) and on paper at the vaccination center. Furthermore, the presence of interpreters was assured in healthcare settings dedicated to refugees, including the vaccination center (21).

A total number of 24 of the 64 HCPs working as vaccinators in LHA of Bologna also worked for the vaccination campaign dedicated to Ukrainian refugees.

3. Statistical analyse

Participants' characteristics and responses were summarized using mean and standard deviation, and absolute and relative frequencies, where requested.

Based on previous research findings (22,23), the authors hypothesized that individuals with different demographic characteristics or different working experience and qualification background may have different perceptions of problems related to language barriers. A multiple logistic regression model was employed to analyze the associations between socio-demographic variables and HCPs' perceptions about

the problems investigated. A first model was employed analyzing age, gender, country of origin and English language proficiency as determinants of considering linguistic barriers as obstacles in obtaining informed consent. The same model was used to analyze those socio-demographic factors as determinants of considering linguistic barriers as obstacles in patient-doctor relationship and of the perceived usefulness of strategies adopted in improving patients' adherence to other vaccinations. Outcome variables were analyzed as dichotomous variables created by "Likert-type Scale" questions about consent, patient-doctor relationship and usefulness of strategies, considering as '1' those individuals that responded 'agree' or 'strongly agree', and '0' those individuals that responded 'neither agree nor disagree', 'disagree' or 'strongly disagree'.

The statistical significance level was set as $p < 0.05$. All analyses were performed using R-Studio statistical software (R version 4.1.2 (2021-11-01), R-Studio version 2021.09.2, PBC, Boston, MA, USA).

Results

1. Sample Characteristics

A total of 60 HCPs participated in the study, with 65% (n=39) females and 33% (n=20) males. The mean age of the participants was 37 (SD=14). The response rate was 75% for the LHA of Bologna and 61% for the LHA of Romagna.

The sample consisted mostly of resident doctors (70%, n=42), followed by specialty doctors (20%, n=12), graduate doctors (6.7%, n=4) and nurses (3.3%, n=2). The vast majority of the participants worked for the LHA of Bologna (77%, n=46), 12 (20%) worked for the LHA of Romagna, while the remaining 2 (3.3%) worked for both. Of the respondents, 92% (n=55) were Italian. Regarding specifically the professional area of language proficiency, 95% (n=57) of the participants referred to be proficient in English, 6.7% (n=4) reported to be proficient in Spanish, 13% (n=8) reported to be proficient in French, and 10% (n=6) of participants reported to be proficient in other languages. Complete sample characteristics are summarized in Table 1.

2. Language barriers during BAU work

When asked about how frequently they experienced language barriers in a professional setting, 37% (n=22) of the sample answered "often", 50% (n=30)

Table 1 - Sample characteristics.

Characteristic	N = 60[1]
Gender	
F	39 (65%)
M	20 (33%)
Other	1 (1.7%)
Age	37 (14)
Professional qualification	
Nurse	2 (3.3%)
Resident doctor	42 (70%)
Graduated doctor	4 (6.7%)
Specialty doctor	12 (20%)
Local Health Authority	
Bologna Local Health Authority	46 (77%)
Romagna Local Health Authority	12 (20%)
Both	2 (3.3%)
Country of origin	
Italy	55 (92%)
Albania	2 (3.3%)
Colombia	1 (1.7%)
Moldova	1 (1.7%)
United States	1 (1.7%)
Having a high level of English language proficiency	
No	3 (5.0%)
Yes	57 (95%)
Having a high level of Spanish language proficiency	
No	56 (93%)
Yes	4 (6.7%)
Having a high level of French language proficiency	
No	52 (87%)
Yes	8 (13%)
Having a high level of proficiency in other languages	
No	54 (90%)
Yes	6 (10%)

[1] n (%); Mean (SD).

"sometimes" and 13% (n=8) "rarely". In facing language barriers, 42% (n=25) of the HCPs reported often relying on a relative or acquaintance of the patient for translation, while 38% (n=23) reported often using a language that is not native to neither the patients nor themself, such as English. Furthermore, 47% (n=28) reported never asking for the help of a colleague to translate. Of the participants, 27% (n=16) reported never using a translation application/software

Table 2 - Linguistic barriers during "business-as-usual" work.

Characteristic	N = 60
How often do you interact with patients who have a lack of knowledge of the Italian language?	
Rarely	8 (13%)
Sometimes	30 (50%)
Often	22 (37%)
How often do you use the following tools to communicate with patients who have a lack of knowledge of the Italian language?	
I speak the same language as the patient	
Never	13 (22%)
Rarely	22 (37%)
Sometimes	20 (33%)
Often	5 (8.3%)
I communicate with the patient in a common language (e.g., English)	
Never	2 (3.3%)
Rarely	5 (8.3%)
Sometimes	19 (32%)
Often	23 (38%)
Always	11 (18%)
A relative/acquaintance of the patient translates	
Never	4 (6.7%)
Rarely	4 (6.7%)
Sometimes	26 (43%)
Often	25 (42%)
Always	1 (1.7%)
A colleague translates	
Never	28 (47%)
Rarely	15 (25%)
Sometimes	14 (23%)
Often	3 (5.0%)
I communicate in writing through apps/sites of translation	
Never	16 (27%)
Rarely	18 (30%)
Sometimes	19 (32%)
Often	7 (12%)
I communicate orally through translation apps/sites	
Never	22 (37%)
Rarely	25 (42%)
Sometimes	11 (18%)
Often	2 (3.3%)
I use material translated by an interpreter	
Never	34 (57%)
Rarely	17 (28%)
Sometimes	7 (12%)
Often	2 (3.3%)
I make use of an interpreter via call/video call	
Never	51 (85%)
Rarely	6 (10%)
Sometimes	3 (5.0%)

I make use of an interpreter in the presence

Never	47 (78%)
Rarely	8 (13%)
Sometimes	5 (8.3%)

Language barriers could be an obstacle to obtaining informed consent

Strongly disagree	2 (3.3%)
Disagree	4 (6.7%)
Neither agree nor disagree	7 (12%)
Agree	15 (25%)
Strongly agree	32 (53%)

Language barriers could be an obstacle to the doctor-patient relationship

Disagree	3 (5.0%)
Neither agree nor disagree	9 (15%)
Agree	23 (38%)
Strongly agree	25 (42%)

The tools used facilitated the patient's adherence to other doses/vaccinations

Strongly disagree	2 (3.3%)
Disagree	5 (8.3%)
Neither agree nor disagree	22 (37%)
Agree	21 (35%)
Strongly agree	10 (17%)

What measures do you consider a priority to enhance to overcome the difficulties of language barriers?

Paper medical history form in foreign language

No	17 (28%)
Yes	43 (72%)

Printed material in foreign language with information regarding the vaccine

No	17 (28%)
Yes	43 (72%)

Printed material in foreign language with administrative/bureaucratic information

No	15 (25%)
Yes	45 (75%)

Possibility to call an interpreter remotely

No	25 (42%)
Yes	35 (58%)

Possibility of having an interpreter in attendance

No	40 (67%)
Yes	20 (33%)

In which languages do you think it is a priority to enhance the measures you marked in the previous question?

Arab

No	19 (32%)
Yes	41 (68%)

Chinese

No	8 (13%)
Yes	52 (87%)

English

No	40 (67%)
Yes	20 (33%)

Urdu

No	19 (32%)
Yes	41 (68%)

Bengali	
No	38 (63%)
Yes	22 (37%)
Russian	
No	48 (80%)
Yes	12 (20%)
Romanian	
No	49 (82%)
Yes	11 (18%)
Ukrainian	
No	46 (77%)
Yes	14 (23%)
Albanian	
No	53 (88%)
Yes	7 (12%)
Other Languages	
No	51 (85%)
Yes	9 (15%)

to communicate by written text, while 32% (n=19) reported sometimes using it and 12% (n=7) reported using it often. Moreover, 37% (n=22) of respondents reported never using a translation app/software for oral communication, 42% (n=25) reported rarely using it, and 18% (n=11) reported using it often. Moreover, most of the participants reported never using an interpreter, either remotely (85%, n=51) or in person (78%, n=47).

Most of the HCPs identified the translation in different languages of administrative/bureaucratic information materials (75%, n=45) and medical modules and materials (72%, n=42) as a priority. Furthermore, 58% of the participants (n=35) also highlighted as a priority the possibility of contacting an interpreter remotely when needed. The willingness/urgency to improve the aforementioned tools was indicated as particularly relevant for Chinese (87%), Arabic (68%), Urdu (68%), Bengali (37%) and English (33%) languages.

A large percentage of the participants agreed or strongly agreed that language barriers are an obstacle to informed consent (78%, n=47) and to doctor-patient relationship (80%, n=48). Moreover, 52% of the participants (n=31) agreed or strongly agreed in considering the tools and strategies used to overcome language barriers as helpful in increasing adherence to additional doses/vaccinations.

Results from the descriptive analyses are summarized in Table 2.

3. Logistic regression results

The results of the logistic regression analysis are reported in the Supplementary Materials (File S1). No statistically significant associations were found between socio-demographic variables of participants and their perceptions about informed consent and patient-doctor relationship problems related to language barriers. Additionally, no predictor variable resulted as a determinant of the perception of usefulness of the strategies adopted in improving the adherence to other vaccinations.

4. Linguistic barriers during the refugees' reception

A total of 24 HCPs participated in the second part of the survey. The majority of the participants were female (71%, n=17), with a mean age of 39 (SD=15). The response rate of those who worked as vaccinators for Ukrainian refugees was 100%. In terms of professional qualifications, all were medical doctors. In particular, 62% (n=15) of the participants were medical residents, 21% (n=5) were specialized physicians, and 17% (n=4) were medical doctors without specialty training and not enrolled in a residency. Only 8.3% (n=2) of the participants reported to be proficient in English.

Only 1 doctor communicated with the refugees in their mother tongue (Ukrainian or Russian language). Regarding communicating with the refugees in shared language, i.e., English, 21% (n=5) of participants reported never doing so, while 29% (n=7) reported often

communicating in a common non-native language. Of the participants, 54% (n=13) often communicated with patients through a family member or an acquaintance, and 46% (n=11) of them never asked for the help of a colleague for translation purposes. About the use of translation apps for communication, 38% (n=9) of participants never used them, while 29% (n=7) sometimes used them. Half of the participants (n=12) never used a translation app orally.

Only 1 participant (4.2%) had received specific training in working with interpreters, while 50% (n=12) of the participants thought that such training should be integrated into medical education.

The majority of the participants (79%, n=19) reported they sometimes, often, or always experienced difficulties in ensuring that the patient received all the information. Similarly, 67% (n=16) of the participants reported they sometimes, often, or always experienced uncertainty whether the interpreter was accurately reporting the words used by the healthcare professional, and an even higher percentage of participants (75%, n=18) reported having doubts about the correct transposition of medical terminology into the patient's mother tongue. Furthermore, only 13% (n=3) of the participants always asked the interpreter to verify if the patient understood everything. Finally, 67% (n=16) of the participants agreed or strongly agreed that the presence of the interpreters and the interventions used facilitated the adherence to other doses/vaccinations.

The results of this descriptive analysis are summarized in Table 3.

Table 3 - Linguistic barriers during Ukrainian refugees' vaccination program.

Characteristic	N = 24[1]
Age	39 (15)
Professional qualification	
Nurse	0 (0%)
Resident doctor	15 (62%)
Graduated doctor	4 (17%)
Specialty doctor	5 (21%)
Having a high level of English language proficiency	
No	2 (8.3%)
Yes	22 (92%)
How often do you use the following tools to communicate with patients who have a lack of knowledge of the Italian language?	
I speak the same language as patient (Ukrainian/Russian)	
Never	22 (92%)
Rarely	1 (4.2%)
Always	1 (4.2%)
I communicate with the patient in a common language (e.g. English)	
Never	5 (21%)
Rarely	6 (25%)
Sometimes	5 (21%)
Often	7 (29%)
Always	1 (4.2%)
A relative/acquaintance of the patient translates	
Never	1 (4.2%)
Rarely	2 (8.3%)
Sometimes	5 (21%)
Often	13 (54%)
Always	3 (12%)
A colleague translates	
Never	11 (46%)
Rarely	7 (29%)
Sometimes	6 (25%)
I communicate in writing through apps/sites of translation	

Never	9 (38%)
Rarely	3 (12%)
Sometimes	7 (29%)
Often	5 (21%)
I communicate orally through translation apps/sites	
Never	12 (50%)
Rarely	4 (17%)
Sometimes	4 (17%)
Often	4 (17%)
Have you ever received specific training in working with an interpreter?	
No	23 (96%)
Yes	1 (4.2%)
Do you think that specific training in working with an interpreter should be part of the training of a healthcare professional?	
No	12 (50%)
Yes	12 (50%)
How often do you experience the following difficulties in working together with an interpreter?	
I am not sure if the patient has received all the information	
Never	4 (17%)
Rarely	1 (4.2%)
Sometimes	11 (46%)
Often	6 (25%)
Always	2 (8.3%)
I'm not sure if the interpreter translated my exact words	
Never	5 (21%)
Rarely	3 (12%)
Sometimes	7 (29%)
Often	7 (29%)
Always	2 (8.3%)
I'm not sure if the interpreter translated the medical terminology correctly	
Never	2 (8.3%)
Rarely	4 (17%)
Sometimes	10 (42%)
Often	5 (21%)
Always	3 (12%)
I felt excluded from the conversation when the interpreter and the patient spoke to each other	
Never	5 (21%)
Rarely	4 (17%)
Sometimes	8 (33%)
Often	5 (21%)
Always	2 (8.3%)
How often do you ask the patient, through an interpreter, if he/she understood all the information given?	
Rarely	2 (8.3%)
Sometimes	6 (25%)
Often	13 (54%)
Always	3 (12%)
The tools used facilitated the patient's adherence to other doses/vaccinations	
Strongly disagree	1 (4.2%)
Neither agree nor disagree	7 (29%)
Agree	10 (42%)
Strongly agree	6 (25%)

[1] Mean (SD); n (%).

Discussion

1. Summary of the results

The results of this study highlighted that HCPs perceive linguistic barriers as an obstacle to optimal vaccination practices, particularly when trying to obtain an informed consent or fostering an effective doctor-patient relationship. Conceivably, effective communication is considered a crucial part of vaccination practice by HCPs, enabling them to clearly convey the risks and benefits of vaccines to the patients (24). This process may be hindered by linguistic barriers, which can lead to misunderstandings, confusion, and inaccurate information process on the part of both physician and patient (25). In the context of linguistic barriers, obtaining a truly informed consent is often reported as challenging and can compromise patient autonomy (26). Such barriers may also compromise the establishment of a positive doctor-patient relationship (24), which is essential in fostering trust and facilitating effective healthcare delivery (27).

Considering these issues, it is not surprising that non-native speakers are often considered "hard-to-reach" populations in vaccine hesitancy discussions (12). Due to several obstacles, the migrant population may find difficulties in reaching vaccination services (28). Linguistic, cultural, communication and legal barriers are the main obstacles preventing migrants from accessing vaccination services, and more generally, the healthcare system (12). Furthermore, according to the International Organization for Migration (IOM), in most countries, vaccination campaigns do not include migrants in irregular situations (28). A study by Crawshaws et al. suggested that migrants need more linguistically tailored information to allow informed decisions about vaccination. Strategies aimed at improving migrant population's access to vaccination included the translation of the needed information, the provision of tailored messages, the inclusion of interpreters into the staff, and the implementation of specific training for HCPs (11).

The survey findings suggest an overlap between the languages spoken by local migrant populations and the languages identified by HCPs as relevant for the translation of informative materials and anamnestic modules (29). Most HCPs defined the improvement of materials in non-European languages as a priority, suggesting that most difficulties were encountered when communicating with non-European users. This finding may represent a positive indication of the HCPs responsiveness to the needs of the local migrant community, highlighting the importance of considering the linguistic diversity of a given population when designing and disseminating health-related information (30).

The Ukrainian refugees' COVID-19 vaccination experience showed that an ad hoc intervention to overcome language-related problems was perceived as useful by the majority of the participants. The use of professional interpreters has been shown to significantly impact healthcare providers' work-related satisfaction in healthcare settings. Professional interpreters are shown to facilitate effective communication between healthcare providers and patients, and may lead to improved satisfaction, safety, and increased adherence to the treatment plans of patients (31). However, a large part, or the majority of HCPs declared to rely also on other strategies to overcome language barriers with refugees, such as translation apps and triadic communications with a refugee's family member.

This study highlighted the nearly complete lack of training in working with an interpreter in the HCPs' curricula. However, to enhance communication with non-native speakers, literature examples suggest that training in working with linguistic interpreters is needed in medical doctors and nurses' curricula (32,33). This training should aim at developing culturally and linguistically appropriate communication skills and strategies for working with interpreters. Effective communication with linguistic interpreters requires careful planning, active listening, the use of plain language, triadic communication, and cultural awareness (34). By employing these strategies, HCPs can effectively communicate with non-native speakers, enhancing patient care quality. Additionally, this study highlighted that vaccinators were unsure about the interpreters' translation during the medical history collection. Other literature examples highlighted the existence of insecurities of healthcare providers during triadic communication with patients and interpreters (35). The lack of training in working with professional interpreters in HCPs education may represent a cause of these insecurities. The timely implementation of translated material and the use of professional interpreters may represent important strategies to overcome linguistic barriers in public health complex emergencies. The HCPs' difficulties in working with interpreters may be addressed by enhancing the presence of specific training in the medical curricula.

Most of the HCPs involved in the Ukrainian refugees' vaccination were satisfied with the ad hoc strategies used to overcome linguistic barriers, considering them useful in facilitating adherence to

other doses or treatments. The results highlighted the lack of training in working with interpreters in the participants' educational background. This may partly explain the difficulties reported in working with professional interpreters. Further studies with wider samples are needed to analyze the prevalence of training programs related to language barriers in medical curricula, and to provide a detailed analysis of the difficulties that HCPs may face while working with interpreters.

The results of the logistic regression analysis highlighted that no sociodemographic variables were associated with HCPs' perceptions about informed consent and patient-doctor relationship problems related to language barriers, and about the usefulness of the strategies adopted in improving adherence to other vaccinations.

2. Study limitations

There are some limitations that should be acknowledged. First, the design of the study involving the use of self-report measures may be associated with a higher risk of information bias. Second, this study is based on a small sample and refers to the experience of a small number of vaccination centers, affecting the generalizability of the findings to other vaccination centers, and generally, to other healthcare settings. Moreover, the response rates were high but not 100%, respectively 75% for HCPs that were working for the LHA of Bologna and 61% for HCPs that were working for the LHA of Romagna, providing a less comprehensive view of vaccinators' perceptions. Third, it is important to acknowledge that the present study utilized a non-validated questionnaire to collect responses from participants. As such, this choice may introduce potential limitations and impact the overall reliability and validity of the findings. Future research should consider employing rigorously validated instruments to enhance the robustness of data collection and strengthen the study's conclusions.

Despite the generalizability issue and the compromised validity of using a non-standardized questionnaire, this study provides a valuable insight into HCPs' perceptions and perceived difficulties related to linguistic barriers at BAU and in a particular emergency setting.

Conclusions

The results of this study highlighted that language barriers during vaccination practice are perceived

as an obstacle in obtaining informed consent and in achieving a valuable doctor-patient relationship by vaccinators. Moreover, language barriers may affect adherence to further vaccinations. HCPs reported difficulties and a lack of training in working with interpreters. Addressing those problems during medical education may improve the effectiveness of communication between HCPs and non-native speakers in vaccination centers.

Further studies are needed to explore language barriers in vaccination centers in different geographical context and to investigate the impact of specific training and strategies aimed to address them.

In conclusion, this study represents a valuable example of providers' involvement in understanding the complexities behind the problem of language barriers in vaccination practice. Providing effective communication in languages originally spoken by the migrant population may contribute to reducing health disparities and improving health outcomes. The collection of feedback from the HCPs involved could assist in implementing new tools capable of countering language barriers. As an example, new translated materials may be implemented in those languages that are described as a priority by the majority of the participants. In addition, strengthening the possibility of contact remotely with professional interpreters may represent a valuable help for the HCPs facing language barriers during their practice.

Riassunto

Barriere linguistiche nella pratica vaccinale, il punto di vista degli operatori sanitari

Premessa. Le barriere linguistiche rappresentano uno dei principali ostacoli incontrati dai migranti nell'accesso ai servizi sanitari. Una comunicazione compromessa tra migranti e operatori sanitari nel contesto della vaccinazione può comportare un aumento dell'esitazione vaccinale e una diminuzione dell'adesione al vaccino. L'obiettivo del presente studio è quello di indagare la percezione degli operatori sanitari riguardo alle barriere linguistiche affrontate sia durante la pratica vaccinale di routine che durante il programma di vaccinazione straordinaria per i rifugiati ucraini nelle Aziende Sanitarie Locali di Bologna e della Romagna (Italia).

Metodi. È stato condotto uno studio trasversale attraverso la somministrazione di un questionario che esamina le percezioni degli Operatori Sanitari. Per analizzare i dati raccolti sono stati

adottati un'analisi descrittiva e un modello di regressione logistica multipla.

Risultati. Le barriere linguistiche sono risultate un ostacolo al consenso informato e al rapporto medico-paziente. Le strategie adottate sono state percepite come utili per aumentare l'adesione alla vaccinazione, nonostante si riscontrassero ancora difficoltà di comunicazione durante le vaccinazioni dei rifugiati. I risultati suggeriscono che l'implementazione di materiale tradotto e l'uso di interpreti professionisti possono rappresentare strategie importanti per superare le barriere linguistiche, insieme alla formazione degli operatori sanitari. Le opinioni degli operatori sanitari potrebbero aiutare l'implementazione di nuovi strumenti in grado di contrastare le barriere linguistiche.

Conclusioni. Lo studio attuale rappresenta un esempio del coinvolgimento degli operatori sanitari nella comprensione delle complessità dietro la questione delle barriere linguistiche nella pratica vaccinale.

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Supplementary material

Table S 1 - Analyses of associations between healthcare professionals' characteristics and their perceptions about informed consent, doctor patient relationship and usefulness of strategies used in increasing adherence.

Predictors	Odds Ratios	95% CI	p
Informed consent			
Gender			
Female	-	-	-
Male	0.75	0.18 – 3.41	0.702
Age	0.97	0.93 – 1.02	0.237
Country of origin			
Foreigner			
Italian	4.55	0.43 – 48.51	0.184
Good proficiency in English language			
No	-	-	-
Yes	3.74	0.18 – 107.65	0.380
Doctor-patient relationship			
Gender			
Female	-	-	-
Male	1.06	0.23 – 5.74	0.941
Age	0.97	0.92 – 1.01	0.138
Country of origin			
Foreigner			
Italian	4.62	0.43 – 49.75	0.182
Good proficiency in English language			
No	-	-	-
Yes	3.75	0.17 – 109.94	0.383
Usefulness of strategies used in increasing adherence			
Gender			
Female	-	-	-
Male	0.43	0.13 – 1.32	0.147
Age	1.01	0.97 – 1.05	0.705
Country of origin			
Foreigner			
Italian	0.28	0.01 – 2.82	0.338
Good proficiency in English language			
No	-	-	-
Yes	1.46	0.05 – 43.53	0.803

Corresponding author: Alessandro Bianconi, Department of Biomedical and Neuromotor Sciences, University of Bologna, Via San Giacomo 12, 40126 Bologna, Italy
e-mail: alessandro.bianconi4@studio.unibo.it

The psychometric evaluation of the Italian version of the Surgical Fear Questionnaire in adult patients waiting for major cardiac surgery

Vincenzo Damico[1], Luca Cossalter[1], Liana Murano[2], Antonella D'Alessandro[3], Lara Fermi[4], Margherita Milani[5], Giuseppe Demoro[6]

Abstract

Background and aim. *Preoperative surgical fear is an emotional reaction that can be observed in many patients who are waiting to undergo a surgical procedure. The Surgical Fear Questionnaire was originally developed to determine the level of fear in patients who are expected to undergo elective surgery. This study aims to test the validity and reliability of this Italian version in a population of patients waiting for major cardiac surgery.*

Study design. *Methodological research model.*

Methods. *The population of this methodological study included the patients who presented to Lecco Hospital in Italy between January 2022 and October 2023 and were scheduled to undergo valve surgery, aortic surgery or coronary surgery; the sample involved 416 patients who met the inclusion criteria.*

Results. *Results of the analyses showed that the Surgical Fear Questionnaire can be used with two subscales; the "Surgical Fear Questionnaire-S", which shows the fear of the short-term consequences of cardiac-surgery, and the "Surgical Fear Questionnaire-L", which shows the fear of the long-term consequences of cardiac-surgery. The mean score of the patients was 26.32±9.23 on the former, 27.62±11.89 on the latter, and 53.94 ±19.16 for the entire questionnaire. The Cronbach's α coefficient was 0.952 for the "Surgical Fear Questionnaire-S", 0.920 for the "Surgical Fear Questionnaire-L", and 0.914 for the entire questionnaire.*

Conclusion. *Based on the validity and reliability tests, we consider the questionnaire adaptable to the Italian reality, specifically to the population waiting for major cardiac surgery.*

[1] *Department of Anesthesia and Critical Care, Azienda Socio Sanitaria Territoriale of Lecco, Italy*
[2] *Residenza Sanitaria Assistenziale Madonna della Neve Onlus of Premana, Italy*
[3] *Presidio Ospedaliero "S. Elia" of Caltanissetta, Italy*
[4] *Department of Foreign Languages, Literatures and Modern Cultures, University of Bergamo, Italy*
[5] *Department of Neurosciences, Azienda Socio Sanitaria Territoriale of Lecco, Italy*
[6] *Department of Neuroscience, Azienda Socio Sanitaria Territoriale Sette Laghi, Varese, Italy*

Introduction

Surgical or preoperative fear is a well recognizable emotional state for many patients waiting for surgery and is a risk factor for socio-economic burden and major personal problems (1-2). Various studies have found that surgical fear is associated with impaired psychosocial and physical recovery, such as increased levels of acute and chronic postoperative pain, anxiety and depression (1-3). Therefore, preoperative assessment of surgical fear could provide essential information for improving perioperative care and could be a first step towards targeted intervention bringing the patient to the center of the care plan.

Objects of surgical fear can be heterogeneous. Different studies have listed more than twenty objects of fear, arising from fear of the surgical procedure itself to fear of the anaesthesia, having to undergo blood transfusions, being stung with needles, losing dignity or even dying (4-5).

During surgical operations, patients experience disparate emotions, such as the fear related to the lack of control over their own bodies and lives or to the loss of an organ or tissue, as well as the hope and expectation of recovering from their condition (6).

If fear is present among patients evaluated before elective surgery, it is hypothesized that the fear itself may be even worse and more evident among patients undergoing major surgery.

Currently, post-operative mortality after cardiac surgery has decreased significantly (7-8) which highlights the progress in the care of these patients, however the incidence of postoperative morbidity still remains significant (8). Approximately 10% of cardiac surgery patients require prolonged postoperative care (9) with longer intensive care unit (ICU) stays and worse long-term outcomes (10-12). Cardiac surgery performed to correct functional mitral insufficiency, cardiogenic shock or aortic stenosis are still a significant cause of morbidity and mortality today (13). Functional mitral valve regurgitation is frequently observed in patients with ischemic and non-ischemic cardiomyopathy and is associated with poor clinical outcomes in patients with heart failure with reduced ejection fraction due to dilated remodeling of the left ventricle (14). Many patients with cardiogenic shock are referred for coronary artery bypass grafting (CABG) due to coronary anatomy unsuitable for percutaneous coronary intervention (PCI) and/or due to mechanical complications such as rupture of the ventricular septum or muscle papillary (14). Existing evidence highlights the importance of patients' clinical condition and frailty before cardiac surgery as predisposing factors for poor post-transcatheter aortic valve replacement (TAVR) outcomes (13). However, to date, patients undergoing TAVR typically have an advanced age and multiple comorbidities and the prevalence of frailty can reach 50-63% of observed cases (13).

Most patients when exposed to stressors, such as chronic diseases and surgeries, are prone to adverse events, procedural complications, prolonged recovery, physical and psychological functional decline, and mortality (15).

Considering all these factors, therefore, the anxiety and fear should be clearly asked when evaluating patients before surgery, and the causes related to the fear and anxiety should be analyzed. It is clear that such interventions can instill fear and apprehension in patients awaiting surgery.

Although there are studies in the Italian literature regarding the general anxiety, depression or post-traumatic stress disorders of patients, according to tools that have been tested for validity

and reliability, there are no tools that have been tested for validity and reliability of preoperative fear.

Therefore, this study aims to test the validity and reliability of the Surgical Fear Questionnaire (SFQ) translated to Italian in a population of patients waiting for major cardiac surgery.

Methods

Study design

Before starting with the study, a quick bibliographic review was conducted by the first three authors to evaluate whether the SFQ (16) had already been validated in Italian. The bibliographic review was conducted on Pubmed, Cinhal, Ilisi and on Google Scholar.

After bibliographic review and before starting with the validation study of the SFQ, authorization was requested via-email contact from the author of the questionnaire (Professor Maurice Theunissen) (16). During contact with Professor Theunissen, we learned that an Italian language translation study was already underway. However, in agreement with the author and creator of the FSQ, we decided to test the questionnaire anyway, continuing with the study on cardiac surgery patients because its reliability and validity had never been tested on this specific

population or in adult patients waiting for major surgery. However, in agreement with Professor Theunissen and Dr. Eva Koetsier of the Cantonal Hospital of Italian Switzerland, who was following the linguistic translation study, a comparison of our and their translation before administration to patients was deemed appropriate.

The methodological research model was used in this validation study, which was conducted between January 2022 and October 2023 with patients who were scheduled to undergo major cardiac surgery admitted to Lecco Hospital in Italy.

Sample and setting

The population of this study consisted of the all patients who presented to cardiology, rehabilitation cardiology or preoperative cardiac surgery department at the Lecco hospital in Italy between January 2022 and October 2023 and were scheduled to undergo valve surgery, aortic surgery, coronary surgery.

For inclusion in this study, patients had to be older than 18 years, in a conscious state, voluntarily consent to cooperate and communicate, not previously diagnosed with any mental disorders, be scheduled to have major cardiac surgery procedure under general anaesthesia and be included in either Class 1 (Patient in good health conditions, without systemic, organic or psychiatric diseases) or Class 2 (Patient with modest, mild systemic disease, without functional limitations (e.g. diabetes or hypertension), according to the categorization of the American Society of Anesthesiologists (ASA) Physical Status Classification (ASA I; ASA II).

The study sample involved 416 patients from within this population who met the inclusion criteria.

Data collection

The data were collected through face-to-face interviews conducted after the patients were informed

about the study and their oral consents were obtained. The data collection tools were administered to the patients the day before the surgery.

It took approximately 10 to 20 minutes to complete the personal information form and the scales,

which included the SFQ (16) and the Hospital Anxiety and Depression Scale (HADS) (17). The parallel form reliability method (18) was used during data collection to determine the reliability of the SFQ, and HADS was used as the second scale to assess the fear and anxiety or depression level of the patients.

Questionnaires

The questionnaires used for the study and administered to the patients consisted of three sections.

The first section concerned the collection of the demographic data (eg. age, gender, marital status, type of cardiac surgery, family type, occupation and ASA Physical Status Classification).

The second section concerned the collection of the Surgical Fear Questionnaire (SFQ) (16). This questionnaire was developed by Theunissen and colleagues in 2014 to determine the level of fear that patients expecting to undergo elective surgery felt regarding the short-term and long-term results of the surgical procedure (16). Arranged as an 11-point Likert type scale, the questionnaire includes eight items, which are scored between 0 and 10, with a score of 0 indicating not fear at all and a score of 10 indicating a profound fear. The questionnaire has two subscales, each of which feature four items on the cause of fear. Items 1 to 4 assess the fear caused by the short-term results of the surgery, whereas items 5 to 8 assess the fear caused by the long-term results of the surgery. The sum of the scores of the four items on each of the subscales yields the subscale scores, and the sum of both subscale scores yields the total score of the entire questionnaire. The minimum and maximum subscale scores are 0 and 40, respectively, whereas the minimum and maximum total score of the questionnaire are 0 and 80, respectively. A high score indicates a high level of surgical fear. No cut-off was well identified among the fear scores. However, the expressed score can be used as a percentage of the level of fear expressed (0% or 100%).

The third section concerned the collection of the Hospital Anxiety and Depression Scale (HADS) (17). This scale was developed by Zigmond et al in 1983 to determine the risk of anxiety and/or depression and to assess the change in their severity (17). The HADS scale is a 4-point Likert-type scale, which includes 14 questions: seven on the symptoms of depression (HAD-D) and seven on the symptoms of anxiety (HAD-A). The odd-numbered questions assess anxiety, whereas the even numbered questions assess depression. For each scale, the scores collected indicate: no problem score 0-7; mild problems score 8-10; moderate problems score 11-14; severe problems score 15-21. The scale aim to determine the risk group by conducting a quick scan of the anxiety and depression levels of those with physical diseases rather than to make a diagnosis. The scale is also used to analyze the changes in the emotional status of the

patient and therefore does not include any physical symptom.

Statistical Analysis

The study size was based on the total number of patients meeting inclusion criteria and admitted to the Lecco Hospital from January 2022 and October 2023 waiting for major cardiac surgery. A descriptive analysis was used to study the frequency distribution of all variables of interest. For normally distributed data, mean and standard deviation (SD) were applied, while median and interquartile range were used for data that did not exhibit normal distribution.

Data were analyzed using SPSS 22.0 software package (IBM, Armonk, NY). The demographic data derived from the personal information form were analyzed using numbers and percentage.

As part of the reliability analysis, the Cronbach's coefficient, and Pearson's product-moment correlation coefficient were used to determine internal consistency and homogeneity.

The validity of the questionnaire was determined through the i) opinions of specialists, ii) the Barlett test, iii) the Kaiser-Meyer-Olkin (KMO) Index, iv) the exploratory factor analysis, v) the confirmatory factor analysis, vi) the principal component analysis, and vii) the varimax rotation test.

No missing data and no sensitivity analyses were addressed.

Ethical considerations

Before starting with the study, authorization was requested from the local Ethics Committee (No. 6642/2022), the Institutional Review Board of Lecco Hospital and the Director of the Departments involved. All participants provided their informed written consent to participate at the time of interview. Consent was obtained by the nursing staff 24-36 hours before surgery.

The dataset was pseudonymized before data analysis. The study protocol was in line with the Oviedo Convention for the protection of human rights and dignity of the human being with regard to the application to biology and medicine (1996) and with the Helsinki Declaration, as revised in 2013.

Results

Sample

A total of 416 patients were included in the study; 328 of them (78.8%) were males and 88 (21.2%)

Table 1 - Characteristics of patients.

Characteristics (n= 416)	
Gender	
Male n; %	328; 78.8
Female n; %	88; 21.2
Age (year) mean; sd	68.1; 9.2
Weight (kg) mean; sd	79; 12.9
Body Max Index mean; sd	25.26; 8.9
Type of Cardiac-surgery	
Valve surgery n; %	142; 34.1
Aortic surgery n, %	136; 32.7
Coronaric surgery n, %	108; 26
Mixed surgery n, %	30; 7.2
Presence of at least one comorbidity before surgery n; %	411; 98.8
Comorbidities	
Hypertension n; %	312; 75
NYHA class II-III n; %	298; 71.6
Arrhythmia n; %	69; 16.6
History of myocardial infarction n; %	52; 12.5
Type I diabetes without insulin therapy n; %	40; 9.6
Chronic obstructive pulmonary disease n; %	28; 6.7
Type I diabetes on insulin therapy n; %	15; 3.6
Osteoarthritis and musculoskeletal disorders n; %	4; 0.9
Marital Status	
Single n %	143; 34.4
Married n %	273; 65.6
The ASA score	
Group 1 n %	361; 86.8
Group 2 n %	55; 13.2

ASA, American Society of Anesthesiologists; SD, standard deviation

females. The mean age was 68.1±9.2 years. The patients mainly underwent valve surgery (34.1%), aortic surgery (32.7%) and coronary surgery (26%) (Table 1). The 98.8% of patients had at least one comorbidity before surgery, and hypertension was present in the medical history of 75% of patients (main comorbidity). The 86.8% were included in Group 1 of the ASA Physical Status Classification (Table 1).

Linguistic validity and adaptation

Although we were aware that an Italian translation study was in progress, we still had to carry out a language translation ourselves, in order to be able to test the questionnaire on cardiac surgery patients.

To test the validity of the SFQ in its adaptation to Italian culture and in its adaptation to major surgery context, the following process was performed. The SFQ was first translated into Italian by VD and GD and then by one academic member. After conducting a review of the translated forms, a single version of the questionnaire was developed and adapted to the cardiac surgery context. The translated forms were then back-translated into English by a linguist fluent (master's degree in languages, with 5 years' experience in translations) in both languages and closely familiar with both cultures (author: LF). The original questionnaire and its Italian translation were compared, and it was determined that the meaning of the items did not change. The translations made in both of the forms that had been determined to best reflect each of the items were selected and then submitted to ten specialists for their opinions. The ten specialists who contributed to the evaluation of the linguistic translation were: 3 cardiac-surgeons, 2 anesthesiologists and 5 critical care nurses.

Finally, our translation of the questionnaire was compared with the translation carried out by Dr. Koetsier. No substantial differences were found between the translated versions. The versions were considered compatible and usable in the Italian cardiac surgery context.

Content validity

The content validity index was used to confirm the language and culture equivalence of the items, as well as their content validity with numerical values, and to properly evaluate the specialists' opinions. The specialists were asked to assess each item with a minimum and maximum score between 1 and 4, where 4 indicates completely appropriate, 3 very appropriate,

Table 2 - Results of Surgical Fear Questionnaire

Subscale	Minimum and Maximum scores	Mean scores of the questionnaire mean, sd
SFQ-S	0-40	26.32±9.23
SFQ-L	0-40	27.62±11.89
Total score	0-80	53.94±19.16

Sd, standard deviation; SFQ-S, Surgical Fear Questionnaire-Short; SFQ-L, Surgical Fear Questionnaire-Long

2 appropriate but small changes needed, and 1 not appropriate. The result of the content validity criterion/content validity index was 1.00. At the end of the assessment, as the content validity of the questionnaire was found to be statistically significant, none of the items were excluded from the questionnaire.

Finally, it was decided not to make additions or modifications to the questionnaire in relation to the specific population under study.

Results of SFQ

The results of the SFQ are summarized in Table 2.

The mean score of the cardiac surgery patients is shown to be 26.32±9.23 on the SFQ-S subscale (short-term consequences of cardiac surgery), 27.62±11.89 on the SFQ-L subscale (long-term consequences of cardiac surgery), and 53.94 ±19.16 on the entire questionnaire.

Reliability and Factor analysis of the SFQ

The total score correlation of all items was between 0.80 and 0.90, and the Cronbach's α coefficient was 0.914 for the entire questionnaire, 0.952 for the SFQ-S subscale, and 0.920 for the SFQ-L subscale (Table 3).

Table 3 - Cronbach's a Coefficients of the Questionnaire and total Item Correlations

SFQ	n	Mean	SD	Total Item Correlation	Cronbach's α value when the item is deleted
Item 1: Operation	416	4.91	3.18	0.721	0.928
Item 2: Anesthesia	416	4.52	3.21	0.719	0.928
Item 3: Pain	416	4.11	3.20	0.709	0.930
Item 4: Side effects	416	4.46	3.19	0.768	0.927
Item5: Health deterioration	416	4.73	3.19	0.800	0.923
Item 6: Failed operation	416	5.10	3.17	0.821	0.922
Item 7 Incomplete recovery	416	4.97	3.15	0.819	0.923
Item 8: Long rehabilitation	416	4.81	3.05	0.812	0.921

Cronbach's α of the SFQ-S Subscale: 0.952; Cronbach's α of the SFQ-L Subscale: 0.920; Cronbach's α of the entire SFQ: 0.914; SD, standard deviation; SFQ, Surgical Fear Questionnaire; SFQ-S, Surgical Fear Questionnaire-Short; SFQ-L, Surgical Fear Questionnaire-Long

The KMO index was used to determine whether the sample size was adequate for factor analysis, and the Bartlett's test of sphericity was used to evaluate the appropriateness for factor analysis and to determine whether the variables were in correlation with each other before assessing the factor structure of the SFQ. The KMO index was 0.89, Barlett's test was $x^2(416) = 2992.089$, and P< .001. The significance of this test shows that the sample size was adequate for factor analysis and that the correlation matrix was appropriate.

Correlation Between the SFQ and the HADS

Because people's moods change from time to time, the parallel form reliability method was used to determine the reliability of the SFQ. The HADS, which assesses the depression and anxiety level of the patients, was used as the second scale. A positive significant relationship was found between the mean scores of all subscales of the HADS and the mean scores of all subscales and total score of the SFQ.

Parallel forms equivalence results are summarized in Table 4.

Table 4 - Parallel Forms Equivalence Results

Subscales-SFQ		HADS-A	HADS-D
SFQ-S	*r*	0.802	0.754
	P	.000	.000
SFQ-L	*r*	0.804	0.746
	P	.000	.000
Total SFQ	r	0.888	0.832
	P	.000	.000

HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; SFQ, Surgical Fear Questionnaire; SFQ-S, Surgical Fear Questionnaire-Short; SFQ-L, Surgical Fear Questionnaire-Long. Bold text denotes statistical signifcance.

Results of exploratory factor analysis

The explained variance was 82.742 for the total SFQ score, whereas the factor load of all items of the SFQ was greater than 0.40 (Table 5). These results show that the SFQ consisted of two subscales and that its factor structure was adequate.

Results of confirmatory factor analysis (CFA)

The index values were found to be x^2/standard deviation = 3.51, goodness of fit index = 1.00, adjusted goodness of fit index = 1.00, comparative fit index = 1.00, root mean square error of Approximation =

Table 5 - Results of Factor Analysis

SFQ's Items	SFQ-S	SFQ-L
Item 1: Operation	0.247	**0.907**
Item 2: Anesthesia	0.324	**0.891**
Item 3: Pain	0.298	**0.823**
Item 4: Side effects	0.361	**0.833**
Item5: Health deterioration	**0.866**	0.296
Item 6: Failed operation	**0.800**	0.344
Item 7 Incomplete recovery	**0.887**	0.319
Item 8: Long rehabilitation	**0.871**	0.346
Explained variance (%)	**43.573**	40.132

Total explained variance (%) = 82.742
SFQ, Surgical Fear Questionnaire; SFQ-S, Surgical Fear Questionnaire-Short; SFQ-L, Surgical Fear Questionnaire Long. Factor loadings .0.7 are in bold.

0.076, and standardized root mean square residual = 0.030. These index values indicate that the SFQ was at an acceptable level and consisted of two subscales (Table 6).

As seen in the path diagram, the original structure of the SFQ was accepted without any modification. The factor loads of the SFQ ranged between 0.81 and 0.92, and the *t* value was greater than 1.96 for all items (Figure 1).

Table 6 - Fit Index Values for the SFQ

Index	Acceptable Value	Normal Value	Values Found
X^2/SD	< 5	< 2	3.51
GFI	> 0.90	> 0.95	1.00
AGFI	> 0.90	> 0.95	1.00
CFI	> 0.90	> 0.95	1.00
RMSEA	< 0.08	< 0.05	0.076
SRMR	< 0.08	< 0.05	0.030

AGFI, adjusted goodness of fit index; CFI, comparative fit index; GFI, goodness of fit index; RMSEA, root mean square error of approximation; SD, standard deviation; SFQ, Surgical Fear Questionnaire; SRMR, standardized root mean square residual.

Discussion

Although there are many scales used in Italy to assess the anxiety of patients, no specific tools were found to assess the fear that patients experience waiting for cardiac surgery. Therefore, this study was conducted to analyze the validity and reliability of the SFQ in Italy, in a specific patient population
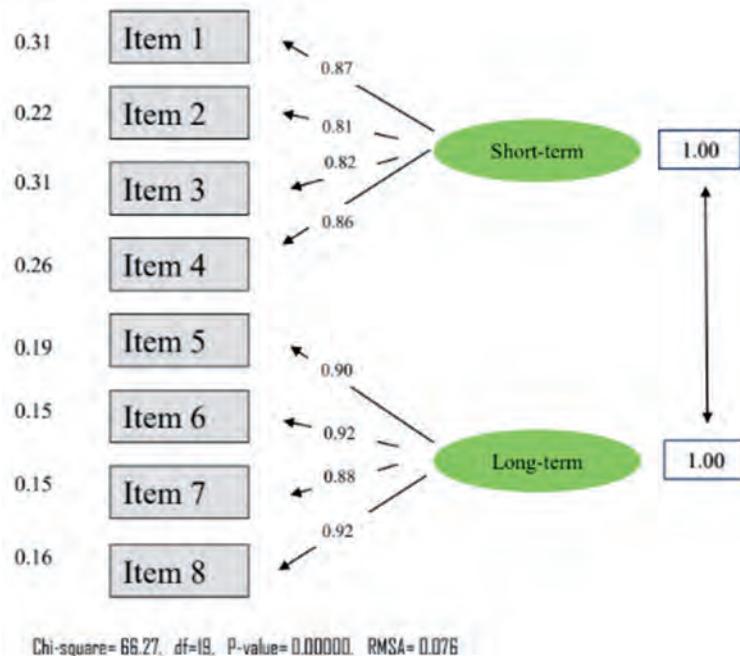
Figure 1 - The path diagram for the Surgical Fear Questionnaire Italian version. RMSEA, root mean square error of approximation.

for major cardiac surgery. The results regarding the SFQ, which consists of eight items and two factors, look promising.

Cronbach's α coefficient is frequently used in the scale development and adaptation studies to determine the reliability of internal consistency. Its aim is to reveal the consistency level of the items in the scale with each other (18). In the present study, the Cronbach's α coefficient was 0.914 for the entire questionnaire, 0.952 for the SFQ-S subscale, and 0.920 for the SFQ-L subscale. Theunissen et al found the Cronbach's α coefficient to be 0.89 for the entire SFQ, 0.86 for the SFQ-S subscale, and 0.87 for the SFQ-L subscale in their three studies (16). These findings show that the SFQ has high reliability in assessing the fear patients experience waiting for surgery.

The parallel form reliability method was used to determine the stability of the SFQ and the HADS Scale, which assesses the depression and anxiety level of the patients, was used as the second scale. A positive significant relationship was found between the two scales. However, we would have liked to compare the stability of the SFQ even better with another scale that evaluates surgical fear but, unfortunately, we did not find any in the literature (tools validated in Italian).

Theunissen et al (6) and Ba digen et al (16) in their validation studies also used the parallel form reliability

method and found a significant relationship. These results indicate that the SFQ has high reliability.

In the present study, the factor load of all items was found to range between 0.80 and 0.90, whereas that of Theunissen et al was shown to be in the range between 0.65 and 0.93 (16). These findings indicate that the items of the SFQ have high factor loads. When interpreting, by one rule of thumb in confirmatory factor analysis, factor loadings should be 0.70 or higher to confirm that independent variables identified *a priori* are represented by a particular factor, on the rationale that the 0.70 level corresponds to about half of the variance in the indicator being explained by the factor.

The explained variance rate was 82.7% in this study on the adaptation of the SFQ to Italian cardiac surgery patients. Theunissen et al on the other hand, found the explained variance rate to be 60.2% for the original form of the SFQ (16). Nonetheless, the findings of the explained variance rate reveal that the SFQ consists of two subscales (SFQ-S and SFQ-L) and that its factor structure is adequate, just as in the original questionnaire.

The index values were found to be $= 3.51$, goodness of fit index $= 1.00$, adjusted goodness of fit index $= 1.00$, comparative fit index $= 1.00$, root mean square error of approximation $= 0.076$, and standardized root mean square residual $= 0.030$. The relevant fit index

values observed in our study validation, indicate the form to be at an acceptable level as it is.

Compared to the initial validation studies by Theunissen et al (16) or the Turkish validation by Ba digen (6), we observed much higher scores regarding the perception of pre-operative fear, with a total mean of the scale of approximately 58.4. In the Turkish validation study it was 37.5 (6). However, this is normal data for us, considering that we administered the questionnaire to patients waiting for major cardiac surgery which can increase fear and tension compared to a different elective surgery.

Finally, the confirmatory factor analysis, performed to confirm the exploratory factor analysis for the original questionnaire, also shows that the SFQ had two subscales. From a methodological point of view, there are a lack of a confirmatory analysis including the Tucker-Lewis Index (TLI), that is used to evaluate the goodness of adaptation of the data to the proposed model. However, previous studies have adopted different strategies to achieve acceptable fit indices (19, 20). Some have modified the basic model, whereas others have used different estimation methods. Several different estimation procedures are available for CFA and there are statistical arguments in favor of the alternative approaches. The widely used maximum likelihood and generalized least squares methods assume of multinormal distributions (19, 20). Using CFA, it is possible to estimate the correlation between the hypothesized latent factors; thus the effect of random measurement error can be partialled out. The effect of one form of systematic measurement error, acquiescence, be addressed using an independent measure of that response style (20). Because there is no conclusive evidence for the superiority of any single approach and because several have previously been used in SFQ analyses, we tested the models using these estimation methods (19).

This study demonstrated that the SFQ is a concise and generic instrument for the assessment of surgical fear, suitable for major adult surgery. For further research we suggest additional testing of the convergent validation using biomarkers such as preoperative stress hormone levels. Also the effect of linguistic and cultural influences on the SFQ needs further study. Finally, for diagnostic use, optimal cut-of points of the SFQ need to be established. The results of which are expected to contribute to nursing or healthcare interventions made to eliminate the fear patients may experience while waiting for surgery.

Fear of death, fear of unknown origin, and fear of postoperative complications can be significant predictors of preoperative anxiety (21). The preoperative nursing care focused on appropriate fear-reducing methods such as preoperative education, family-centered preparation for surgery, providing psychological care and medication can be required for surgery patients who develop high levels of preoperative fear.

Strong fear of surgery is very common and sometimes leads the patient to postpone the scheduled operation. The fear in question, in fact, can become marked and persistent, reaching the characteristics of a specific phobia (22). The patient generally reports being afraid of dying during surgery or having adverse reactions to local or general anesthesia and difficulty remembering what he should eat the night before an operation. Fear before surgery, therefore, represents an important problem for patients, because it can cause emotional fluctuations, mental and physical disorders. It is therefore essential to detect the patient's fear to best assist him (22).

Fear generates anxiety. Patients who have fear of death have statistically significantly higher anxiety scores than the patients who do not have this fear (22). Patients who have fear of waking up during surgery have statistically significantly higher anxiety scores than those who do not have this fear (22).

The use of the SFQ is useful in increasing shared decision making with the patients or the quality/quantity of information to be provided before surgery.

Before carrying out surgery it is possible to contact a specialist and undertake specific pharmacological therapy and/or a psychotherapy program working on the management of emotions that lead to the avoidance of operations.

We think that being aware of patients' fears and finding appropriate approaches to their fears can be valuable. The SFQ is an effective method for measuring patients' fear and may be useful to use during preoperative visits. In this way, patient satisfaction and superior results can be achieved.

Limitations

Our validation study has the following severe limitations.

The most important limitation we report is that although the questionnaire assesses fear before surgery, we have tested the validity of the questionnaire only on cardiac surgery patients even if they were still undergoing elective surgery. This may have exposed our findings to a selection bias.

We did not define a sample size before the study.

However the significance of KMO index test shows that the sample size was adequate for factor analysis and that the correlation matrix was appropriate.

We report the lack of test-retest reliability, a statistical measure commonly used to assess the consistency and reproducibility of results obtained. Once a test-retest reliability coefficient has been found, the scores can be used to officially determine the stability and consistency of an assessment.

Nonetheless, the reproducibility over time, otherwise known as test-retest reliability, is just one of various methods to evaluate and measure reliability, which also includes internal consistency, inter-rater reliability and convergent validity compared to the gold-standard tool. In addition, as already reported in the discussion, there are the lack of a confirmatory analysis including the Tucker-Lewis Index (TLI).

This is a single-center validation study so we do not guarantee that fear before surgery will emerge with the same perceptions in other hospitals or settings.

Finally, we performed a parallel form reliability method between SFQ and HADS. Methodologically it was more correct to perform this test by comparing the SFQ with another scale that evaluates fear and anxiety, and not depression and anxiety. The choice of the HADS as the gold-standard comparison scale and the lack of use of The Amsterdam Preoperative Anxiety and Information Scale (APAIS) (23) in the comparative evaluation, were done because the HADS scale had been in use for some time in our hospital setting (24, 25). So even if it is not methodologically correct, we are confident that this approach makes our results very close to clinical reality and is not only suitable for the purpose of pure research.

Conclusions

On the basis of our findings, which aimed to add the Italian version of the SFQ to the literature for cardiac surgery patients, we concluded that the SFQ can be used in the Italian culture and context, as no differences were found between the opinions of the specialists regarding the items of the SFQ that had been translated into Italian using content validity and inter observer reliability criteria. Each item can be reliably used, as confirmed by the statistically significant relationship found between the items and the questionnaire according to the total item score correlations of the items of the SFQ, which resulted in none of the items being excluded from the questionnaire. The Italian SFQ has a high

internal consistency reliability coefficient for the study sample, which means that each item represents the questionnaire. In addition, we confirm that the Italian SFQ has two subscales, as in the original questionnaire. We conclude, to summarize, that the SFQ is a valid and reliable eight-item index of surgical fear, consisting of two subscales: fear of the short-term consequences of major cardiac surgery and fear of the long-term consequences of major cardiac surgery. The SFQ can be used to determine the level of fear that patients experience waiting for a major cardiac surgery in Italy.

Riassunto

Valutazione psicometrica della versione italiana del Questionario sulla Paura Chirurgica tra i pazienti adulti in attesa di cardiochirurgia

Introduzione e obiettivo. La paura chirurgica preoperatoria è una reazione emotiva che può essere osservata in molti pazienti in attesa di sottoporsi ad un intervento chirurgico. Il questionario sulla paura chirurgica (SFQ) è stato originariamente sviluppato per determinare il livello di paura nei pazienti che devono sottoporsi a un intervento chirurgico in elezione. Questo studio si propone di testare la validità e l'affidabilità di questa versione italiana in una popolazione di pazienti in attesa di intervento di chirurgia maggiore di cardiochirurgia.
Disegno dello studio. Modello di ricerca metodologica.
Metodi. La popolazione di questo studio metodologico comprendeva tutti i pazienti che si sono presentati all'Ospedale di Lecco in Italia tra gennaio 2022 e ottobre 2023 e dovevano essere sottoposti

a intervento chirurgico valvolare, chirurgia aortica o chirurgia coronarica. Il campione ha coinvolto 416 pazienti che soddisfacevano i criteri di inclusione.

Risultati. I risultati delle analisi hanno mostrato che il questionario sulla paura chirurgica può essere utilizzato con due sottoscale; lo "SFQ-S", che mostra la paura delle conseguenze della cardiochirurgia a breve termine, e lo "SFQ-L", che mostra la paura delle conseguenze della cardiochirurgia a lungo termine. La media dei punteggi del questionario era di 26.32±9.23 per la SFQ-S, di 27.62±11.89 per la SFQ-L e di 53.94 ±19.16 per l'intero questionario. Il coefficiente di Cronbach era di 0.952 per la SFQ-S, 0.920 per la SFQ-L, e di 0.914 per l'intero questionario.

Conclusioni. Sulla base dei test di validità e affidabilità, riteniamo il questionario adattabile alla realtà italiana, in particolare alla popolazione in attesa di intervento di cardiochirurgia maggiore.

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Corresponding Author: Vincenzo Damico, Department of Anesthesia and Critical Care, Azienda Socio Sanitaria Territoriale of Lecco, Via dell'Eremo 9/11, 23900 Lecco, Italy
e-mail: vi.damico@asst-lecco.it
ORCID: V. Damico: https://orcid.org/0009-0007-1278-5705.

Effectiveness of hydrogen peroxide wipes for surface disinfection in healthcare facilities

Marco Lopuzzo[1,2], Maria Teresa Montagna[2], Francesco Triggiano[2], Giuseppina Caggiano[2]

Abstract

Introduction. The correct method of surface disinfection in hospitals is an essential tool in the fight against the spread of healthcare-associated infections caused by multi-resistant microorganisms. Currently, there are many disinfectants on the market that can be used against different microorganisms. However, the effectiveness of different active molecules is controversial in the literature.

Study design. The aim of this study was to evaluate the effectiveness of wipes based on hydrogen peroxide (1.0 %) and highly specific plant-based surfactants, contained in $H_2O_2^{TM}$ (Hi-speed $H_2O_2^{TM}$) products, against some hospital-associated microorganisms.

Methods. The effectiveness of the wipes was tested against nosocomial and control strains of methicillin-resistant Staphylococcus aureus, carbapenem-resistant Pseudomonas aeruginosa, Klebsiella pneumoniae carbapenemase, Aspergillus fumigatus and Candida parapsilosis. Specifically, in vitro activity was assessed using three different techniques: stainless steel surface testing, surface diffusion testing and well diffusion test.

Results. The three different methods tested confirm the wipes' good effectiveness against the most common multi-resistant bacteria and against fungi.

Conclusions. These data show that the tested wipes could be a valid adjunct to the disinfection process and could assist in the prevention of healthcare-associated infections.

[1] Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), University of Bari Aldo Moro, Bari, Italy
[2] Interdisciplinary Department of Medicine, Hygiene Section, University of Bari Aldo Moro, Bari, Italy

Introduction

Healthcare-associated infections (HAIs) are the most common adverse events worldwide, causing significant morbidity, mortality and financial burden to patients and the healthcare systems (1). The European Center for Disease Prevention and Control (ECDC) estimates that more than 3.5 million cases of HAIs occur in the European Union and European Economic Area (EU/EEA) each year, resulting in more than 90,000 deaths and approximately 2.5 million Disability Adjusted Life Years (DALYs). In the EU/EEA, this burden is estimated to be greater than the cumulative burden of other infections, including influenza and tuberculosis. Furthermore, 71% of HAIs are caused by bacteria that are resistant to antimicrobials, including bacteria that are resistant to final-line antimicrobials, such as carbapenem-resistant *Enterobacteriaceae* (2).

In addition to respiratory, fecal-oral and sexual transmission, the transfer of pathogens via surfaces also plays an important role in human infections (3,4). In hospitals, the probability of microbial environmental spread can be influenced by the tenacity of the circulation of microorganisms and the presence of immunocompromised subjects (5,6). The Worldwide Outbreak Database (7) is the largest collection of nosocomial epidemics. According to this database, the bacteria that play a main role in epidemic events are *Staphylococcus aureus* (11.9%), *Klebsiella pneumoniae* (7.9%) and *Pseudomonas aeruginosa* (7.1%), followed by methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, vancomycin-resistant *Enterococcus* (VRE) and *Acinetobacter* spp. (8). These microorganisms can persist in the environment for hours to days (and in some cases for months), especially if the circulating bacteria are *Klebsiella pneumoniae* (from 2 hours to 30 months) and *Pseudomonas aeruginosa* (from 6 hours to 16 months) (9). Their movement is facilitated by the inadequate use of personal protective equipment by healthcare workers. In fact, healthcare workers have frequent contact with the equipment present in patients' rooms (accessories, bed, bedside table, door or window handles), so they can easily contaminate their hands or gloves. In addition, they can transmit microorganisms using mobile phones, as well as through the use of computers during healthcare activities or surgical procedures (10). According to Paleckyte et al. (11), the management of control measures by healthcare workers is also associated with multi-resistant bacteria. The lack of education and training on infection control policies and other essential working practices remain a major barrier to the effective implementation of control measures.

Among the different prevention methods necessary to reduce the risk of infections in healthcare settings, disinfection plays an essential role. The intervention must be carried out by choosing the disinfectants that best meet the needs of use. These products, depending on the mechanism of action, can block the reproduction of the microorganism (bacteriostatic action) or prevent it completely (bactericidal, virucidal, fungicidal or sporicidal action). Their effectiveness and speed of action are linked to various factors including the type of disinfectant adopted, the conditions of use, the microbial species on which to act, the presence of organic substance. Also, in daily practice, method of use, concentration, contact time, presence of inactivating substrates can largely influence the effectiveness of a disinfectant, influencing the expected level of disinfection. For example, if a high-level disinfectant (i.e. active across the entire microbial spectrum, except for spores present in high concentrations) is used at concentrations lower than the effective ones or for an insufficient contact time or in the presence of substances that interfere with the action of the active components, certainly it does not provide the expected results.

In recent years, there has been a growing consensus on the need for improvement in the cleaning and disinfection of surfaces in healthcare facilities (12).

During the COVID-19 pandemic, interest in contrasting microbial contamination of surfaces has increased significantly both in the community setting (13-17) and in the healthcare setting (18-20). Some authors have reported that SARS-CoV-2 is transmitted by touching surfaces on which a sick person has recently coughed or sneezed (21-23). Rooms occupied by patients with multidrug-resistant organisms, if not adequately disinfected, can represent a relevant risk for transmission to other patients using the same room (24). Thorough cleaning and/or disinfection of surfaces, especially at the time of patient discharge, are essential elements for an effective prevention program. It is mandatory not only to use disinfectants appropriately, but they must be effective (biocides) on a broad spectrum of microorganisms if the risk of patients developing infections from healthcare-associated pathogens is to be reduced (25).

Among different disinfection products generally used in the healthcare setting, the action of hydrogen peroxide is particularly interesting for its bactericidal, virucidal, sporicidal, and fungicidal properties (26,

27). It is an oxidizing agent that works by producing free hydroxyl radicals that can attack membrane lipids, DNA, and other essential cellular components. Oxidizing agents are used for hard surface disinfection and high-level disinfection of medical devices (28). Among the main advantages, hydrogen peroxide has broad-spectrum activity as a biocide, which includes effectiveness against bacterial endospores. Furthermore, its decomposition does not produce toxic by-products (29).

Although hydrogen peroxide has been used for many years as a disinfectant, Bharti et al. 2022 (30) underline that this molecule releases oxygen over time as the product formed after the decomposition is the mixture of hydrogen and water.

In 2015, a new formulation of 1.0% hydrogen peroxide impregnated wipes (Incidin™ Oxy Wipe, Ecolab Deutschland GmbH, Monheim am Rhein, Germany) was first developed and launched in the United States. It was called "enhanced" or "accelerated" with Hi-speed H_2O_2 because it allows hydrogen peroxide to penetrate microorganisms faster and more efficiently and can be used as a ready-to-use cleaner and disinfectant against bacteria and viruses. Recently, these wipes have been introduced in Italy (Incidin™ Oxy Wipe, produced by Ecolab srl, Vimercate - MB, Italy).

The aim of this study is to evaluate the effectiveness of Incidin™ Oxy Wipe, whether in the form of wipes or liquid disinfectant, against some microorganisms of nosocomial origin using different laboratory techniques in order to verify whether different methods confirm the same results.

Methods

The effectiveness of Incidin™ Oxy Wipe wipes (dimensions 20 x 20 cm) made of viscose (40%) and polyethylene terephthalate (60%) was tested against bacteria and fungi (specifically, five strains of nosocomial origin and five reference strains) divided into three different groups:

Group A (nosocomial strains subjected to disinfectant treatment): methicillin-resistant *Staphylococcus aureus* (MRSA), Carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA), *Klebsiella pneumoniae* carbapenemase (KPC), *Aspergillus fumigatus* and *Candida parapsilosis*.

Group B (reference strains subjected to disinfectant treatment): *P. aeruginosa* (NCTC 10662) and *S. aureus* (NCTC 6571) provided by the National Collection of

Type Cultures; *K. pneumoniae* (ATCC 43816), A. fumigatus (ATCC 46645), and *C. parapsilosis* (ATCC 22019) provided by the American Type Culture Collection.

Group C (control strains: reference and nosocomial strains not treated with disinfectant): group A (*Staphylococcus aureus*, MRSA; *Pseudomonas aeruginosa*, CR-PA; *Klebsiella pneumoniae*, KPC; *Aspergillus fumigatus* and *Candida parapsilosis*) and group B (*P. aeruginosa* NCTC 10662; *S. aureus* NCTC 6571; *K. pneumoniae* ATCC 43816; *A. fumigatus* ATCC 46645 and *C. parapsilosis* ATCC 22019).

The strains of nosocomial origin were selected from stock cultures preserved in glycerol at -80°C at the Hygiene Laboratory of the University of Bari Aldo Moro. Neither ethical approval nor patient consent was deemed necessary, as we did not use patient data or additional samples beyond those obtained during routine laboratory work.

To ensure the viability and purity of the bacterial strains, each strain was plated on Petri dishes containing Brain-Heart Infusion Agar (BHIA; Biokar Diagnostics, Beauvais, France). After incubation for 24 hours at 36°C ± 1°C, individual colonies were subcultured onto Triple-Sugar-Iron agar (TSI, Biolife Srl, Milan, Italy) and incubated for 24 hours at 36°C ± 1 °C. The same procedure was performed with the fungal strains, using Petri dishes containing Sabouraud gentamicin-chloramphenicol agar and incubating at 25°C for 24-48 hours (*C. parapsilosis*) and for five days (*A. fumigatus*).

The study was conducted using three different methods, and the tests were repeated three times for each method and each strain.

1. Method I (stainless steel surface test)

Stainless steel sheets (42 cm² each) were plated via sterile cotton swabs with 200 µl of each bacterial or fungal suspension (in saline solution) at a concentration of 0.5 McFarland (approximately 1.5 x 10⁸ cfu/mL). After spreading the suspensions, the plates were dried at 30 °C for 1 hour to promote adhesion of the bacteria/fungi to the surface. Immediately after incubation, IOW wipes were streaked for 5 seconds onto the steel surface contaminated with Group A and B microorganisms, while Group C microorganisms were not treated.

For each plate of A and B groups, a sterile swab was smeared on the contaminated surface, then suspended in 10 ml of neutralization solution (Easy Surface Checking-Neutralization Rinse Solution; Liofilchem Srl, Roseto degli Abruzzi, Italy) to block the action

of the disinfectant.

According to UNI EN ISO 4833-1:2013 (31), for the determination of the Total Bacterial Count (TBC), 1 mL of neutralization solution of each suspension and the corresponding dilutions were mixed and plated on Plate Count Agar (Microbiol Snc, Cagliari, Italy). They were incubated at 30 ± 1 °C and monitored daily for 72 ± 3 hours.

According to NF V08-059:2002 (32), for the determination of Total Fungal Count (TFC), 1 mL of neutralization solution and each dilution were mixed with Sabouraud gentamicin-chloramphenicol agar (Liofilchem, Roseto degli Abruzzi, Italy). The samples were incubated at 25 ± 2 °C and monitored for 5 days.

Although the group C microorganisms did not meet the disinfectant, swabs with neutralizer were also used on these plates to standardize the methods used.

After incubation, the presence of colonies was expressed as colony forming units per cm^2 (cfu/cm^2).

The arithmetic mean of each test per microorganism was used to calculate the inhibitory effect of the test product.

2. Method II (surface diffusion test)

Surface diffusion tests were performed in 90 mm diameter Petri dishes containing Wurtz lactose agar for bacteria, and Sabouraud gentamicin-chloramphenicol agar (Liofilchem, Roseto degli Abruzzi, Italy) for Fungi. Each plate was thoroughly inoculated with sterile swabs that had been soaked in the respective bacterial and fungal suspensions at a concentration of 0.5 McFarland (approximately 1.5 x 10^8 cfu/mL).

Meanwhile, under sterile conditions, 20 mm diameter wipe discs were prepared and then placed on the surface of each inoculated plate. Before starting the experiment, we cut discs of different diameters (5 mm, 10 mm, 20 mm) from the wipe under sterile conditions. The results were comparable, but we opted for the 20 mm disc because the inhibition zone was more delineated and easily measurable. Furthermore, given the filamentary structure of the wipes, making 20 mm discs was easier.

Plates inoculated with bacteria were incubated for 72 ± 3 h at 30 ± 1 °C, those inoculated with fungi for 5 days at 25 ± 2 °C. The effectiveness of the test was evaluated by measuring the diameter of the microbial inhibition zone around the discs. Microorganisms were considered susceptible when the zone of inhibition was > 28 mm in diameter. This value is given by the diameter of the disc (20 mm) plus an inhibition of four mm to the left and to the right of the disc.

3. Method III (well diffusion test)

The discs were removed to evaluate the presence or absence of underlying growth (33).

In agreement with other authors (34,35) we wanted to carry out the diffusion test in the well to evaluate the effectiveness of the product to be studied, making some modifications. This test was performed in 90 mm diameter Petri dishes containing Wurtz lactose agar for bacteria, and Sabouraud gentamicin-chloramphenicol agar (Liofilchem, Roseto degli Abruzzi, Italy) for Fungi. A direct suspension of colonies of each test isolate was prepared in sterile 0.9% saline solution. Turbidity was adjusted to 0.5 McFarland (approximately 1.5 x 10^8 cfu/mL). Agar plates were thoroughly inoculated with each test suspension by swabbing.

For each plate, three wells were made, one larger (diameter 10 mm) and two smaller (diameter 5 mm), filled respectively with 100 μl and 50 μl of disinfectant liquid obtained by squeezing and twisting the wipes.

The reason that led us to apply two smaller holes is that their sum corresponds to a large hole and therefore we can understand if the inhibiting effect is achieved with both two half doses and a full dose of disinfectant. The effectiveness of the test was evaluated by measuring the diameter of the microbial inhibition zone around the well. Microorganisms were considered sensitive when the zone of inhibition had a diameter > 7 mm for small holes and > 14 mm for large holes. For the small one, a 5 mm diameter hole was considered containing 50 mcL plus 1 mm on the right and 1 one the left with a total diameter of 7 mm, while for the large one, as there was a double quantity of disinfectant (100 mcL), the limit was set at 14 mm. The plates for bacteriological investigations were incubated at 30 ± 1 °C for 72 ± 3 h, while for the mycological ones at 25 ± 2 °C for 5 days.

In order to obtain the certainty of the results from the two repetitions, the values from the two small wells were expressed as an average value.

Results

The results are given below for each of the individual methods and refer to the mean value obtained from the tests carried out in triplicate.

Table 1 - Results obtained from the stainless steel surface test (*Method I*), expressed as the average value of three time for each strain tests.

Tested strains	Surfaces treated with wipes H_2O_2 Group A	Group B	Surfaces no treated with wipes H_2O_2 Group C
	Nosocomial strains	Reference strains	Control
	(cfu /cm²)	(cfu /cm²)	(cfu /cm²)
Staphylococcus aureus (MRSA)	0	0	260
S. aureus (NCTC 6571)	0	0	270
Pseudomonas aeruginosa (CR-PA)	0	0	250
P. aeruginosa (NCTC 10662)	0	0	280
Klebsiella pneumoniae (KPC)	0	0	280
K. pneumoniae (ATCC 43816)	0	0	300
Aspergillus fumigatus	0	0	330
A. fumigatus (ATCC 46645)	0	0	350
Candida parapsilosis	0	0	290
C. parapsilosis (ATCC 22019)	0	0	300

1. Method I (stainless steel surface test)

Incidin™ Oxy Wipe wipes soaked in H_2O_2 resulted effective on all strains tested in triplicate (100%): the strains of Group A (nosocomial strains) and B (reference strains) treated with H_2O_2 wipes produced negative results (0 cfu /cm² each). On the contrary, the Group C strains (control strains) tested as controls developed colonies with a bacterial load between 250 and 350 cfu/cm² (Table 1).

2. Method II (surface diffusion test)

All the strains examined presented an inhibition zone > 28 mm in diameter, therefore they were all considered sensitive to the action of the disinfectant. However, a difference in inhibition values between bacteria and fungi was detected. In particular, MRSA strains were the most sensitive (40 mm), followed by KPC (31 mm), *P. aeruginosa* (30 mm), *A. fumigatus* and *C. parapsilosis* (30 and 29 mm, respectively). When the discs were removed, no bacterial or fungal growth was detected. An example of the surface diffusion test is shown in Figure 1.

Group C strains (control strains) tested as controls, not having come into contact with the disinfectant, didn't register any inhibition (Table 2).
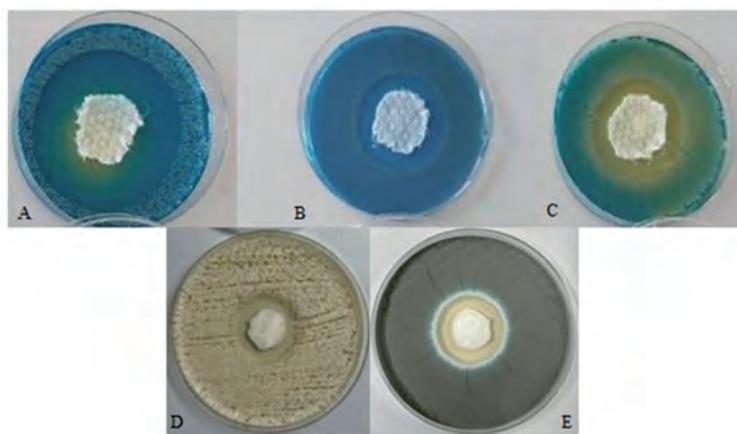

Figure 1 - Inhibition halos of bacterial and fungal growth on the strains tested: *Staphylococcus aureus* (MRSA) (A), *Pseudomonas aeruginosa* (CR-PA) (B), *Klebsiella pneumoniae* (KPC) (C), *Candida parapsilosis* (D) and *Aspergillus fumigatus* (E).

Table 2 - Results obtained from the surface diffusion test (*Method II*), expressed as the average value of three time for each strain tests.

Tested strains	Group A e B treated with wipe discs	Group C, as control
	Inhibition growth (mm)	Inhibition growth (mm)
Staphylococcus aureus (MRSA)	40 mm	0 mm
Pseudomonas aeruginosa (CR-PA)	30 mm	0 mm
Klebsiella pneumoniae (KPC)	31 mm	0 mm
Aspergillus fumigatus	30 mm	0 mm
Candida parapsilosis	29 mm	0 mm

3. Method III (well diffusion test)

Satisfactory results were obtained with both 5 mm and 10 mm diameter holes. The inhibitory effect obtained from the two smaller holes is roughly equivalent to the inhibitory effect obtained from one large hole. In fact, after repeating this method three times, the average values deriving from the inhibition zone measurements in triplicate were calculated: *S. aureus* MRSA was the most sensitive (mean value of big and of two small hole 30 mm), followed by *P. aeruginosa* CR-PA and *Klebsiella* KPC (mean value of big and two small hole 18 and 15 mm, respectively). As regards the fungal strains, *Candida parapsilosis* was more sensitive (big hole 20 mm, mean value of the two small hole 10 mm) than Aspergillus fumigatus (big hole 12 mm, mean value of the two small hole 8 mm) (Figure 2).

Discussion

The effective use of disinfectants is part of a multibarrier strategy to prevent HAIs. The surfaces are generally considered non-critical items because they meet intact skin. Therefore, contact with surfaces, although in a healthcare environment, is wrongly considered to pose minimal risk of causing infection in patients or nosocomial staff. Even today, the routine use of germicidal substances to disinfect hospital surfaces and other non-critical objects are object of debate across the world (36, 37).

Indeed, environmental surfaces can potentially contribute to cross-transmission of HAIs. Some authors have pointed out that it is easy to transfer microorganisms from the hands or gloves of healthcare workers to patients and from patient to patient, because
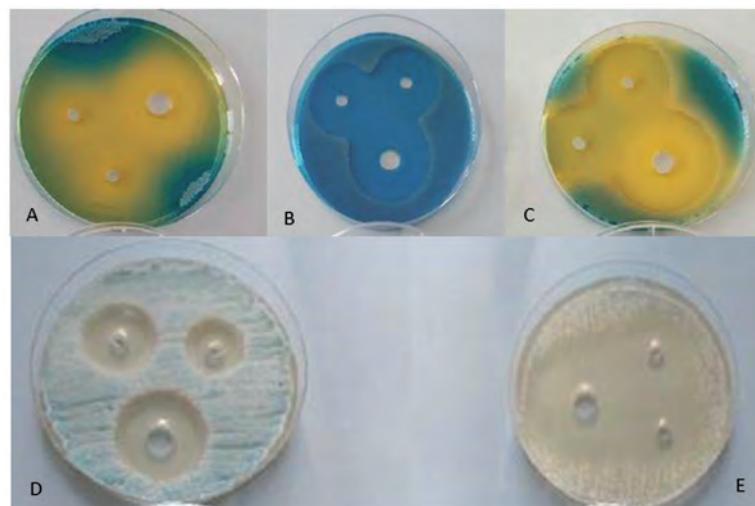

Figure 2 - Inhibition halos of bacterial and fungal growth on the strains tested: *Staphylococcus aureus* (MRSA) (A), *Pseudomonas aeruginosa* (CR-PA) (B), *Klebsiella pneumoniae* (KPC) (C), *Aspergillus fumigatus* (D) and *Candida parapsilosis* (E).

Table 3 - Results obtained from the well diffusion test (*Method III*), expressed as the average value of three time for each strain tests on big and small hole.

Tested strains	Group A e B treated with wipes H_2O_2		Group C, as control
	Inhibition growth (mm)		Inhibition growth
	Big hole	Small hole	(mm)
Staphylococcus aureus (MRSA)	30	30	0
Pseudomonas aeruginosa (CR-PA)	18	15	0
Klebsiella pneumoniae (KPC)	18	15	0
Aspergillus fumigatus	12	8	0
Candida parapsilosis	20	10	0

the healthcare worker's contact with the contaminated environment is as likely as the direct contact with a patient (25, 38). Likewise, all the equipment usually used in hospitals for patient care (e.g., X-ray machines, instrument trolleys, sphygmomanometers, stethoscopes, electronic thermometers), including walls, tabletops, bedside tables, bed bars and header, mobile phones, personal computers, etc., can be contaminated and, consequently, represent a potential source of infection (39).

An article researched epidemiological and microbiological data regarding the use of disinfectants on non-critical surfaces (40). Other meta-analysis studies (41, 42) have shown that patients admitted to hospital are more likely to contract nosocomial infections if the room had previously been occupied by HAI-positive patients (43, 44).

Surfaces represent a real and important source of transmission of pathogenic microorganisms in hospitals (14, 45), therefore careful disinfection leads to a decrease in surface contamination and to the reduction of HAIs (25, 46).

Various factors such as the characteristics of the built environment, the circulation of staff, patients, and visitors can increase the type and quantity of microorganisms present in the environment and lead to cross contamination (39). Also, climatic conditions (in particular, the degree of humidity) can influence the survival of environmental microorganisms (47, 48).

Considering these issues, surface disinfection becomes a fundamental infection prevention practice. Scientific evidence (25, 49) has shown that appropriate surface disinfection is a key practice in reducing the incidence of HAIs, as conventional disinfection procedures performed with inappropriate products do not always eliminate pathogens from the environment.

Numerous products are listed in the guidelines for disinfection and sterilization in healthcare.

Among these, hydrogen peroxide is one of the most effective (50). These data are consistent with a study that evaluated the in vitro antibacterial activity of five disinfectants used in hospital practice (phenolic compounds, quaternary ammonium compounds, sodium hypochlorite, alcoholic compounds, hydrogen peroxide). Hydrogen peroxide was the most active against both clinical isolates (*K. pneumoniae* sensitive and resistant to carbapenems, MRSA, *P. aeruginosa*, *Enterococcus faecalis*) and environmental isolates (*P. aeruginosa*) (33). Other studies have evaluated no-touch automated room disinfection (NTD) systems. The most used in healthcare facilities are hydrogen peroxide aerosol systems, H_2O_2 vapor systems, and ultraviolet C radiation systems (51, 52). Some authors (53) have evaluated the bactericidal activity of products based on 0.5% hydrogen peroxide, both alone and in combination with other molecules with disinfectant activity. The study was carried out on stainless steel surfaces against Gram-positive and Gram-negative bacteria. The best results were obtained when the molecule was tested in combination with other antimicrobial products against *Enterococcus hirae* and *P. aeruginosa* compared to *S. aureus*.

In recent years, the use of ready-to-use disinfectants in the form of pre-moistened wipes has become widespread (54). These wipes are made of different materials to allow the disinfectant to act differently on different surfaces (23, 24). Kelley et al. (55) tested five wipes with different contact times (30 seconds, one minute, two minutes, three minutes, and 10 minutes), one impregnated with 0.5% hydrogen peroxide and four based on quaternary ammonium compounds at different concentrations. Only the hydrogen peroxide impregnated wipes were more effective against *S. aureus* and *P. aeruginosa*. It was hypothesized that hydrogen peroxide performed better due to the shorter contact time (1 minute) compared to quaternary ammonium impregnated wipes (55).

The disinfection process using a wipe impregnated with a disinfectant can be divided into two parts (mechanical action and disinfectant action) which make up the overall decontamination activity. The wipes include a cleaning process by mechanical action, which is performed by the healthcare worker and is capable of removing organic dirt and at the same time acting as a disinfectant. It is important to consider that during the rubbing process with the wipe, some microorganisms may simply be transferred from one part of the surface to be treated to another, rather than being removed. This mechanical action depends on the retention capacity of the wipe and the bactericidal activity of the disinfectant adsorbed on the wipe, including the intrinsic properties of the wipe such as surface energy, fabric structure and fiber type, as well as the pressure applied, the number of steps and the type of microbial adhesion mechanism (54, 56). In addition, the bactericidal activity is mainly due to the disinfectant solution that the type of wipe can release onto the surface. Depending on the interaction between the wipe and the disinfectant, the amount and concentration of the active ingredient, the absorbency of the wipe and the amount of solution released onto the surface are important predictors of effectiveness.

To the best of our knowledge, our study is the first scientific contribution evaluating the effectiveness of wipes impregnated with 1.0 % hydrogen peroxide (Incidin™ Oxy Wipe) in the "enhanced" and "accelerated" formulations (Hi-Speed H_2O_2™) and containing highly specific plant-based surfactants. This product allows the hydrogen peroxide to penetrate microorganisms faster and more efficiently. The study was conducted on both nosocomial bacteria known to be multidrug-resistant and fungi, using three different methods. All the results confirmed the effectiveness of this molecule on the strains tested, with no differences between the nosocomial and reference strains (ATCC and NCTC). If we consider the product data sheet, Incidin™ Oxy Wipe leaves no toxic residue after use as it decomposes into oxygen and water, without any risk to the user or the environment. Furthermore, the product is considered an effective cleaning agent, presents no health risks for operators, requires short contact times with surfaces and has excellent compatibility with materials. These latter claims were not the subject of our study and, to our knowledge, are not supported by other experiments. It is our intention to expand this investigation, increasing the number of strains to be tested, including other microorganisms responsible for HAIs such as *Acinetobacter baumanii*, *E. coli*, *Serratia marcescens*, *Clostridium difficile* and

vancomycin-resistant *Enterococcus* and verifying their effectiveness on other types of surfaces normally present in healthcare facilitieZs (e.g. glass, wood and plastic). However, in our opinion, the introduction of Incidin™ Oxy Wipe into common disinfection procedures could contribute to reducing the number of hospital infections, with a reduced consumption of antibiotics planned in the therapeutic protocols and a consequent reduction in healthcare costs. Furthermore, the use of pre-impregnated wipes allows us to reduce the quantity of water and disinfectant solutions that are thrown into the sewage every day (57).

In addition to laboratory research, we would like to verify the effectiveness of the wipes directly on ward surfaces and investigate environmentally sustainable disinfection techniques that are effective against multi-resistant microorganisms. Considering that these studies are scarce in the literature (58), it will be necessary in the near future to enhance research on the effectiveness of disinfectants in hospitals to reduce the incidence of cross-contamination and avoid chemical damage to patients and healthcare workers.

Conclusions

The role of the hospital environment in the transmission of HAIs is still debated across the world. However, scientific evidence supports the hypothesis that, in addition to hand disinfection, surface disinfection is one of the most important prevention tools to limit the transmission of pathogens in healthcare facilities. Surfaces in the immediate vicinity of the patient and surfaces with high hand contact or frequent skin contact should be disinfected regularly. It is important to observe proper protocols such as the use of the appropriate disinfectant, the correct dosage, complete wetting, and exposure times, without neglecting the practicality of the method to be used depending on the circumstances; otherwise, disinfection could be less effective.

Our study demonstrates that the Incidin™ Oxy Wipe 1.0 % hydrogen peroxide-based wipes have an evident and significant antimicrobial action against all the microorganisms examined (Gram positive and Gram-negative bacteria, Fungi). The different methods used confirmed the same results.

These data underline that the tested wipes can exert an effective disinfectant action in the healthcare environment and represent a valid aid in the prevention of HAIs, especially against multi-resistant microorganisms.

This environmental remediation action could be used as a prevention tool in indoor environments, especially where disinfection processes can be particularly complex.

Riassunto

Efficacia delle salviette al perossido di idrogeno per la disinfezione delle superfici nelle strutture sanitarie

Introduzione. Il metodo corretto di disinfezione delle superfici negli ospedali è uno strumento essenziale nella lotta alla diffusione delle infezioni nosocomi causate da microrganismi multiresistenti. Attualmente, in commercio sono disponibili numerosi disinfettanti che possono essere utilizzati contro diversi microrganismi. Tuttavia, l efficacia delle diverse molecole attive è controversa in letteratura.

Disegno dello studio. Lo scopo di questo studio è stato quello di valutare l efficacia delle salviette a base di perossido di idrogeno (1.0 %) e tensioattivi di origine vegetale altamente specifici, contenuti nei prodotti H_2O_2™ (Hi-speed H_2O_2™), contro alcuni microrganismi ospedalieri.

Metodi. L efficacia delle salviette è stata testata contro ceppi nosocomiali e di controllo di *Staphylococcus aureus* resistente alla meticillina, *Pseudomonas aeruginosa* resistente ai carbapenemi, *Klebsiella pneumoniae* carbapenemasi, *Aspergillus fumigatus* e *Candida parapsilosis*. Nello specifico, l'attività in vitro è stata valutata utilizzando tre diverse tecniche: test su superficie di acciaio inossidabile, test di diffusione superficiale e test di diffusione in pozzetto.

Risultati. I tre diversi metodi testati confermano la buona efficacia delle salviette contro i più comuni batteri multiresistenti e contro i funghi.

Conclusioni. Questi dati mostrano che le salviette testate potrebbero essere un valido complemento al processo di disinfezione e potrebbero aiutare nella prevenzione delle infezioni correlate all'assistenza sanitaria.

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Corresponding author: Francesco Triggiano, Interdisciplinary Department of Medicine, Hygiene Section, University of Bari Aldo Moro, Piazza G. Cesare 11, 70124 Bari, Italy
e-mail: francesco.triggiano@uniba.it