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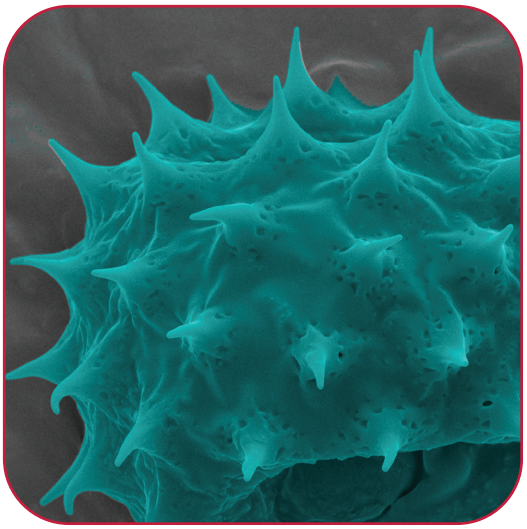

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COMMENTARY
The European legislation on the restriction on intentionally added microplastics

Tiziana Catone, Silvia Alivernini, Leonello Attias and Maria Antonietta Orrù

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Abstract

The potential impacts of microplastics pollution on the environment and possibly human health have raised concerns in various parts of the world. Once in the environment, microplastics do not biodegrade and cannot be removed. Several Member States have adopted or proposed specific measures. However, a patchwork of national restrictions can hinder the functioning of the internal market and therefore requires harmonization at Union level.

The European Commission, on 9 November 2017, requested the European Chemicals Agency to prepare possible proposals for restrictions regarding oxo-plastics and intentionally added microplastic particles.

On 25 September 2023, the restriction on microplastics intentionally added was published on the *Official Journal of the European Union*.

By the end of 2024 it is envisaged the publication of a Guidance on the application of the microplastic restriction under Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

Key words

- microplastics
- PBT/vPvB
- environment
- REACH restriction

INTRODUCTION

Microplastics are intentionally added to a variety of products used in different agriculture applications such as fertilizers and crop protection products, everyday products like cosmetics and household detergents and industrial cleaners, paints, and products used in the oil and gas industry.

In consumer products, microplastic particles are used for their characteristic of being abrasive (e.g., as exfoliating and polishing agents in cosmetics, known as microbeads).

It is estimated that about 145,000 tons of microplastics are used annually in the EU and, about 42,000 tons of microplastics end up in the environment due to the use of products containing them.

The largest source of pollution is granular infill material used for artificial turf fields, with a release of 16,000 tons. In addition, the release of unintentionally formed microplastics (when larger pieces of plastic wear out) is estimated at about 176,000 tons per year in European surface waters [1].

According to the European Chemical Agency (ECHA) "*Microplastics* are synthetic, water-insoluble polymer items smaller than 5 mm, which are considered to be of particular concern for the aquatic environment" and "*oxo-plastics* or *oxo-degradable plastics* are conventional plastics that contain additives which promote the oxidation of the material under certain conditions. They are used in applications such as agricultural films, rubbish and carrier bags, food packaging, and landfill covers. They can break down into very small particles, potentially contributing to environmental contamination by microplastics" [2].

Intentionally added microplastics have been the subject of great interest in their management both in scientific and regulatory fields in Europe due to their persistence characteristics and their potential bioaccumulation. In fact, once in the environment, they do not biodegrade and tend to accumulate in organisms and environmental compartments.

Microplastics have been found in fish for food consumption and, as a result of biomagnification, they can penetrate and accumulate in the human body [3-5].

In a study conducted on different types of edible fish, microplastics were found in different areas (gastrointestinal tract, dorsal muscle and gills) and oxidative

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damage to lipids in the brain, muscles and gills and an increase in activity were found of cerebral AChE (acetylcholinesterase, an enzyme whose primary function is to degrade acetylcholine and complete neurotransmission) in fish containing microplastics [6]. Microplastics were recently found in human feces for the first time, indicating that humans ingest and eliminate these particles [7].

In 2016 the European Food Safety Authority (EFSA) reviewed the available evidence on micro- and nanoplastics in food identifying the need to generate more data on levels of presence in foods and potential effects on human health.

Where action needs to be taken to manage hazardous substances, restrictions under the European Regulation (EC) n. 1907/2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals – REACH regulation [8] – are used to limit or ban the production, placing on the market (including import) or use of a substance, and may also be used to impose any relevant conditions, such as technical measures or particular labelling.

The National Centre for Chemicals, cosmetics and consumer protection of the National Institute of Health (Istituto Superiore di Sanità, ISS), in Italy, deal with REACH regulation actively participating in both RAC and Member State Committee, by submitting both proposals for harmonised classification of chemicals and proposals for restriction.

THE REACH RESTRICTION ON ADDED MICROPLASTICS

Added microplastics, once released, remain in the environment for thousands of years due to their persistence and bioaccumulation properties. In addition, they are likely to raise human health concerns, and the impact of such long-term exposure on the environment cannot currently be determined. Based on these concerns, the restriction adopted under REACH to protect human health and the environment from the presence of solid particles of polymer-based materials is justified.

Laboratory studies have made it possible to link exposure to microplastics to a series of adverse (eco)toxic and physical effects on living organisms. Microplastic particles ingested by fish can cause several disruptions to regular metabolic activity and can damage the gastrointestinal tract and nervous system, leading to serious health implications, including reduced feeding capacity, impaired gill function, altered immune system function, and compromised endocrine and liver systems [9].

Several EU Member States have already adopted or proposed national bans on the intentional uses of microplastics in consumer products, such as a ban on the use of microbeads in cosmetics that are rinsed after use, or bans in cases where microplastics are used as abrasive and polishing agents [10].

In 2017 the Commission has requested ECHA to prepare an Annex XV restriction dossier concerning the use of intentionally added microplastic particles to consumer or professional use products of any kind and an Annex XV restriction dossier concerning the placing on the market and use of oxo-degradable plastics as potential risk to the environment may arise from the use of oxo-degradable plastics in various products for consumer and professional use, because of their potential to initiate the generation of microplastics.

On 17 January 2018 ECHA notified the intention to prepare the restriction proposals by Registry of the Intention (RoI).

On 8 May 2019, ECHA withdrew the intention to investigate the need for a restriction on oxo-degradable plastics.

The withdrawal comes after a Commission request following the adoption of the directive on the reduction of the impact of certain plastic products on the environment. The new legislation restricts the placing on the EU market of any product made from oxo-degradable plastics [11].

In 2019, ECHA, proposed a broad restriction on microplastics in products placed on the EU/EEA market to avoid or reduce their release into the environment.

The initial concern identified for microplastics is based on PBT (persistent, bioaccumulative and toxic) and vPvB (very persistent and very bioaccumulative) properties. Given the wide variety of synthetic polymer microparticles (in terms of composition, properties, and size), the risk assessment was done on a case-by-case basis. The result was that the intentional use of microplastics, which inevitably leads to releases into the environment, presents a risk that is not adequately controlled unless a restriction is adopted under REACH. This measure prevents exposure to microplastics from causing adverse ecotoxicological effects, which would be difficult to address in the future.

The restriction process foresees the involvement of the Risk Assessment Committee (RAC) and the Socioeconomic Analysis Committee (SEAC) of ECHA. After the adoption of the final opinion by RAC and SEAC and after a positive evaluation by the Council and Parliament European Commission, the European Commission approved the restriction which was published in the European Official Journal on 25 September 2023 [12]. As a result, Annex XVII of Regulation (EC) n. 1907/2006 is amended by the addition of entry 78 for microplastics.

Once the restriction enters into force industry needs to comply with the restriction and Member States are responsible for enforcing the restriction.

The scope covers intentionally added microplastics in different types of commonly used products such as detergents and household cleaning products, cosmetics, encapsulated fragrances, and products such as medical diagnostic devices, synthetic turf football field infill materials, paints and coatings and fertilizers and pesticides in which microplastics are added to improve performance.

Given the complexity of the scope, exemptions have been provided for the entry into force of the restriction in consideration of both the socio-economic aspects and to allow some sectors (such as, for example, the production of diagnostic medical devices) to find adequate alternatives that do not affect the product reliability (*Table 1*).

Table 1
Summary scheme of application dates by product type

Product type	Derogations
Diagnostic medical devices	• from 17 October 2029 for medical devices and accessories for human use within the scope of Regulation (EU) 2017/745 of the European Parliament and of the Council [13]
Detergents and home care products	• from 17 October 2028 for detergents as defined in Regulation (EC) n. 648/2004 on detergents [14], waxes, polishes, and household fragrance products • from 17 October 2029 if they contain microparticles for fragrance encapsulation.
Cosmetics*	• from 17 October 2027 to rinse-off products • from 17 October 2035 to lip and nail products
Fertilizers and pesticides	• from 17 October 2028, to "fertilizer products" as defined in Article 2(1) of Regulation (EU) 2019/1009 [15], which do not fall within the scope of that Regulation • from 17 October 2031, to plant protection products as defined in Article 2(1) of Regulation n. 1107/2009 of the European Parliament and of the Council ("Pesticides Regulation") [16] and seeds treated with such products, as well as to biocidal products as defined in Article 3(1)(a) of Regulation (EU) n. 528/2012 of the European Parliament and of the Council ("Biocidal Products Regulation") [17] • from 17 October 2028 for products intended for agricultural and horticultural uses that are not pesticides or biocides, such as seeds coated with dyes or lubricants
Filling materials for the synthetic turf fields	• from 17 October 2031 for granular infill for use on synthetic sports surfaces
Encapsulation of fragrances	• from 17 October 2029 to synthetic polymer microparticles for use in the encapsulation of fragrances

*From 17 October 2031, and until 16 October 2035, lip and nail products containing synthetic polymer microparticles must include the statement, "This product contains microplastics" while products placed on the market before 17 October 2031, need not carry that statement until 17 December 2031.

CONCLUSIONS

The restriction on microplastics intentionally added, triggered by the great concern for the environment and human health, because of its complexity and wide range of uses covered, is a modern example of integration of risk assessment and management processes conducted on the basis of sound scientific information and current socio-economic considerations.

Transition periods and derogations for certain sectors proposed will allow industry to have enough time to develop and move to suitable alternatives, that is one of the aims of REACH Regulation.

Since the restriction on microplastics is based on current scientific knowledge and uses, the future impact of the proposed restriction may be different from what has been estimated now.

To take into account any scientific developments concerning polymer degradation and solubility, the Forum for Exchange of Information on Enforcement (Forum) recommends to review the standardised test methods and pass criteria to demonstrate degradability or solubility (including new test methods specifically developed to assess the degradability or solubility of synthetic polymer microparticles).

The Commission is working to finalize a guidance document containing explanation to better apply the restriction with a Q&A section. The draft guidance document has been shared with participants in the *ad hoc* working group (in which CNSC researchers participate) and the first version of the Guidance is expected to be published by the end of 2024.

A rapid publication of the guidance is of essence, in particular for sectors to which the restriction applies as of 17 October 2023 because they were not granted a transitional period.

The effects of the restriction are expected to be significantly perceptible in the early 2030s as envisaged by the European Green Deal, which has as one of its goals a 30 percent reduction in the amount of microplastics released into the environment, with increasing effectiveness over the subsequent years. Over the 20 years period following its entry into force it is estimated that this restriction to result in a cumulative emission reduction of approximately 400 thousand tonnes of microplastics.

Conflict of interest statement

The Authors declare that there are no conflicts of interest.

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COMMENTARY

The Italian National Vaccine Prevention Plans, 1999/2020-2023/2025: challenges and obstacles to vaccine coverage goals

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Abstract
Five consecutive national vaccination plans (from 1999 to 2025) were revised, outlining their objectives, challenges, and results. Vaccination coverage for children consistently approached target levels, though regional differences emerged. In contrast, coverage for adolescents, the elderly, and vulnerable groups, consistently fell short of targets. While vaccination policies in Italy over the past 25 years were ambitious and well-planned, success was primarily limited to newborns immunization, thanks to effective organizational activities. Failure to achieve goals for other population groups was partly due to inconsistent implementation of regional vaccination prevention plans.

Key words
- national vaccination plan
- Italy
- immunization schedule
- coverage rates

INTRODUCTION

Italy has consistently been at the forefront of vaccination policies, thanks to its publicly funded "National Health Service" (NHS), which has always prioritized prevention campaigns and offered effective vaccines, free of charge, to target populations. Among the most significant public health successes achieved through mass immunizations, the extensive polio vaccination campaigns in the '50s and '60s [1, 2], the early introduction of universal hepatitis B vaccination (HBV) in 1991 [3, 4], the trial of the acellular pertussis vaccine [5], the introduction of the human papilloma virus (HPV) vaccine for adolescent girls in 2007, extended also to boys in 2017 [6], as well as the more recent introduction of vaccines against meningitis B, rotavirus, and zoster [7] should be mentioned. Since the late 1990s, the Ministry of Health (MoH) aim was not only to extend the offer of vaccines, but also to improve delivery methods, and to support actions finalized at the success of vaccination campaigns, as specified in each vaccination plan.

The first two plans were named "National Vaccination Plan" (NVP). From the third onwards the name was modified into "National Vaccination Prevention Plan" (NVPP). We think it is extremely important now to revise the main objectives, challenges in implementation, and the results achieved, the five NVPs/NVPPs adopted so far, taking into account the political, legislative, and healthcare contexts of the different historical periods [8], and assessing the output of the plans in terms of vaccination coverage [9, 10].

The time span differed for the five vaccination plans from 2 years (one plan) to four years (one plan), with 3 plans having a 3-years duration. On average, 4.25 years passed between the conclusion of one plan and the adoption of the next one, periods during which the expired plans were always considered, even if there were not specifically extended. Between the first and the second plan, a significant amendment to the Italian Constitution was introduced, with the Constitutional Law 1/2001 [11], which brought "concurrent" legislation to healthcare matters, giving therefore more legislative and administrative power to the 19 regions and the 2 autonomous provinces with regard to the delivery of healthcare services, opening to the era of "Regional Vaccination Prevention Plans" (RVPPs). However, regional plans were approved only by some regions and, usually, after the NVPP had come into action.

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The technical support for the development of the national plans was provided by a National Vaccine Committee, which was established within the MoH, but it was abolished in 2012 as part of a legislative effort to reduce public spending [12]. It wasn't until 2017 that Italy, following World Health Organization (WHO) recommendations, established the National Immunization Technical Advisory Group (NITAG), which provides technical advice on vaccination-related decisions, including the NVPPs [13].

National Vaccination Plan 1999-2000

The 1999-2000 plan (Minister: Rosy Bindi; Chief Medical Officer: Fabrizio Oleari) [14] was issued to address the existing disparities in vaccination offer across Italy, to pursue the health objectives set by the WHO, and to overcome the fragmented method of introducing new vaccines through individual ministerial decrees. The increase of measles, mumps, and rubella (MMR) vaccination coverage from below 70% up to 95% was also among the priorities of this plan, as well as changing the polio vaccination schedule from oral to intramuscular to avoid the risk of vaccine-associated paralysis, introducing the *Haemophilus influenzae* type B (HiB) vaccine, and gradually introducing flu vaccination for the elderly population (whose coverage was still below 30%). The plan also included several detailed guidelines on the requirements for vaccination centers and on monitoring the achievement of its goals.

National Vaccination Plan 2005-2007

The 2005-2007 plan (Minister: Girolamo Sirchia; Chief Medical Officer: Donato Greco) [15] was approved after the 2001 constitutional modification and the adoption of the 2003 plan for the elimination of measles and rubella [16]. The extensive and well-documented plan (a total of 126 pages) set ambitious goals, including eliminating measles by 2007, reducing the incidence of mumps, pertussis, and HiB to an incidence of less than 1 case per 100,000 population by 2010, and reducing the incidence of chickenpox, meningococcal C invasive disease, and pneumococcal invasive diseases, following the availability on the market of the respective new vaccines. The plan paid particular attention to identifying adverse events and establishing pathways to eliminate the mandatory vaccination requirements, which, at that time, were in place for four diseases (polio, diphtheria, tetanus, and hepatitis B). The latter address was adopted by the Veneto Region which, in 2008, suspended the mandatory vaccinations, even if the final results, evaluated subsequently, were not encouraging [17].

National Vaccine Prevention Plan 2012-2014

The 2012-2014 plan (Minister: Renato Balduzzi, Chief Medical Officer: Giuseppe Ruocco) [18] systematically incorporated the concept of a "life-course vaccination schedule" rather than just a childhood vaccination schedule, partly due to the advocacy of the most relevant scientific societies in the field (public health, pediatrics, family medicine) [19]. It included the introduction of the HPV vaccine for adolescent girls, which started in 2008, with the goal of gradually achieving 95% coverage. The plan also provided the introduction of universal chickenpox vaccination and acknowledged the need for careful monitoring vaccination coverage following the suspension of mandatory vaccinations in the Veneto Region. Additionally, the plan described the decision-making process for introducing new vaccines, including the use of Health Technology Assessment (HTA), and emphasized the importance of annual local evaluation of the achievements of vaccination programs.

National Vaccine Prevention Plan 2017-2019

The 2017-2019 plan (Minister: Beatrice Lorenzin, Chief Medical Officer: Ranieri Guerra) [20] was considered one of the most innovative in Europe, due to the introduction of five additional vaccines (HPV for boys, menB, zoster, pneumococcal for the elderly and rotavirus) and for implementing strategies aimed at achieving population protection goals in a context increasingly characterized by widespread vaccine hesitancy and a consequent decline in vaccination coverage. The plan included the establishment of a national vaccination registry, a systematic communication and training campaign, the adoption of sanctions against healthcare personnel who did not participate in vaccination campaigns (no-vax) and the potential introduction of new mandatory vaccinations in emergency situations (a measure later adopted by the Parliament in July 2017, when it expanded the number of mandatory vaccines from 4 to 10) [21, 22]. The plan received significant political support (including substantial funding) and involved collaboration with various stakeholders in the decision-making processes. Furthermore, since 2017, vaccines included in the national plan have been automatically considered part of the essential levels of care (*Livelli essenziali di assistenza*, LEA) of the National Health Service (Servizio Sanitario Nazionale, SSN) [23].

National Vaccine Prevention Plan 2023-2025

The 2023-2025 plan (Minister: Orazio Schillaci; Chief Medical Officers: Giovanni Rezza, Francesco Vaia, Maria Rosaria Campitiello) [24] was developed in a context marked by a transition between two different governments and approved by the new – and stable – political majority, characterized by a decline in vaccination coverage, partly due to the COVID-19 pandemic, persistent vaccine hesitancy among the population [25, 26], and a shortage of healthcare personnel within the NHS. This plan maintains the approach of the 4th plan, keeping an immunization schedule that is essentially identical to the 2017 plan, but giving the possibility to modify the schedule at the time, based on new epidemiological evidence and the availability of new vaccines. The few new elements include the introduction of the quadrivalent (ACWY) meningococcal vaccine instead of the C-monovalent one, and the recognition of the right to receive free vaccination at any time other than those scheduled in the plan.

The plan also allows the regions to use different providers for vaccine delivery, as it was done during the

Table 1
Vaccination coverage in Italy

Antigen	Uptake indicator	Targets (National Plan 2017-2019) to the year 2019	National coverage (year 2022)
Poliomyelitis	24 months, completed cycle	≥95%	95.15%*
Dyphteria	24 months, completed cycle	≥95%	95.14%*
Tetanus	24 months, completed cycle	≥95%	95.14%*
Pertussis	24 months, completed cycle	≥95%	95.14%*
Hepatitis B	24 months, completed cycle	≥95%	95.05%*
H. influenzae type b	24 months, completed cycle	≥95%	95.08%*
Measles	24 months, 1st dose	≥95%	94.40%*
Rubella	24 months, 1st dose	≥95%	94.39%*
Mumps	24 months, 1st dose	≥95%	94.37%*
Chickenpox	24 months, 1st dose	≥ 95%	93.35%*
Rotavirus	24 months, completed cycle	≥95%	74.39%*
Meningococcal B	24 months, completed cycle	≥95%	80.91%*
Meningococcal C	24 months, completed cycle	≥95%	85.60%*
Pneumococcus conjugate	24 months, completed cycle	≥95%	91.73%*
Human papilloma virus	12 years, completed cycle	≥95%	♀ 38.78% ♂ 31.81%
Influenza, elderly	≥65 years old, every year	≥75% minimum target ≥95% optimal target	53.3%**§
Pneumococcus	65 years old, one dose	75%	<15%
Zoster	65 years old, one dose	50%	<15%

*Paediatric vaccinations. Year 2022 (2020 cohort); ♀: girls ♂: boys (2010 cohort); **influenza vaccination 2023-2024; § HCP: healthcare professional -54% (2020-2021); approximately 33% (2019-2020); approximately 23% (2018-2019).

COVID-19 vaccination campaign, with explicit references to hospitals, pharmacies, vaccination hubs, and family doctors.

The major indicator considered in all the five plans was "vaccination coverage for the different vaccine antigens in the target populations". In childhood, vaccination, uptake levels achieved have consistently been very close to the goals set by the plans, albeit with regional variation. However, for adolescents, the elderly, and "vulnerable" individuals, the results have always fallen significantly below the targets (*Table 1*).

The plans also included the formulation of specific actions in support to vaccination campaigns, such as communication, training, and the involvement of various stakeholders, although these actions have only rarely been implemented systematically and objectively evaluated. For the 2012-2014 plan, an evaluation made by scientific experts was published [27], while for the 2017-2019 plan, several scientific contributions (mostly published on "grey" literature and non-indexed journals) highlighted the achievement of the objectives, such as target thresholds for measles and rubella, the introduction of mandatory vaccinations as an extreme action to meet the coverage targets and the sanctioning of anti-vax doctors by the National Order of Doctors, Surgeons and Dentists.

In summary, throughout the whole time period considered, the priority has been to introduce updated, effective, and safe vaccines aimed at reducing the impact of vaccine preventable diseases in the population. The coverage goals set by the plans have been achieved or approached only in childhood and often only after a long period after the introduction of the respective vaccines into the schedules. Examples include the chickenpox vaccine (which only reached 93.3% coverage in 2022 despite being mandatory), the meningococcal B vaccine (introduced in 2017, reaching 80.9% coverage in 2022), and the rotavirus vaccine (also introduced in 2017, with coverage increasing to 74.4% in 2022). It is noteworthy that satisfactory coverage levels were also achieved for non-mandatory childhood vaccines, even during the critical phase of the pandemic. However, coverage goals for vaccinations among adolescence, the elderly, and vulnerable individuals have consistently fallen below the threshold, with variations between different Regions. Furthermore, the data regarding these population are partial or even lacking, and derive from non-official sources of information.

The automatic inclusion of vaccines provided by the national plan into the essential levels of care (LEA) in 2016 [23] was an important milestone in Italian vaccination policies. However, it ties the introduction of new vaccines to specific funding from the Ministry of Economy. This mechanism could slow down the process of updating the national vaccination schedule, encouraging regional initiatives to expand (obviously the law does not permit any reduction) the immunization offer, as it has recently happened with the introduction of the

meningococcal B vaccine for adolescents and prevention/prophylactic tools against respiratory syncytial virus (RSV) infections in the elderly and vulnerable individuals, with one of the three vaccines currently available, and monoclonal antibodies for newborns [28-30].

CONCLUSIONS

In conclusion, Italian National Vaccination Prevention Plans represented the basis for ambitious vaccination policies over the past 25 years, though innovative planning has not always been matched with adequate achievements in terms of vaccination coverage. Many of the goals and supporting actions have been re-proposed across different plans with the purpose of fitting the expected goals. Finally, the recent availability of monoclonal antibodies for preventive use against RSV in newborns will lead to the definition of an immunization schedule, rather than a vaccination schedule, representing a real paradigm change for the upcoming years.

Conflict of interest statement

None of the Authors had a conflict of interest.

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Efficacy of sodium oxybate plus disulfiram for the maintenance of alcohol abstinence in treatment-resistant patients with alcohol use disorder: a multicentre retrospective study

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Abstract

Introduction. Disulfiram (DF), acamprosate, naltrexone, baclofen and sodium oxybate (SO) are currently the medications approved for the treatment of alcohol use disorder (AUD). In this context, combined pharmacological interventions and sex differences are an interesting area in the treatment of non-responder AUD patients.

Aim. To evaluate the efficacy of SO in combination with DF in maintaining alcohol abstinence in patients with AUD who failed to achieve abstinence either with SO or DF alone.

Methods and results. 126 detoxified AUD patients, previously treated with only SO or DF, were retrospectively enrolled from 2018 to 2022. At the end of treatment, a higher number of females than males (74.1% *vs* 66.3%: p=0.03) maintained continuous abstinence from alcohol, and all the females responded completely or partially to the treatment.

Conclusions. This study shows that the combination of SO and DF may be considered a further pharmacological opportunity for AUD patients (particularly in females) who do not respond to mono-therapy.

Key words

- alcohol use disorder
- combined pharmacological treatment
- disulfiram
- sodium oxybate
- sex differences

INTRODUCTION

Alcohol consumption is responsible for approximately 5.9% of all deaths (3.3 million) accounting for 5.1% of the global disease burden [1]. In addition, alcohol consumption can lead to roughly 200 different diseases (including fourteen types of cancer) and can be addictive with the risk of triggering alcohol use disorder (AUD) [1]. AUD has a worldwide prevalence of 20-30% or 10-15% in men and women, respectively [1]. Although AUD is an important public health concern, it remains severely undertreated with only 7% of adults with AUD in the US [2] and less than 10% in Europe [3] receiving pharmacotherapy and/or psychotherapy.

Currently, disulfiram (DF), acamprosate, and naltrexone are medications approved by both the FDA and EMA, and nalmefene approved solely by the EMA

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for the treatment of AUD. In addition, baclofen is approved by the French agency for the treatment of AUD, and sodium oxybate (SO) is approved by the Italian agency for the treatment of alcohol withdrawal syndrome. In this context, combined pharmacological interventions are of interest for treating non-responder AUD patients [4]. A recent systematic review has shown that so far, no drug combinations have significantly better beneficial effects than individual medications. However, targeting combined pharmacological interventions to address specific symptoms of AUD may prove more successful [5].

DF was the first medication approved by the FDA for the treatment of AUD, back in 1951. It acts as a deterrent, i.e., an aldehyde dehydrogenase inhibitor blocking the metabolism of alcohol and increasing acetaldehyde concentration. Acetaldehyde, a toxic metabolite of ethanol, produces an alcohol-induced aversive response, characterized by nausea, vomiting, sweating, flushing, and heart palpitations [6, 7]. The administration of disulfiram under supervision by a referred family member to ensure adherence, is associated with significantly better success rates compared to non-supervised treatment [6, 7].

SO, or the sodium salt of gamma-hydroxybutyrate, is approved in Italy for the treatment of alcohol withdrawal syndrome and, until 2022 for the maintenance of alcohol abstinence in AUD patients [6, 7]. SO acts on the GABA system both directly as a $GABA_B$ agonist and indirectly through SO-derived GABA [6, 7]. It has an alcohol-mimicking effect. A Cochrane meta-analysis found that SO was effective compared to placebo in the treatment of alcohol withdrawal syndrome and in preventing relapses in previously detoxified participants [8].

Many studies using combined medications for the treatment of AUD have been published without investigating in-depth gender differences [5], and only one study using DF in combination with SO for the treatment of AUD has been carried out. In this study, 52 treatment-resistant AUD patients irrespective of achieving total alcohol abstinence, remained in treatment for a statistically significant longer time when SO was co-administered with DF than with SO alone [9].

Thus, our study aims to evaluate the efficacy of SO plus DF in maintaining alcohol abstinence in patients with AUD who failed to achieve abstinence with either SO or DF alone.

METHODS

We retrospectively enrolled 126 detoxified AUD patients consecutively admitted over a period of 24 months to four outpatient clinics: two in the north (Lugo and Ravenna), one in the center (Pisa) and one in the south (Soverato) of Italy. AUD was defined according to Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria [10]. All patients failed to achieve abstinence either with SO (101 patients) or DF (25 patients) alone, so they were treated with oral doses of SO (50-100 mg/kg of body weight, *tid*), and DF (250 mg daily) in combination for 12 weeks. SO and DF were administered by a referred family member. Each subject underwent weekly outpatient visits for 12 weeks, recording the degree of abstinence from alcohol and the amount of any daily alcohol intake (expressed as standard US drinks; one standard US drink =12 g of absolute alcohol) [1]. Based on the treatment response, patients were divided into three groups: total responders (complete alcohol abstinence), partial responders (reduction of at least 30% of alcohol intake), and non-responders (incomplete abstinence or reduction of <30% of alcohol intake). These parameters were assessed on the basis of participant self-evaluation, the interview with a family member and alcohol concentration in the blood and saliva (Assay for the Qualitative Detection of Alcohol in Saliva; Alcohol OnSite, Varian Inc., USA). Laboratory parameters of alcohol abuse – aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltraspeptidase (GGT), and mean red blood cell volume (MCV) – were assessed (*Figure 1*) at the beginning of treatment and at the end of the third month. A more accurate investigation of the quantity of the abused SO or the possible association of DF and alcohol was carried out with the assistance of patients and their family members, to whom the SO and DF had been entrusted. In addition to weekly counselling sessions and pharmacological therapy, self-help groups, such as alcoholics anonymous (AA) and social services, were recommended.

The study was carried out in accordance with the ethical standards of the 1975 Declaration of Helsinki, as revised in 2013.

Statistical analysis

The sociodemographic and medical characteristics of the sample were expressed as mean and standard deviations (SD) or median and interquartile range (IQR) for quantitative variables (based on their normal or non-normal distribution), and as absolute and relative frequencies for categorical variables. The characteristics and treatment outcomes of the participants were compared for men and women using the Student t-test, the Mann-Whitney U-test, and the Chi-square test, as appropriate. Intra-individual changes in biochemical parameters from the beginning of treatment to the 3-month assessment were evaluated using the non-parametric Wilcoxon test for paired samples. All analyses were performed using R statistical software. P-values less than 0.05 were considered statistically significant.

RESULTS

The sample included 126 patients (99 males and 27 females) with AUD, whose clinical and demographic characteristics are shown in *Table 1*. Males and females did not differ in terms of age and education, while the former were more likely to have a longer alcohol addiction, a higher alcohol intake, more use of illegal drugs, less psychiatric co-morbidity, and higher Cloninger type II alcoholism (*Table 1*).

At the end of treatment, significant differences in the response rate were observed between males and females (p=0.03) (*Table 2*). In particular, continuous abstinence from alcohol was maintained by 85 patients (68%), with a higher frequency in females than males (74.1% *vs* 66.3%) and the same trend was observed in the 22

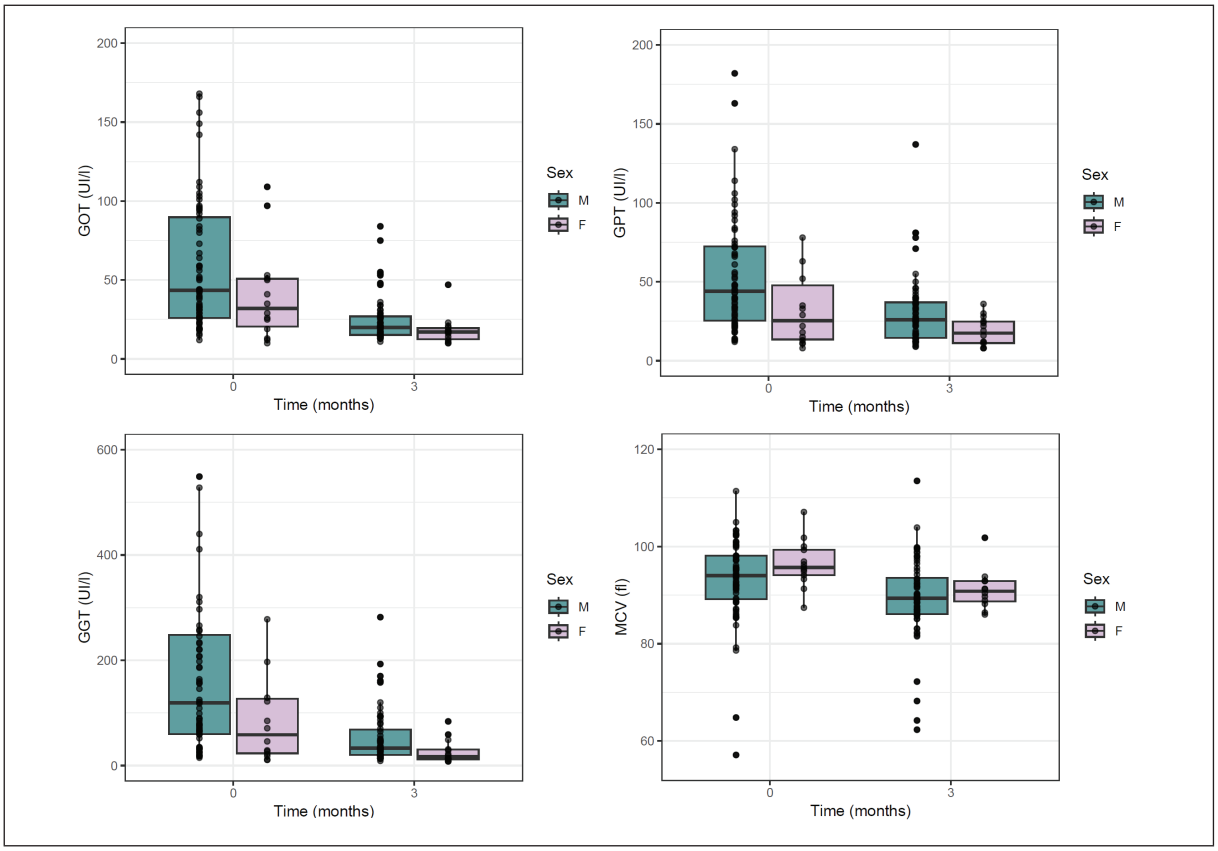

Figure 1
Difference between the beginning (T0) and end of treatment (T1) for the laboratory markers of alcohol misuse. A statistically significant difference between T0 and T1 was found for all the parameters and for both males and females (males: p<0.001 for GOT, GPT, GGT, and MCV; females: p=0.005 for GOT, p=0.02 for GPT, p=0.002 for GGT, and p=0.02 for MCV).
GOT: glutamic-oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; GGT: γ-glutamyltraspeptidase; MCV: mean cellular volume.

Table 1
Characteristics of the total sample and by sex

	Overall (n=126)	M (n=99)	F (n=27)	p-value
Age: mean (%)	45.56 (9.57)	46.12 (9.72)	43.48 (8.87)	0.205
Education: subjects (%)				0.304
primary school	83 (68.0)	66 (68.0)	17 (68.0)	
secondary school	35 (28.7)	29 (29.9)	6 (24.0)	
degree	4 (3.3)	2 (2.1)	2 (8.0)	
Units of alcohol: mean (SD)	10.97 (5.69)	11.84 (5.37)	7.78 (5.81)	0.001
Time of alcohol intake: mean of years (SD)	14.94 (8.52)	16.01 (8.47)	11.00 (7.62)	0.006
Use of illicit drugs: subjects (%)	35 (28.0)	32 (32.7)	3 (11.1)	0.049
Previous use of illicit drugs subjects (%)	15 (41.7)	14 (43.8)	1 (25.0)	0.858
Illicit drugs: subjects (%)				0.001
heroin	10 (27.8)	9 (27.3)	1 (33.3)	
cocaine	13 (36.1)	13 (39.4)	0 (0.0)	
cannabis	10 (27.8)	10 (30.3)	0 (0.0)	
others	3 (8.3)	1 (3.0)	2 (66.7)	
Organic comorbidity: subjects (%)	36 (29.3)	28 (29.2)	8 (29.6)	1
Psychiatric comorbidity: subjects (%)	55 (45.1)	38 (39.6)	17 (65.4)	0.034
Cloninger type II of alcoholism: subjects (%)	60 (50.8)	55 (58.5)	5 (20.8)	0.002

M: male; F: female; n: number.

Table 2
Treatment outcomes of the total sample and by sex

	Overall (n=126)	M (n=99)	F (n=27)	p-value
Side effects (%)				0.055
no	87 (70.2)	73 (75.3)	14 (51.9)	
yes, tolerable	35 (28.2)	23 (23.7)	12 (44.4)	
yes, drop-out	2 (1.6)	1 (1.0)	1 (3.7)	
Type of side effects				
nausea	4 (3.2)	3 (3.0)	1 (3.7)	1
abdominal pain	6 (4.8)	2 (2.0)	4 (14.8)	0.024
dizziness	15 (11.9)	10 (10.1)	5 (18.5)	0.389
paresthesia	5 (4.0)	2 (2.0)	3 (11.1)	0.112
sonnolence	5 (4.0)	5 (5.1)	0 (0.0)	0.525
sexual alterations	5 (4.0)	5 (5.1)	0 (0.0)	0.525
craving for sodium oxybate	4 (3.2)	3 (3.0)	1 (3.7)	1
Outcome (%)				0.039
total responders	85 (68.0)	65 (66.3)	20 (74.1)	
partial responders	22 (17.6)	15 (15.3)	7 (25.9)	
not responders	18 (14.4)	18 (18.4)	0 (0.0)	

M: male; F: female; n: number.

patients (17.6%) who reduced their alcohol intake by more than 30% (25.9% of females *vs* 15.3% of males) (*Table 2*). Overall, all 27 females included in the study had a complete or partial response to the treatment (20 achieved abstinence and 7 reduced alcohol intake).

At the end of treatment, all laboratory markers of alcohol misuse both for males and females were significantly reduced (*Figure 1*). The incidence of side effects was higher in females than males, although the difference was not statistically significant (p=0.055, *Table 2*). Indeed, women had a higher frequency of tolerated adverse effects (44.4% *vs* 23.7%) or leading to drop-out (3.7% *vs* 1%) than men, especially concerning abdominal pain (14.8% *vs* 2%, p=0.024). The two patients who dropped out for side effects reported paresthesia.

At the end of treatment, four individuals (3.2%) – 3 males (3.0%) and one female (3.7%) – developed craving for SO. One (male) eluded the control of his family member to whom SO was entrusted and voluntarily abused SO, increasing the dose two- to three-fold. However, SO-abuse was an isolated episode following the thorough explanation of the toxic consequences of SO-abuse provided during weekly counselling sessions. No patient developed withdrawal symptoms at SO discontinuation. The patient who abused SO manifested sedation and sleepiness. No additional sedative effects due to alcohol/SO interaction were observed in patients failing to maintain abstinence. In addition, of the 22 patients (17.6%) who did achieve total abstinence, 8 used alcohol in association with DF with tolerable flushing and nausea not leading to quit the treatment, while the other 14 patients, to avoid the side effects induced by the association of alcohol with DF, used alcohol without taking DF. Finally, the 18 non-responder males, due to the possibly serious side effects they would likely have undergone with the continuous use of alcohol in association with DF [11] were encouraged to discontinue treatment, offering other pharmacological options (acamprosate, naltrexone or baclofen) [11].

DISCUSSION

This study demonstrates the efficacy of SO and DF in maintaining complete alcohol abstinence in almost 70% of patients resistant to monotherapy. In particular, 100% of females responded positively with 74.1% achieving complete alcohol abstinence, and 25.9% reduced alcohol intake by more than 30%; only males were non-responders. Psychiatric comorbidity and Cloninger I type of alcoholism was more frequent in females than males, while males had higher alcohol consumption, longer alcohol use, and more use of illegal drugs than females.

The high percentage of complete abstinence in the group as a whole is a promising result, confirmed by the significant reduction of all laboratory markers of alcohol misuse both in males and females. However, data for total abstinence are not comparable with previous experience with SO and DF [9] since the main aim of the previous study was continued treatment, irrespective of achieving complete alcohol abstinence. In addition, concerning combined therapy studies, this is the first to evaluate possible sex difference. Of note, the number of females recruited by studies involving the pharmacological treatment of AUD is usually very low [12]. Furthermore, the high rate of abstinence is likely due to the different action of the two drugs. Indeed, SO with its alcohol-mimicking effect, acts as a replacement therapy for subjects who did not achieve abstinence with DF alone, while DF, considered an aversive drug, acts as a deterrent in patients who did not achieve abstinence

with SO alone. These two types of mechanism cover the major symptoms of patients affected by AUD: the discomfort induced by the discontinuation of alcohol intake and the fear of a slip or relapse.

Considering the observed sex differences in our sample, in accordance with the current literature, we found a higher percentage of females with psychiatric comorbidities, and a higher frequency of males with Cloninger type II alcoholism [13-15]. The classification of Cloninger belongs to an old but still useful differentiation of AUD typologies. Cloninger type I affects both men and women, requires genetic as well as environmental predisposition, commences late in life after years of heavy drinking, can take on either a mild or severe form, and has a characteristic personality trait (harm avoidance). Cloninger type II, in contrast, affects mainly the sons of male alcoholics, often beginning during adolescence or early adulthood, and is characterized by moderate or severe intensity, with a different characteristic personality trait (novelty seeking) [15, 16].

Another interesting finding is that the side effect that led to two cases of drop-out was paresthesia. This is likely related to DF, one of the most frequent side effects documented during treatment with this drug [6, 7, 11]. In addition, serious side effects have not been recorded during the use of DF in combination with alcohol, likely due to abandoning the drug the day the patient decided to drink alcohol; however, in order to avoid stronger and life-threatening side effects, DF was discontinued in the 18 males who continued daily alcohol consumption in combination with DF. Indeed, because DF blocks the effect on the aldehyde dehydrogenase enzyme, the use of alcohol during treatment with DF induces an increase in acetaldehyde concentration with important side effects (acetaldehyde syndrome) characterized by facial flushing, nausea, vomiting, and further severe effects such as hypotension, arrhythmias, and respiratory depression [6, 7, 11].

Another important issue is craving and the potential for the abuse of SO [6, 7]. These effects may limit SO use, although, at therapeutic doses, they appear to be relatively rare in clinical trials [6, 17, 18]. Indeed, craving and the abuse of SO are more frequent in patients with psychiatric comorbidities or poly-drug use [17, 18]. In our study, although 28% and 45% of subjects respectively were diagnosed with poly-substance abuse and psychiatric comorbidity, craving and abuse were very low, respectively at 3.2% and 0.7%; the patient who abused SO was diagnosed with borderline personality disorder, confirming the risk of abuse in this kind of patient [16].

A further concern is the prescription of SO. All our data are for patients treated for relapse prevention before 2018. In 2018 the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) modified the clinical prescription of SO leaving only the indication for the treatment of alcohol withdrawal syndrome, removing the indication for maintaining abstinence. Despite this, important data regarding the use of SO for maintaining and for relapse prevention have been published in recent years. Specifically, a meta-regression analysis has shown that in studies with alcohol-dependent patients, a high-severity population and lengthier treatment were associated with larger SO effects [19]. Moreover, the results of a phase IIb double-blind, randomized, placebo-controlled trial for the maintenance of abstinence demonstrated a significant and clinically relevant sustained effect of SO on cumulative abstinence duration (+32.4 days, p=0.014) compared to a placebo during the 6-month treatment period [20], and *post-hoc* analysis showed that treatment with SO was associated with a significant improvement in severe AUD patients [21]. The significance of these results may contribute to scientific discussion regarding the possible review of the clinical indications for SO.

This study has some limitations. First, this is a retrospective study based on medical records; therefore, we could only use data collected during routine practice. The second limitation is the lack of a control group, which would have given the study greater impact, confirming or disproving the efficacy of the combined therapy compared to the use of a single medication. However, all patients were previously unsuccessfully treated with one or other of the drugs, singly, so it seems likely that combined therapy is more efficient in achieving alcohol abstinence or the reduction of alcohol intake. Third, carbohydrate-deficient transferrin was not collected. This marker is considered the most sensitive and specific marker of alcohol misuse [22]. Still, it is important to underline that, in our study, all markers of alcohol misuse fell significantly, confirming complete abstinence or the reduction of alcohol intake in total and partial responders.

CONCLUSIONS

In conclusion, this study suggests that SO and DF may be considered a pharmacological option for the treatment of AUD patients (particularly females) who are non-responders to monotherapy. As previously demonstrated [5], combined pharmacological therapy for the treatment of AUD may be directed to targeted symptoms or populations when monotherapy fails. This is highly significant since patients who failed to achieve abstinence or to reduce alcohol intake with one medication may be discouraged and abandon treatment; the addition of another drug may help patients to stay in treatment [9, 23], and may increase complete abstinence from alcohol or drastically reduce alcohol intake. Thus, controlled clinical trials to evaluate the efficacy of targeted combined pharmacological therapy are now warranted.

Authors' contributions

The Authors confirm their contribution to the paper as follows: study conception and design: FC, TV; papers collection: FC, TV, AGIM, FM, GC, LL, AC, FM, GC, GT, ES, SV, RDG; analysis and interpretation of results: FC, CT. All Authors reviewed the results and approved the final version of the manuscript. All Authors approved the final manuscript.

Conflict of interest statement

The Authors declare no conflict of interest.

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ORIGINAL ARTICLES AND REVIEWS

Evaluation of four common electronic mosquito repellers on *Aedes albopictus* and *Culex pipiens*

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Abstract

Introduction. Mosquitoes represent a way of spreading infectious diseases, as vectors of pathogens. Many types of ultrasonic devices have recently been promoted as effective and suitable alternatives to the use of biocides known as toxic to humans and environment.

Materials and methods. Four ultrasonic mosquito repellers have been analysed and tested on females of two species, *Culex pipiens* and *Aedes albopictus*, in laboratory conditions. The behavior of the mosquitoes of reaching the attractant, with the repellers both at ON and OFF, was observed.

Results. The total mean number of *Cx. pipiens* interested to attractant when the repellers were ON was 2.8 versus 2.9 at OFF. The total mean number of *Ae. albopictus* interested to attractant when the repellers were ON was 5.5 versus 6.1 at OFF.

Conclusions. The repellence efficacy resulted not significant (P>0.05) in all the electronic ultrasound repellers tested. The number of mosquitoes of both species, displaying the attractant's search behavior appeared independent from the switch ON/OFF mode. Open questions remain: the need of conducting further research to establish a relationship between ultrasonic emission and mosquito effective disturbance.

Key words
- mosquito acustic repellers
- ultrasounds
- efficacy

INTRODUCTION

Widespread attention, at a global level, for the use of pest-repeller devices sustainable for the environment and attentive to animal welfare has translated into a broad and continuous commercial proposal of devices not based on biocides. Sonic pest devices are noisy sound tools designed to repel unwanted animals including insects, various birds and mammals, mainly rodents. These devices cover a wide range of the acoustic spectrum from below what humans perceive (infrasonic, characterized as sound below 20Hz), to above our hearing range (ultrasonic, characterized as sound above 18,000 Hz), depending on the target species. Ultrasonic devices are typically aimed at repelling arthropod and mammal pests, whereas devices targeting birds operate within the human normal hearing range. Many of the instruction booklets use vague wording to describe how the devices operate, such as "the device controls pests with high-frequency sound" or "it repels pests", at least without reporting the operating frequencies of the devices. Moreover, the actual effectiveness is currently supported by conflicting results. Many studies have been conducted to test the effectiveness of sonic pest devices, with most concluding that the devices are ineffective. A comprehensive set of studies conducted by Kansas State University tested five commercially available devices (one of which developed by the University itself), on nine groups of arthropod pests [1, 2].

The most common commercial ultrasonic devices on the market are purposed to repel mosquitoes (Diptera: Culicidae), but most of them are not supported by scientific studies of efficacy; indeed, the devices evaluated by laboratories or field tests failed to repel different species of mosquitoes [3-9]. Up to now frequencies within the range of 20-60 kHz emitted by different commercial ultrasonic devices were evaluated but none showed a clear

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repellent effect. However, despite the almost absence of publications confirming their efficacy, the sale of new electronic mosquito repellent devices is widely spread in many countries, probably due to a lack of a regulatory system by the local authorities. Moreover, the sincere aspiration of consumers to reduce the use of chemicals perhaps encourages the purchase of these devices to limit the problem of mosquito bites. In the present work, we evaluated four commercial devices, claimed to be electronic mosquito repellers, which have not yet been dealt with in the scientific literature. We evaluated the efficacy of the devices on *Aedes albopictus* and *Culex pipiens,* the most common mosquito species of health concern in Italy, as vectors of respectively potentially circulating arboviruses such as Chikungunya [10] and Dengue [11], and seasonally circulating as the case of West Nile [12].

MATERIALS AND METHODS

The tested electronic repellers were signed with the four letters A, B, C, D. The determination of sonic frequency was done in an acoustic isolation room of CNR-INM Labs at Tor Vergata Research Area. The devices were characterized according to the ISO 3744 and ISO 3745 standards [13, 14]. The characterization was conducted inside the treated chamber measuring 19.5 m^2 and 2.8 m in height, with a volume of 54.6 m^3. The devices were connected to the 220V electrical socket located on the wall and placed in the center of the wall, simulating typical use. Measurements and recordings were carried out using the Sinus Apollo Class I sound level meter (ISO 61672-1) [15] with the Samurai management software (SINUS Messtechnik GmbH). It supports Class 0 1/3 octave filter bands according to IEC 61260-1 [16]. The microphones connected to the sound level meter were two ¼ MP401 (BSWA Technology Co, Ltd), with a cut-off frequency of up to 80 kHz. Mathworks® Matlab and Microsoft Excel were used for numerical processing and some graphic representations. *Ae. albopictus* and *Cx. pipiens* mosquito colonies were reared at 26±2 °C and 80±5% relative humidity, offering a sucrose-saturated solution as food. For each assay, 10 *Ae. albopictus* and 10 *Cx. pipiens* females 1 week old were used. A test chamber, made with few adaptations from how described in literature [17], was used to observe the behaviour of mosquitoes in the presence of the ultrasonic signal. The plastic structure used for the test consisted of two sections joined by a tube. The hand of the operator was inserted into a 30×30×30 cm plastic box, connected by a plexiglass 10 cm diameter, 1 m long tube with a section 20 cm diameter, 25 cm long. *Ae. albopictus* and *Cx. pipiens* females were released in the plastic pot section and allowed to fly in the tube towards the sonic waves emitted by each repellers placed close to the hand in section box. Ten repetitions of 10 minutes each for every switch position for five trials ON/OFF for each species and each device were measured. The number of mosquitoes attracted during a 10-minute interval with the devices or software turned off or turned on, was counted. Statistical analysis was done with a χ^2 test [18], comparing the number of females arriving at section C for each switch position (ON/OFF) of the devices. Repelling ability was calculated according to the formula R=100–(ON×100)/OFF, where ON represents the mean percentage of mosquitoes attracted when the repeller was turned on, and OFF the opposite option [9].

RESULTS

Characteristics of the electronic repellers

The sound emissions of the tested devices are very different from each other in terms of both time and frequency levels, as shown by the sound pressure levels and sound power levels (*Table 1*). Some devices emit at fixed frequencies (C) but vary in intensity over time (A and C), while others emit at variable frequencies (A, B and C) (*Figure1A*-C). The maximum noise level measured at a 1-meter distance across the entire spectrum varies from 38.1 dB to 94.1 dB, while in the main frequency band, it varies from 20.6 to 93.9 dB, depending on the devices. *Figure 1B* shows the radiation pattern of each

Table 1
The table shows the main characteristics of the four repellers named A, B, C, D in this study

Device	Working voltage [V]	Frequency range [kHz]	Main frequency[1] [kHz]	Frequency trend	Signal period [s]	$L_{eq,f}$ @ 1m [dB][2]	L_{eq} @ 1m [dB(A)][3]	L_w[4] [dB]
A	220 V	20÷80	25	Symmetrical increasing and decreasing frequency variation at equal times. It has harmonics	2.14	93.9	64.7*	110.2
B	Battery 3 V	6÷80	6.3÷8	Symmetrical frequency ramp ascending and descending at equal times. It has harmonics	60	35.5	36.0	50.8
C	220 V	22÷73	25	Constant frequency. It has harmonics	0.1	33.4	24.2	49.9
D	220 V	4÷62	20	Symmetrical frequency ramp up and down, with different rise and fall times. It has harmonics	52	10.4	24.8	25.5

1: Main emission frequency 1/3 octave band; 2: Equivalent spressure level emitted in the main emission frequency 1/3 octave band, f; 3: Measured in the range 20Hz ÷ 20kHz; 4: Sound power level.
*the device also emits at 20 kHz at the extreme end of the audible band (not all people can hear it).

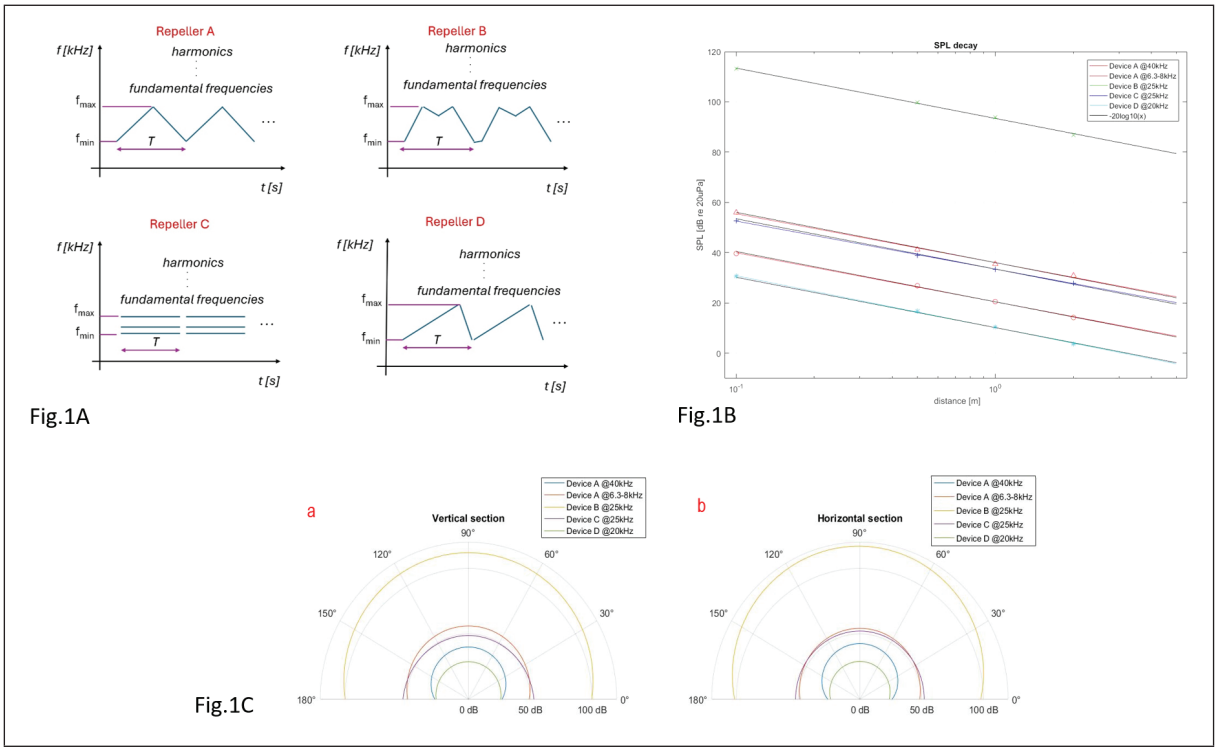

Figure 1
Characteristics of the emissions of the repellers.
Figure 1A: The shaping of the temporal spectra emitted by the tested repellers; *Figure 1B*: Radiation pattern of the tested repellers, a) vertical section perpendicular to the wall, b) horizontal section parallel to the floor; *Figure 1C*: SPL measured inside the acoustical treat chamber at differet distance from the repeller.

repeller, while *Figure 1C* illustrates how the sound pressure level (SPL) changes with distance for each device. Based on measurements conducted in a room without reflections on the walls or floor, the emission appears to be nearly spherical, and the noise levels decay with distance, r, according to the law:

$$y(r)=-20 \log10(r) \text{ dB}$$

equal to the law of geometric divergence for point sources.

Some devices, in addition to emitting in the ultrasonic band, also emit in the audible band, producing a high-frequency whistle or buzz. In *Table 1* the main characteristics of devices under test are reported.

Tests with Aedes albopictus and Culex pipiens mosquitoes

The graphs in *Figure 2* and *Figure 3* show the results of experiments obtained for each of the four devices on *Cx. pipiens* and on *Ae. albopictus* respectively. Twenty mosquitoes for each of the 5 trials, within which 10 minutes off and 10 minutes on, were counted. The colours of the histograms represent the minute in which a certain number of mosquitoes entered cage C, for each trial. Concerning the trials on *Cx. pipiens*, the total mean number of mosquitoes (calculated on the observation of all the four devices) that reached the cage C at switch ON was 2.8, while the same parameter at switch OFF was 2.9. Concerning the trials on *Ae. albopictus*, the total mean number of mosquitoes (calculated on the observation of all the four devices) that reached the cage C at switch ON was 5.5, while the same parameter at switch OFF was 6.1. The results of the single trials are reported in *Table 2*. The repellence efficacy resulted not significant (P>0.05) for all the electronic repellers tested (*Table 3*), as the number of mosquitoes of both species reaching the C-section was independent from the switch ON/OFF.

DISCUSSION AND CONCLUSIONS

In the present study, we tested four ultrasonic mosquito repellers on *Cx. pipiens* and *Ae. albopictus* female mosquitoes. The trials showed that the emission of the ultrasounds did not dissuade the mosquitoes from reaching the host to bite, although the total number of mosquitoes that reached cage C where the operator's hand was positioned appears slightly higher in the presence of the devices turned off. What has been observed concerns both the mosquito species used and the four ultrasonic devices tested. This result is in line with the existing literature on the topic. In fact, to date, the validity of the principle on which the operation of ultrasonic repellents is based is controversial. However, we believe it is important to evaluate the effectiveness of every possible alternative to chemicals aimed at reducing the risk of contact between humans and mosquitoes. [19] pointed out that female mosquitoes are not believed to respond to acoustic *stimuli*, even though the vibration of antennal hairs of *Aedes aegypti* females provides evidence that they perceive oscillations [20]. *Aedes aegypti* and *Culex quinquefasciatus* male attraction to

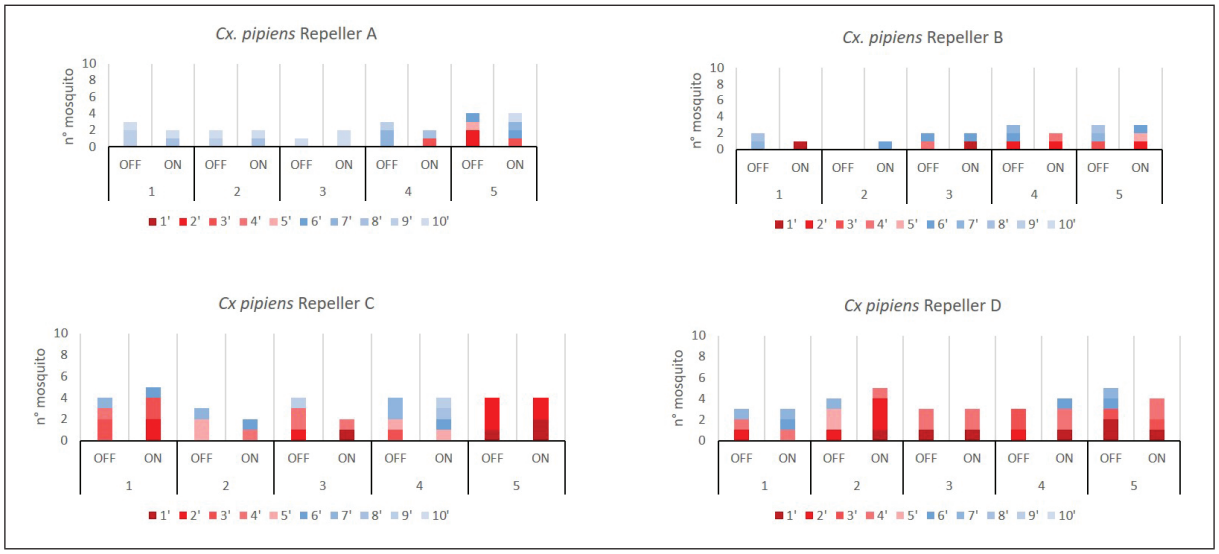

Figure 2
Results of the repellent effect of the four devices on *Culex pipiens*: in the graph, the number of mosquitoes is shown on the y-axis, and the time expressed in minutes on the x-axis.

conspecific female wing beat was demonstrated by [21] and [22]. However, in some devices, a mechanism is described that would exploit the imitation of the sound of the male's flapping wings to repel conspecific females. It should be noted that the wingbeat frequency for male mosquitoes has been recorded between 400 and 900 Hz [19, 21], quite different from that reported for all repellents evaluated in the literature and also in the present study. In the studies conducted by [20] and by [9, 23], the auditory function of the antennas was excluded. Moreover, some devices marketed to repel mosquitoes have been shown to attract mosquitoes. For instance, an electronic repeller tested under field conditions in Africa [24] gathered, in some cases, larger numbers of *Anopheles* spp. when the device was turned on. In another evaluation, four out of six devices showed a significantly higher attraction when turned on [25]. A study on three commercial sonic devices showed that when turned on the devices were attractive, resulting in an increase in bite-rate by as much as 50% [23, 26], confirming the lack of efficacy of the electronic repellers; other Authors showed similar results [27, 28]. A crucial socio-economic point is shown when such repellent measures are offered for sale in those territories where mosquitoes transmit infectious diseases pathogens. In such contexts, having effective repellence is crucial because interrupting contact between humans and the vector is integral to efforts aimed at limiting the spread of the pathogen. Concerning Italy, in several regions West Nile Virus, transmitted by *Cx. pipiens*, is

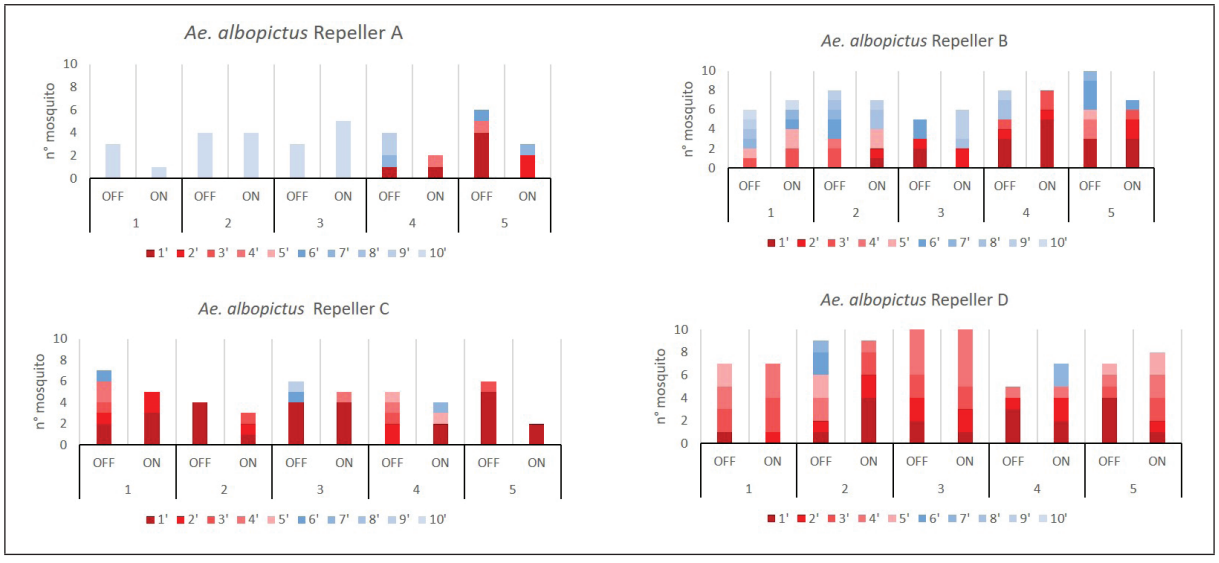

Figure 3
Results of the repellent effect of the four devices on *Aedes albopictus*: in the graph, the number of mosquitoes is shown on the y-axis and the time expressed in minutes on the x-axis.

Table 2
Results of the trials with the four repellent devices, named A, B, C, D in this study, on *Culex pipiens* and *Aedes albopictus*, espressed as mean number of mosquitoes that reached the box with the hand of the operator at switch ON and switch OFF position. Total mean number of mosquitoes observed reaching the box is also reported per species

	Mean number of mosquitoes entering the C cage								Total mean number per species	
Device model/ON-OFF	A/ON	A/OFF	B/ON	B/OFF	C/ON	C/OFF	D/ON	D/OFF	Devices ON	Device OFF
Culex pipiens	2.4	2.6	1.8	1.8	3.4	3.8	3.8	3.4	2.8	2.9
Aedes albopictus	3.2	4	7	7.4	3.8	5.6	8.2	7.6	5.5	6.1

Table 3
Statistical analysis by χ 2 test for *Culex pipiens* and *Aedes albopictus* (P=0.05)

Repellers	*Culex pipiens*	*Aedes albopictus*
A	0.841	0.400
B	1.000	0.814
C	0.739	0.192
D	0.869	0.736

now endemic. Autochthonous *Ae. albopictus* has acted as a vector in two outbreaks of Chikungunya virus in 2007 and 2017 and in three outbreaks of Dengue virus namely in 2020 in Veneto region, in 2023 in the metropolitan territory of Rome both in 2017 and 2023 and in 2024 in Marche region [29]. In these circumstances, relying on a repellent measure whose effectiveness is doubtful or non-existent can be very risky, as reported by Curtis in 1994 [30], who pointed out the risk of malaria infection due to some doctors in the UK prescribing electronic repellers instead of prophylactic measures for travellers to tropical areas. He also mentioned that some manufacturers have been sued and their repellers banned from sale. In the USA, the managers of a Company were charged and prohibited by the Federal Trade Commission (FTC) in 2002 from commercializing their electronic repellers for a period of 5 years. This was due to false allegations and unsubstantiated claims made in their advertisements for electronic mosquito and pest repellers. According to the FTC, the company had advertised that their device repels mosquitoes from the user and provides an effective alternative to using chemical pesticides in the prevention of the West Nile Virus. On the base of these considerations and the results observed in our study, we may assume that the here-tested electronic repellers are ineffective in repelling *Cx. pipiens* and *Ae. albopictus* female mosquitoes. Apps that "simulate" or emit sounds like ultrasound to repel mosquitoes have also recently been introduced on the market. These devices may represent a new challenge for research to determine whether they can serve as valid alternative tools or instead may pose a health problem. Pinto *et al.* [31] reported an episode of hospitalization for Tinnitus in a user who had used an "ultrasound" App to repel mosquitoes.

The Ultrasound App used to repel mosquitoes in Pinto *et al.* [31], was measured under controlled laboratory conditions and the results are available on the Physical Agents Portal website [32]. Important to note that the professional use of equipment that employ physical agents, including ultrasound, requires that the employer provides workers with "training and information couses" to protect their health during the processing phases. A recent publication by the Working Group on Physical Agents specific to Ultrasound is available on the Physical Agents Portal [33].

Based on the information presented thus far, we recommend conducting further research to validate whether there is a relationship between ultrasonic emission and mosquito disturbance. If such a relationship exists, efforts should be made to identify a frequency that could effectively dissuade mosquitoes from landing on the host to bite. Finally, as previously mentioned, government authorities need to regulate the marketing of electronic repellents by requiring the applicant to conduct scientific studies, based on statistically significant and reproducible data on their effectiveness before placing them on the market, similar to the requirement for chemical repellents.

Authors' contributions

LT, FLC: conceptualization, investigation, methodology, software, data curation, formal analysis, writing original draft,; FS, FC: methodology, software, formal analysis; RP, MM, MDiL, MDeL, PS: methodology review and editing. All the Authors have read and approved the final version of the manuscript.

Conflict of interest statement

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

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ORIGINAL ARTICLES AND REVIEWS

Dementia among migrants in Italy: a qualitative study of the ImmiDem project

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Abstract

Introduction. In recent years, the number of migrants referred to centres for cognitive disorders and dementias has increased. The aim of this study was to provide information on the provision of care for migrants with dementia through the perceptions and experiences of the professionals and caregivers involved.

Methods. The study is an exploratory qualitative research. Between 2020 and 2021, three focus group, involving caregiver and professionals were organized.

Results. The study explored several areas of care provision including needs, cultural representation of dementia, strengths and weaknesses and opportunities for improvement in care provision.

Discussion and conclusions. The perceptions of people directly involved in dementia care provide critical insights into the functioning of the care system, capturing nuances that standard care practices may overlook. Disorientation between services, language barriers and cultural representations of the disease are the main obstacles to continuity of care. A more holistic approach, which also addresses the emotional and social implications of dementia, is essential in ensuring equitable, timely and culturally sensitive care.

Key words

- dementia
- migrants
- provision of care
- culture-sensitivity

INTRODUCTION

Contemporary international migration has been a growing phenomenon over the past 30 years [1], due to socio-political, demographic, economic, and environmental influences [2]. The global ageing of the population leads to an increase in the number of older individuals also within migrant communities. At mid-year in 2020, globally, migrants aged 65 and older accounted for an estimated 34.3 million (12.2%) of all international migrants (i.e., people living in a country but born abroad) [1]. In Italy, a total of 316,796 elderly migrants are estimated to reside in 2023, with inter-regional heterogeneity ranging from 674 in Valle d'Aosta to 63,436 in Lombardy [3]. This demographic change is leading to substantial changes in health needs among migrants, including an increased prevalence of age-related chronic diseases and multimorbidity [4]. For instance, in recent years, there has been an increase in the number of migrants referred to Italian centres for cognitive disorders and dementias (CCDDs), especially in northern and central regions [5]. The application of age- and sex-specific prevalence rates [6-8] allowed estimating nearly 10,351 cases of dementia and 23,893 cases of mild cognitive impairment (MCI) in the age group of 65 years and over [9]. The female-to-male ratio is 2.5 in dementia and 1.86 in MCI [9]. Alongside the growth of this phenomenon, there is clear evidence of the need for action to improve help-seeking and promote timely diagnosis of dementia in migrant populations [10]. Migrants often access dementia care services later than the general population and experience difficulties in meeting their needs. This results in a higher dependency

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on support from caregivers and healthcare professionals [11]. Even though the symptoms of dementia are similar across races and ethnicities, the diagnosis of dementia in a cross-cultural context can be challenging [12]. The complexity of the clinical approach arises from language barriers and the lack of validated cross-cultural cognitive tools and dementia assessment scales [12]. Furthermore, in some cultures and populations, the stigma surrounding mental health problems can constitute an additional barrier [13].

To enhance accessibility, equity, and effectiveness in local healthcare systems, it is recommended to analyse the target population's needs to foster an effective reorganization of services that includes cultural mediation, peer-to-peer education and support, and the training of health professionals [14]. In addition, current public health initiatives should prioritize promoting cross-cultural dementia care that considers the values and preferences of different migrant populations [15]. However, there is limited knowledge of the experiences of migrant populations accessing dementia care services. This is the framework for the ImmiDem project, which aims to identify and promote good practices and care pathways for migrants with dementia and cognitive disorders.

The aim of this qualitative study was to provide information on the provision of care for migrants with dementia living in Italy, its strengths and weaknesses, and the perceptions and experiences of health and social care professionals and caregivers from their own perspectives.

MATERIALS AND METHODS

An exploratory qualitative study was carried out [16]. Three focus groups (FGs) were organized to collect the opinions of relevant stakeholders. Two FGs involved health and social care professionals including physicians (neurologists, geriatricians, internists, general practitioners, infectious disease specialists, dentists, and psychiatrists), speech therapists, cultural mediators, psychologists, sociologists, and social care workers with consolidated experience in the provision of care for migrants. These group interviews with professionals also served as a pilot study to test and refine a questionnaire for a national survey of CCDDs on the issue of dementia and migration [5]. One FG involved family caregivers of migrants with dementia. Participants were recruited through a purposeful sampling.

The study was approved by the Italian National Institute of Health Ethics Committee (Istituto Superiore di Sanità, ISS, Comitato Etico). All participants were contacted by an ImmiDem project [17] manager through the project stakeholders' network. Health and social care professionals were recruited from CCDDs that were identified based on their logistical feasibility and the number of migrants they reported to have assisted in the ImmiDem survey [5]. All professionals were invited to participate in the study by telephone calls followed by email invitations. All participants were actively involved in the care of migrants in different settings (hospital and community services) at the moment of the study. FGs with professionals were conducted during 2020, while the one with family caregivers was held in 2021 due to the project setback following the outbreak of the COVID-19 pandemic. They were facilitated by experienced researchers of the Italian National Institute of Health in Rome, following a semi-structured set of questions (*Table 1*). These questions guide was built with the contribution of all researchers and shared with ImmiDem project managers. The following definition of migrants was adopted and shared with participants: any individual living in Italy but born abroad (regardless of reason for migration, length of stay, and legal status) [18]. Each discussion lasted around 90 minutes. All the FGs were audio-recorded and transcribed, with the informed consent of the par-

Table 1
List of aims and questions for the Focus Group

Aim 1. Analysis of the needs of migrants with dementia and their caregivers
1a) In your opinion, what are the bio-psycho-social needs of migrants? • What are yours? 1b) In your experience, what are the cultural representations of dementia, its course, symptoms, and outcomes in the various cultures of origin? • What effect (positive or negative) do these different visions have on the provision of care for migrants?
Aim 2. Strengths, weaknesses and action proposals in provision of care
2a) In your opinion, what are the strengths and weaknesses in the provision of care for migrants with cognitive disorders? The discussion can be about the perspective of: • people with cognitive disorders, caregivers, and professionals; • the available diagnostic tools (e.g., cross-cultural cognitive assessment tools); • communication of diagnosis; • pharmacological treatment; • promotion of healthy lifestyles and other treatments (social, non-pharmacological, living environment, and culturally-sensitive • interventions); • provision of care for caregivers; • provision of care for professionals (e.g., management of burnout). 2b) In your opinion, what are the possible improvements in the provision of care, communities, and policies? • Would improving clinical pathways for migrants improve clinical pathways for the general population?
Aim 3. National survey (after viewing the questionnaire) – *Only for professionals*
3) Concerning the national survey of Italian CCDDs on dementia and migration, which variables do you think it is relevant to assess?

CCDDs: centres for cognitive disorders and dementias.

ticipants. Socio-demographic data of participants were also collected in an anonymous form. A categorical data analysis was performed: categories were developed both deductively, based on the research question, and inductively, based on emerging contents. The data were independently coded by two authors who then discussed the themes and categories for defining the tree-nodes. In case of disagreement, a third researcher was involved. The tree-nodes were applied to the whole transcripts, and the most meaningful verbatim were identified. The software used for the qualitative analysis was NVivo Pro. Data saturation was not required.

The main themes explored during the FGs, according to the main research questions, were:

- the bio-psycho-social needs of migrants with dementia and their caregivers;
- the cultural representation of dementia;
- the strengths and weaknesses of care provision for migrants with cognitive disorders;
- the rooms for improvement in care provision, communities, and policies.

RESULTS

Three FGs were conducted in January 2020 and in October 2021, involving 20 participants (17 health and social care professionals and 3 caregivers). The country of origin for the health and social care professionals was Italy, while the caregivers were from Egypt, Colombia and Romania. The health and social care professionals involved 7 women and 10 men, with a mean age of 50 years. The caregivers included 2 women and 1 man, with a mean age of 62.7 years. Among the professionals, there were 4 neurologists, 1 geriatrician, 2 internists, 1 general practitioner, 1 infectious disease specialist, 1 dentist, and 1 psychiatrist. Additionally, there were 2 psychologists, 1 cultural mediator, 1 sociologist, 1 social worker, and 1 speech therapist. Most of these professionals worked in hospitals.

Table 2 describes the participants' characteristics, while *Figure 1* summarizes the main results.

Table 2
Characteristics of social-health professionals and family caregivers involved in the FGs (n=20)

Data of participants'	N
Country of origin	
Social-health professionals (n=17)	
Italy	17
Family caregivers (n=3)	
Egypt	1
Colombia	1
Romania	1
Mean age in years	
Social-health professionals (n=17)	50 (SD±12.4)
Family caregivers (n=3)	62.7 (SD±2.5)
Gender	
Social-health professionals (n=17)	
Women	7
Men	10
Family caregivers (n=3)	
Women	2
Men	1
Social-health professions (n=17)	
Physician (n=11)	
Neurologist	4
Geriatrician	1
Internist	2
General practitioner	1
Infectious disease specialist	1
Dentist	1
Psychiatrist	1
Psychologist	2
Cultural mediator	1
Sociologist	1
Social worker	1
Speech therapist	1
Social-health professionals' workplace (n=17)	
Hospital	13
Territorial	2
University	1
Association	1

FG: focus group; SD: standard deviation; n: number.

Bio-psycho-social needs of migrants with dementia and their caregivers

The needs of migrants with dementia include difficulties in accessing healthcare services, which are greater for those in irregular situations than for those in regular situations, and for women than for men.

Informal caregivers also recognized that this difficulty in accessing healthcare services was exacerbated by the pandemic: "*because of the Coronavirus, (…) it was impossible for him to access any Centre*".

The difficulty in accessing services is often caused by a lack of knowledge on the available services in the community, which are organised in many cases differently from those in the country of origin. This lack of information requires professionals to dedicate time to provide adequate information to efficiently orientate and access services: "*they are very poorly informed, and accessibility to information is truly an issue (…). I spend a lot of my time giving information, explaining what is done in the Municipality, what is done at the Local Health Authority, (…) just the bureaucratic aspects*".

Barriers to accessibility include difficulties in orientation, including spatial orientation, between services, which undermine continuity of care and lead to loss of follow-up: "*those who enter the hospital environment may also lose the spatial orientation sometimes*".

Language barriers also play a key role in accessing services, due to difficulties in doctor-patient interaction, reporting health problems, and using diagnostic tools. Migrants supported by family or friends and an IT tool for translation may benefit more: "*the lucky ones have a friend who speaks Italian, or, more often, they use an automatic translation tool on their smartphone*" "*Where I worked before, I used to solve the problem by myself (…) I mean, I asked a relative or a friend [of the patient] to be my translator*".

Difficulties in orientation and communication can lead to an inappropriate use, or abuse, of the emergency services: "*very often the migrant goes to the Emergency Room [because] he/she doesn't know which outpatient services are available, due to lack of information; therefore, there is definitely a 'wrong' use of the Emergency Room*".

Although not appropriate, for migrants, the emergency service is probably the first contact with the health

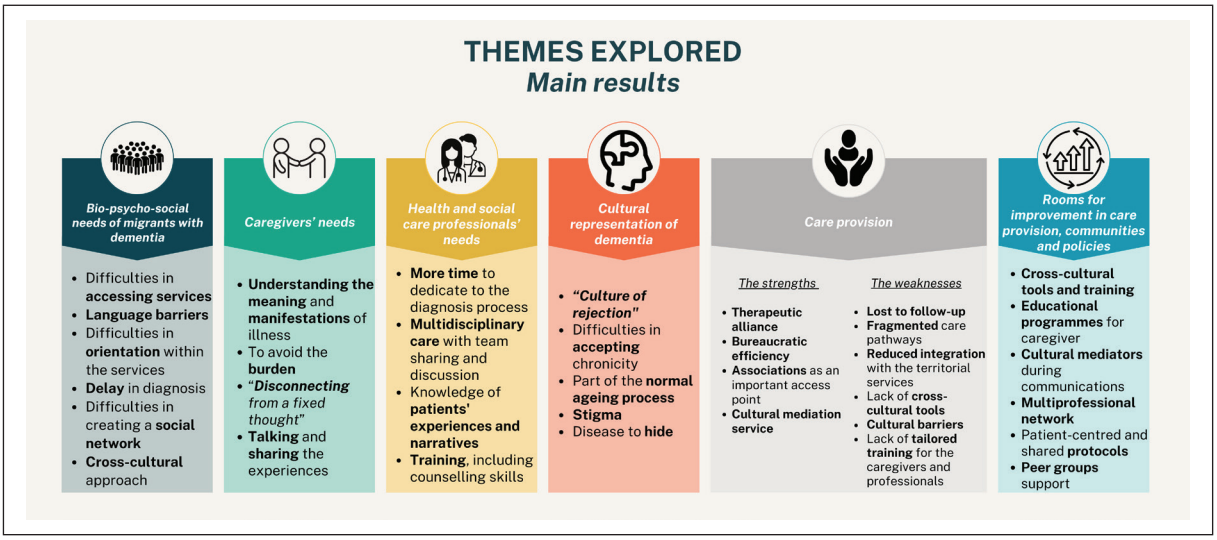

Figure 1
Summary of ImmiDem qualitative main results.

services. This may be challenging for them as "*the Emergency Room is not always able to respond to [their] needs*".

This leads to a delay in diagnosis, as migrants access emergency services when the symptoms of dementia are getting worse. Furthermore, cognitive disorders are not considered a priority compared to other essential needs: "*Often the disease is hidden, unrecognized, at least until it becomes so acute that they go to the Emergency Room*".

Caregivers living with a relative with dementia reported their relative's difficulties in finding or keeping a job, due to the onset and progression of the disease. The inability to attend a job interview or to work reduces the person's self-esteem: "*We looked for [a job for his father] and the sons found it (…) but after a day or two, the restaurant owner tells them: 'Are you sure he was a chef? And that he worked for more than 35 years in a restaurant kitchen?' *"; "*Considering the person's self-esteem, (…) when she had moments of mental clarity, she realised that she had zero income, that she couldn't find a job because (…) she couldn't even pass the first interview*".

In some cases, this situation generated forms of exploitation where adequate remuneration and suitable contractual forms were not always guaranteed. In other cases, the disease was not recognized by institutions (e.g., social security) as the person with dementia successfully answered the simple questions asked during the interview. This led to the loss of welfare benefits: "*Since he was 50 years old, he has been exploited a lot by many companies that hired him, made him work hard, paid him very little, did not offer him a contract*".

In some cases, there is the presence of Non-Governmental Organizations (NGOs) that offer persons with dementia the opportunity to work, however, the latter fear the loss of government welfare benefits if they take advantage of this opportunity. In addition, the fear that the diagnosis of dementia could jeopardise employment status or residence permits, and consequently the access to healthcare services, is another relevant issue. Hence "*the need to be welcomed and to be reassured that access to these services has no [negative] consequences [for them]*". This sense of precariousness, together with an unhealthy lifestyle, is destabilising, with repercussions on a person's health and well-being: "*when residence permits expire and there is that empty time moment, when the health card expires, at that point there is a high risk of strong destabilisation*"; "*The inactivity, the frustration of not working, not having a home, not being able to have a family, not being able to have children, all these things reduce that glimmer of humanity*".

The sense of emptiness is also due to the lack or difficulty in creating a social network, giving rise to loneliness in dealing with cognitive impairment. When a family network exists, the caregivers often work full time with limited time left to care for their relatives. Therefore, it is necessary to promote the creation of a relational network, to "*maximize the emotional and cognitive abilities of that person, that is, provide a relational context*".

The presence of a "strong" caregiver ensures continuity of care and treatment compliance. Conversely, when the caregiver is lacking, this affects the diagnostic process, as the patient alone is unable to find the appropriate information needed for the medical history: "*if there is a strong, precise, punctual caregiver, then the patient comes back, takes the drugs, and does everything he/she is told; if there is no caregiver, the patient may not take care of himself/herself, may not come back to the outpatient clinic*".

Furthermore, to promote the building of a social support network, people with dementia express a strong need to be listened to, understood and to receive positive feedback from professionals. For their part, professionals should devote adequate time to counselling, despite often having limited time: "*It is not enough to give and say things, you have to try to understand if the other person has understood*". "*This is my burning inside. When you have these high-demanding patients and time is what it is*".

For this reason, in order to optimize care, it has been reported that it is essential to go beyond cultural aspects and get to know the narratives and personal experiences of these people: "*you have to go beyond culture.*

It is very important to understand the person, because that person [behind him] has a different story (...) we have to understand who we are dealing with".

For their part, migrants with cognitive impairment need to fully understand the pathology, which is more cognitive/mental than physical, to understand how to manage it: "*[there is] the difficulty of understanding the disease (…) it is not easy for these people to identify where their illness lies*".

In this context, it is important to use a cross-cultural approach, as the care provision they experience in the host country is often different from that in their country of origin. The multi-professional approach, typically implemented to manage dementia, can be difficult to understand and can generate disorientation. Moreover, the same culturally sensitive approach is also important when it comes to interpreting the clinical manifestations of the disease, which may differ from one culture to another: "*sometimes it is difficult to explain why there are two professionals, for example why there is a doctor who deals with the body and a psychologist who deals with the mind*".

Caregivers' needs by professionals' perspective

Who is the *caregiver*? - Participants' definition
The caregiver has been identified not only in the classic form of the person who cares for an elderly family member with a disease, but also as a person whose job it is to care for patients with dementia, as in the case of formal caregivers. As for the migrant population, caregivers may be family members, including adolescent children and, if necessary, all of them also cover the role of cultural mediators.

According to the professionals, the caregivers, as well as the person with dementia, need to understand the meaning and the manifestations of the disease to avoid a sense of frustration due to the inability to understand the evolution of symptoms. Therefore, an accurate and properly communicated diagnosis should be provided: "*relatives feel distressed about this disease that overwhelms them. This applies to Italians but also to migrants, who have great difficulty in understanding the complaints of the person with dementia (…) it is anguish, frustration; we must therefore give them an explanation of any symptoms or [on the contrary] reassure them that, despite the relative's behaviour, there is no pathology*".

The need for explanation and clarification refers to the whole care pathway, from the cognitive evaluation to the communication of the diagnosis. For instance, this need may relate to the explanation of the administered test, which consists of "*questions that are used to understand if there are objective cognitive impairments or if there is something else*".

Caregivers sometimes experience a daily burden of caregiving, both physical and emotional. When this happens, the demand on health professionals to dedicate time to the sick person increase: "*Definitely caregivers are overloaded (…) family members sometimes expect from those who provide care to be extremely available*".

Some emphasised the importance of providing free care benefits to migrant caregivers in socio-economically disadvantaged conditions to enable them to continue caring for their family members in the host country.

It was reported that the second and third generation of migrants may face more problems when they are involved in caring for elderly people with dementia, as they tend to adapt to the culture of the host country, by creating "*fractures in cultural and family habits*"; "*the problem is [greater for] the second and third generation (…). Even the mother says: 'You have to take care of grandpa. Grandpa is like this now and you have to stay home (…)'. For the mother there isn't a problem. The child, however, since he was born here, or arrived as a child, says: 'No, I want to go and play football like my friends' (…) so you break cultural, family habits*".

Caregivers' needs by caregivers' perspective

Family members also express their own needs about their role as caregivers, as described below.

The need for clarity and understanding of the disease was confirmed by the caregivers themselves, which is essential to help their relatives in the right way. Moreover, caregivers declared that they needed to understand how to care for themselves as well and avoid burdens: "*First of all, I need to understand how not to feel bad, because when I feel bad I can't help him much (…) I want to give 100%*".

The need to "*break away from fixed thinking*" and the daily routine was expressed: "*people who have a relative (…) with a history of dementia, memory loss, schizophrenia, need to disconnect. I know I have to feed [my mother], so I have to run home from work (…) I come home stressed. In fact, I can no longer sleep continuously for 10 hours like I used to. In my opinion, the most important thing for family members of people with this type of illness is that they have to unplug, because people also burn out their brains too*".

It was reported how caring for a relative with cognitive impairment can be more difficult for younger caregivers, as they find it harder to accept the worsening of the disease and the increase in care: "*For young people it is very, very hard. (…) because they don't accept [the disease and its symptoms], and they don't have the patience*".

These experiences completely change the caregivers' lives and negatively affect their ability to interact with the sick person. When caring for a family member, there is a strong emotional component that influences the provision of care (e.g., the ability to give rules or restrict freedom of movement outside the home). At some point, the emotional component prevails over rationality and generates denial of the disease progression and hope for a possible improvement: "*having a family member with this type of disease implies the emotional component that blocks you. (…) she is my mother, (…) hope takes over, and I think: 'Maybe tomorrow she will be better; maybe tomorrow she will understand better'. (…) it is difficult, really, to detach the emotional component (…) you struggle because she is always the mother or the wife or the sister*".

These experiences are so pervasive that caregivers run the risk of not living their own lives, because they have to devote themselves to the relative with dementia. Therefore, talking and sharing their experience helps them feel "*lighter*" and relieves them of an inner burden. It has been confirmed how a strong social and family network can help them to cope and deal with the difficulties.

Health and social care professionals' needs

Health and social care professionals expressed the need for more time to dedicate to the diagnosis process, tests, and to communication, and so that multidisciplinary care provision involves also occasions for team sharing and discussions to avoid burnout: "*Share even when you disagree [with a decision], because sometimes disagreement challenges you and maybe makes you change your mind or make other decisions. I would say the mindset is to always work in a project way, because that's how we can move forward*".

Due to the potential emotional implication on professionals' mental health, psychological support was reported as being needed: "*[a] psychological support also for us, not only for the patient and the caregiver, because sometimes we have to communicate something very, very strong*".

Moreover, in some cases, a sense of frustration was also reported due to the fact that organizations do not enable professionals to *"do what is possible*": "*I don't expect to ensure excellence [in all circumstances] (…) but even if you see that it is possible, you are not [always] in a condition to do it*".

Professionals also reported the need to learn about patients' experiences and narratives in order to gather information that could be useful for tailored care, in order to avoid "*thinking as Westerners, proposing some things that (…) might not be good or might be far-fetched*".

Training for professionals is one of the most important needs, not only to improve care but also to give formal recognition to the care pathway of migrants with dementia. The training contents should include counselling skills: "*in my opinion, one of the big gaps in the training of physicians and health professionals is that they do not have adequate training in the field of communication and relations and that they have no support in this area. We are completely abandoned with regard to this aspect, the relational aspect*".

Cultural representation of dementia

The cultural representation of dementia changes across cultures and nationalities. In some cultures, there is the habit of returning to the country of origin when the disease becomes more severe to receive care, and have a family network to rely on, considering that some populations mainly migrate for work: "*when the diseases become a little more severe, they go to be treated in (…) they return home both to be treated and to be cared for (…) because people come here to work, so it would become a burden for those who have the disease*".

Some professionals underlined the "*culture of rejection*" affecting mental disease in some cultures. Some professionals described how mental disease is stigmatized, with the risk of being marginalized by the family and the community: "*I have a patient that I have been taking care of for 25 years (…), who in 25 years has never told her family that she is being treated and has a major depression. She never said it, terrified that her family could marginalize her*".

In some cases, this refusal results in blaming the person with cognitive impairment or dementia. On the other hand, there is the perception that some cultures develop a sense of loving kindness towards the older person with cognitive impairment. In these cultures, even at a young age, there is a sense of having the duty to take care of the patient.

While in some cases, cognitive impairment is believed to be a natural evolution of aging, in other cases, the long-term chronic evolution is more difficult to accept: "*Some people have to ferry themselves into the idea that you are in a limbo, that you have a disease, but this disease will follow you, it characterizes you throughout your existence in the next twenty years, and you have to manage this thing*".

Due to this perception of the chronicity of the disease, it is also difficult to manage chronic treatment regularly and with continuity: "*there is an emergency drug-taking culture because 'when I'm fine, why should I take the drug?' (…). There is a tendency to take the drug [only when] you need it [and then discontinue it]*".

Strengths and weaknesses of care provision for migrants with cognitive disorders

One of the main strengths shared by the professionals was the therapeutic alliance with the patient. On the other hand, caregivers mentioned the bureaucratic efficiency of the practices related to citizenship and recognition of disability. The municipalities were an important support for caregivers by providing information and clarifications to deal with administrative procedures to request allowances: "*For some years, we could talk to a social worker from the municipality who has helped us a lot, especially with information and clarifications because we knew some pieces, we had heard something, like the assistant, support administrator, tutor and various, and therefore we did not understand very well how the request could be made*".

It was stated that the main strength regarding hospital services was the cultural mediation service, available in several languages and several times a week, as well as the support of associations, such as NGOs, in offering an important access point for irregular migrants.

Among the weaknesses, a considerable number of losses to follow up were described. These losses were mostly related to homeless or irregular people, who do not declare their real health conditions, and it is difficult to keep them within the system: "*irregular immigrants are clearly those most exposed to traumatic experiences (...) the more you are integrated and the more it is possible to get a great collaboration*"; "*many patients are lost even at follow-up (...) Very often, they are homeless people who live with friends, who often lie even for all sort of reasons, and it is very, very difficult to gain their trust and keep them hooked up to the outpatients clinics (...) when an acute episode occurs, (…) this is when we discover situations not known to the social services, of people who live in absolutely unhealthy ways*".

These situations adversely affect the treatment plans, as these take a long time and require continuous contact with migrants: "*Maybe they give it [the therapeutic plan] at three months and, clearly, if it is already difficult to cage an Italian patient for about three months, I don't dare imagine a patient like that, (…). There is a practical problem which is the follow-up (…) if you don't have a patient who follows [the therapeutic plan]*".

For some participants, the problem is the fragmented care pathways that reduce accessibility and compliance, especially for vulnerable people. This generates blame for the patient who does not fit into the care pathway: "*we, as institutions, are generally quite repulsive; we are unattractive, not so much as people but especially in the context, how we are close to frailties. (…). So, we slip into measurement, instinctively, and we are rewarded for this. Actually, the question is: what can I do to keep these people on a care pathway?*".

A health professional reported that when care is provided by a private organization, dementia becomes an "*elite*" disease because these types of organizations have more tools and resources, but they are not within everyone's reach.

In some cases, voluntary associations meet the needs but sometimes are occasional services that do not always guarantee continuity of care.

Another weakness of the care system that impacts on patient's everyday life is the difficulty in obtaining welfare benefits and allowances, which is possible only when a diagnosis is established. This also has an impact on the possibility to keep the patient in the care pathway, also due to the limited time and resources of working caregivers: "*because you have to convince the caregiver and the caregiver [who] has his time, his resources, because the caregivers work*".

The reduced integration with the community services was another stated weakness, especially in the relationship with general practitioners, "*who don't send patients*", and this may result in long waiting lists. Caregivers also reported that the long waiting lists lead families to turn to private services, despite economic difficulties, thus further hampering the continuity of care: "*So, the two appointments were so distant, so sporadic; we are trying to have a third appointment with the doctor, but they always tell us that the agenda is full, to call later; every day on the phone to see if we can get an appointment and it wasn't possible. Paying a fee is difficult for us because not having a salary, it is not easy to have paid appointments which are a bit expensive, at least for those who don't have the money*"; "*So far, for two times, we have had the same doctor, very kind and professional. But I asked her: 'What should I do, to meet you next time?' [She said] 'No. You ask for an appointment. If you want have a visit with me, you should book a private visit' ".*

The lack of cross-cultural tools is another critical aspect that emerged during the discussion. Health professionals described this difficulty using these words: "*Concerning diagnoses, the situation is a little more complicated because I use a series of observational, informal tools that are not linguistically adapted. (…) We ask if the patient can go to their country of origin to make a more thorough assessment. This was possible in a few cases. However, it allowed us to reach a diagnosis*"; "*I try with the tools I know because, in this way, I can actually find something, but a specific tool is definitely missing*".

Cultural and linguistic barriers make it difficult to communicate the diagnosis and to understand the difference between disease and illness, between disease and the perception of disease. Moreover, the concept of prevention is accepted with some difficulties "*the separation between disease and illness, between the actual disease and the perception of disease, is perhaps more accentuated in countries with cultures further away from ours*".

These cultural barriers also negatively impact the treatment. In addition, according to the different cultural representations, it is often difficult to accept long-term treatment and cognitive or group interventions "*cognitive treatment (…) we propose something different (…) a group intervention (…) there is also taking care of the emotional aspect, of self-esteem, of socialization*"; "*they do not have the ability to give importance to something that seems intellectual compared to the pill*".

The lack of specific training for the caregivers and patients with a migratory background was another weakness.

Rooms for improvements in care provision, communities, and policies

Rooms for improvement include the strengthening of care services, closely linked to the need for intercultural training to develop a culturally sensitive approach. Regarding the assessment and diagnosis process, the need for more support from intercultural tools and a multidisciplinary network during the assessment phase emerges. Furthermore, the importance of cultural mediators during the communication of the diagnosis is emphasised. In order to develop patient-centred and shared protocols, the use of narrative medicine is proposed, which enables an understanding of the person's life course through their personal stories. It is essential to spend more time on information and building a caring relationship. Finally, the need for educational programmes aimed at migrants is highlighted, with the possibility of creating peer support groups for caregivers to share experiences and emotions.

DISCUSSION

In our study, the perceptions of the professionals and caregivers directly involved in dementia care offer a critical insight into the functioning of the care system. Caregivers' limited awareness of available dementia services [19], due to inadequate communication about both the services themselves and the access procedures, was confirmed in the FGs. This aspect affects the health literacy level of this population [20], leading to significant implications for continuity of care, disease worsening, and delayed or inappropriate use of services, especially emergency-urgency ones. Moreover, as indicated by both interviewed caregivers and the health professionals, the lack of a designated reference health professional throughout the care pathway increases disorientation and the fragmentation of care. In order to overcome the lack of an effective and structured information system, the initiative of individual professionals proves to be crucial in supporting the carer during the care pathway. In addition, this results in the caregivers' spending time in managing bureaucratic aspects that reduce time for care and social relationships, which were reported as a strength to be preserved. Personnel needs to have adequate time to establish meaningful relationships with patients, considering this time as an integral part of the care process. As previously reported [21], the implementation of narrative medicine is a promising ap-

proach, allowing a greater understanding of the patient's experience, and improving the care provision. Our study is in line with the Consensus Conference Guidelines for the use of narrative medicine in clinical care for rare and chronic degenerative diseases, which defines narrative medicine as "a subset of the broader field of medical humanities, which includes the use of narrative methods in health care". These methods are able to capture complex personal and cultural nuances that standard clinical practices may overlook, thereby increasing understanding of migrants' experiences and improving clinical outcomes [22]. This requires a change in the way personnel interact with patients, emphasising the personal histories and emotional experiences of both caregivers and patients related to dementia. Another frequently reported topic, also confirmed in this study, was the presence of language barriers, perceived as a major barrier to effective communication [23-25]. The communication gaps impact not only the ability of the person with dementia and their caregiver to accurately describe symptoms but also the effectiveness of the administered tests, partly due to the limited use or lack of cross-cultural tools. The lack of systematic use of cultural mediation services further exacerbates the situation, complicating the communication of diagnosis and the understanding of information on the characteristics and evolution of the disease. Findings from this study show that the inclusion of a cultural mediation service within facilities, where available, is perceived as a strength, aligning with the results of previous studies [26]. It is clear from the results that dementia represents a source of *burden* for caregivers of the person with the dementia. The risk factors contributing to this burden include female gender, low level of education, living with the patient, spending a high number of hours in caregiving, experiencing depression, facing social isolation, financial stress, and lack of choice in being a caregiver [27]. The emotional and physical burden of caring for persons with dementia can be overwhelming, to the extent that the literature [25, 28] shows how caregivers, mainly female, dedicate considerable effort to care, often reaching impracticable levels. In this way, they are unable to provide the necessary care for their relatives on their own. In fact, the need for caregivers to understand how to take care of themselves to prevent the development of burden was also highlighted by the participants.

Support from local institutions, such as municipalities, in dealing with disability recognition procedures is seen by the participants as a strength. However, there is a difficulty or slowness by institutions in recognising the diagnosis of dementia and providing financial support in a timely manner. The lack of formal recognition represents an additional emotional and financial burden on caregivers and persons with dementia [28] as it results in difficulties in accessing the needed financial support to maintain an optimal level of care. On the other hand, there is widespread concern that formal recognition of the disease may affect the residency permit.

This social perception of dementia can be an obstacle to help-seeking behaviours and building social and support networks, which are crucial to avoiding feelings of isolation. There is often a lack of acceptance of the disease, which is seen as something to be hidden, or an underestimation of cognitive disorders, wrongly perceived as part of the normal ageing process. Furthermore, there are fractures in cultural and family habits between different generations [29], due to the cultural contamination between their current country of residency and their country of origin. This phenomenon results in increased challenges in the caregiving process. A "*culture of rejection*", stigma, and underestimation of symptoms creates a "vicious circle" with delayed access to services, late diagnosis, and late and inappropriate treatment, resulting in a rapid worsening of the disease. The acceptance of the disease emerges as a significant obstacle, both for the person with dementia and the caregiver [30], also due to the difficulty in understanding the nature of the disease. The inability to clearly identify where the disease lies generates considerable distress and frustration, complicating the understanding of the concept of prevention and negatively influencing the evolution of the disease.

The interviewed professionals underline also that many patients are lost to follow-up also due to a lack of integration between hospital and community services (particularly in primary care settings). This is especially true for homeless people, who are often afraid to declare their real life and health conditions. They come to services in the acute stages of the illness, which makes it difficult to keep them within the care system and, consequently, to ensure a continuity of care that allows for gradual and continuous action [31].

In this context, it is evident that specific training on the topic is necessary, both for people with the condition and their caregivers. The organisation of training courses, discussions, and comparisons involving both personnel and caregivers would be helpful to conduct a critical analysis of success and failure strategies. This approach would facilitate the identification of shared solutions to improve care provision, as well as be useful for formal recognition of care pathways for migrant populations with dementia.

This study has some limitations: the smallness of the sample, especially with regard to caregiver, and the limitation to a single national context limit the consideration of all possible experiences in this field. Further research, both quantitative and qualitative, involving a larger sample and in different international contexts, would allow a more comprehensive understanding of the phenomenon from a public health perspective.

CONCLUSIONS

The use of qualitative tools, such as focus groups, proved to be a valuable support to explore health and social needs from caregivers' and health and social care professionals' perspective. Migrants with dementia represent a public health challenge and a more holistic approach is needed, addressing not only the clinical but also the emotional and social implications of dementia. This is useful in order to ensure equitable, timely, and culturally sensitive care. It is also essential to strengthen the training and information system, adopt psychological support strategies, and foster an organisational culture that recognises and addresses these challenges.

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Conflicts of interest statement

Authors have no conflicts of interest.

Authors' contributions

All Authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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ORIGINAL ARTICLES AND REVIEWS

Serious games in child and adolescent health education campaigns: a systematic review

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Abstract

Background. The use of playful tools to promote children's and adolescents' health in schools is growing. Educational games are proven tools for promoting virtuous behaviours. This systematic review explores the significance of serious games in promoting health education among young audiences, particularly about hand, oral and respiratory hygiene, immunisation, antimicrobial resistance (AMR) and sexually transmitted infections.

Methods. This study was conducted in March 2023 on PubMed, Scopus, Web of Science and Embase using the population, exposure, outcome, and study design framework (PEOS). Articles in English and Italian were published within the past decade regarding campaigns with educational games on hygiene for students aged 3 to 19 years who do not have chronic conditions or disabilities. Final screening resulted in including the study of 40 articles of the 1,577 records initially extracted.

Results. The results indicate that play positively influences the quality of learning. Serious games have been demonstrated to have a high potential in child and adolescent health education campaigns.

Conclusions. Games can effectively engage young individuals, promote healthy behaviors, prevent diseases and enhance health literacy. As serious games continue to evolve, further research and collaboration are needed to utilize their full potential to improve children's and adolescents' health and well-being worldwide.

Key words

- public health intervention
- educational campaign
- health literacy
- gamification
- serious game
- knowledge and awareness
- hygiene
- children and adolescent

INTRODUCTION

In recent years, there has been an increasing acknowledgement of the educational value of games, especially regarding children and adolescents' learning process. Games have been crucial to human culture and social interaction since ancient times. It is known that young people are more likely to become healthy adults when positive early experiences sustain childcare and education [1]. As children and adolescents immerse themselves in games and interactive activities, they acquire essential skills and cultivate curiosity and enthusiasm for learning. This dynamic approach to education transcends conventional methods and supports the innate desire for exploration and discovery that resides within every young learner.

The United Nations Convention on the Rights of the Child (UNCRC) is a fundamental document outlining children's rights and the well-being of children worldwide [2]. Article 31 of the above-mentioned convention emphasises every child's right to engage in play, leisure, and cultural activities, highlighting the crucial role of innovative and interactive approaches in promoting holistic development. For this reason, health campaigns in Italy and Europe have adopted a holistic approach to child and adolescent well-being by recognizing the interconnectedness of various aspects of health. Furthermore, a health-promoting school approach has been promoted globally over the past 25 years. Nevertheless, the aim of a fully sustainable health-promoting school approach system has not yet been achieved [3]. The im-

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portance of games in education and learning has also been a key point for public health as it is known that full involvement in activities leads to improved knowledge and better long-term memory retention of learned information. This represented a change for educational campaigns in public health previously limited to disseminating only information. For the promoted virtuous behaviors to be truly adopted, in fact, it is essential that the audience actively participate in educational campaigns and that engaging tools, such as games, are used for the young population.

Collaboration between stakeholders, including healthcare professionals, educators, policymakers, and parents, has been crucial in implementing comprehensive programs over the past two decades [4]. Quality education is also one of the critical components of the United Nations 2030 Agenda for Sustainable Development. Moreover, as in every other field of learning, even in health education campaigns, technology integration has gained significant attention, offering innovative and engaging approaches to enhance knowledge, promote behavior change, and improve health outcomes among children and adolescents. In this setting, serious games have emerged as a promising tool to send health-related messages in a captivating and interactive way.

For an effective education and to create and consolidate correct behaviors it is essential to intervene already in schools. In this setting, children can easily learn essential skills and attitudes for lifelong healthy habits. However, traditional approaches, such as lectures and pamphlets, often struggle to capture and sustain young audience attention. Serious games use interactive gameplay to educate and empower children and teenagers, promoting health knowledge, positive attitudes, and informed decision-making. By employing elements and mechanics of game design, serious games can create an immersive learning environment where users actively participate, make choices, and face consequences. These games can easily incorporate educational content related to various health topics. Through engaging narratives, challenges, rewards, and real-time feedback, serious games offer a unique opportunity to motivate young learners, stimulate critical thinking, and facilitate behavior change. Since serious games have immense potential, it is essential to rigorously evaluate their impact on child and adolescent health education campaigns. Several frameworks for validation exist, but it is unknown which one is the best [5]. Despite the great interest in serious games and some examples of European health campaign implementation in the past twenty years, such as e-Bug in England [6], the literature lacks a recent systematic review regarding serious games' use in health education campaigns for children and adolescents.

With this review, we would like to contribute to the growing research on serious games for child and adolescent health education campaigns to enhance the impact and effectiveness of health promotion efforts among young populations. Indeed, we believe that using the power of technology and interactive gameplay can potentially revolutionize health education approaches, empowering children and adolescents to make informed decisions and embrace healthier lifestyles for a better future.

Thus, this systematic review aims to synthesize and analyze existing literature to determine the effectiveness and potentiality of serious games in improving health knowledge, attitudes, behaviors, and outcomes among young populations focusing on the following topics: hand, oral and respiratory hygiene, vaccines, antimicrobial resistance (AMR) and sexually transmitted infections (STI).

MATERIALS AND METHODS

Search strategy and data source

This systematic review was constructed and elaborated following the Prepared Items for Systematic Reviews and Meta-Analysis (PRISMA) [7]. Structured electronic searches were performed by referencing four databases: PubMed/Medline, Excerpta Medica Database (Embase), Scopus and Web of Science (WOS). Structured searches were conducted across the four databases on March 16, 2023, using a combination of Medical Subject Headings (MeSH) and free text words. Boolean operators AND and OR were combined to create the search strategy. Filters were also applied. The search strategy was first created in PubMed and then applied to the other databases. The search strategy is presented in *Table S1 available online as Supplementary Materials*.

Inclusion/exclusion criteria

We have decided to include the articles that met the subsequent criteria: (i) written in Italian or English; (ii) population: children and adolescents from 3 to 18 years old (both male and female); (iii) exposure: health education intervention based on serious games; (iv) outcomes: knowledge enhancement (both qualitative and quantitative). In addition, no continent restrictions were imposed.

We have decided to exclude: (i) unpublished articles in Italian or English; (ii) population: <3 and >18 years old or with chronic conditions or disabilities; (iii) exposure: health education intervention based on traditional or other kinds of teaching; (iv) outcomes: improved satisfaction. We also excluded non-original articles (e.g., reviews and meta-analyses) and no full-text articles (e.g., conference proceedings, letters to the editor, commentary notes, abstracts, expert opinions). Inclusion and exclusion criteria are reported in *Table 1*.

Selection process and data extraction

All the studies were collected using Rayyan software [8]. Subsequently, we removed duplicates manually and automatically using Rayyan, under the supervision of one Author (AA). After that, we conducted a two-step screening process. Two team members primarily independently screened all the records (AA and CL) based on titles and abstracts. Afterwards, the eligible studies' full texts were downloaded and double-blindly assessed by two Authors (AA and CL). In every screening step, any discrepancy between the Authors regarding the eligibility of papers was solved through discussion; if the disagreement persisted, it was managed by a third

Table 1
Inclusion/exclusion criteria are based on population, intervention, exposure, outcome, and study design (PEOS) strategy

Search strategy	Details
Inclusion criteria	P: children and adolescents from 3 to 18 years old (both male and female)
	E: health education intervention based on serious games
	O: knowledge enhancement (both qualitative and quantitative)
	S: all original study types
Exclusion criteria	P: <3 and >18 years old; individuals with chronic conditions or disabilities
	E: health education intervention based on traditional teaching
	O: missing data; improved satisfaction
	S: non-original papers; papers without data
Language	English; Italian
Time filter	From January 1, 2013 to March 16, 2023
Databases	PubMed/Medline; Embase; Scopus; Web of Science

PEOS: population, exposure, outcome, study design.

senior reviewer (AM). The Authors used a predefined and standardised Excel spreadsheet (Microsoft Excel® for Microsoft 365 MSO, Redmond, WA, USA, 2019) to extract data from the included articles. At first, the spreadsheet was tested on four randomly selected articles to enhance the Authors' concordance. The Authors agreed to extract the following data: first Author, year of publication, the country where the study took place, number of participants, age, the tool used for knowledge about topics assessment, and the game type.

Strategy for data synthesis

A flow chart was produced to map the included references in every stage of the review process according to the PRISMA 2020 guidelines [7].

RESULTS

Literature search

A total of 1,577 articles were extracted from the databases, of which 617 were from PubMed/Medline, 274 from Embase, 393 from Scopus and 293 from Web of Science. After the first screening, 289 articles were excluded because they were duplicates.

After screening by title and abstract, 102 papers were listed as eligible. Thus, 62 articles were removed after full-text assessment, of which 29 were feasibility studies, 20 were conference abstracts (full text was unavailable), while reading the full text of 5 of the articles, it revealed that they focused on a different population than the stated one and 5 had different outcomes. Moreover, 3 studies were removed because they were written in languages other than Italian and English.

At the end of the screening process, 40 articles were included in the current systematic review. The whole selection process is pictured in detail in *Figure 1*.

Main characteristics of included articles

Table 2 describes the characteristics of the included articles in alphabetical order.

A total of 16 of the 40 included studies had been conducted in Asia [9, 10, 12, 15, 17, 18, 22, 28-30, 34, 41-44, 46], 9 in Europe [11, 13, 19, 23, 27, 31-33, 48], 7 in North America [14, 26, 35, 36, 38-40], 4 in Africa [21, 24, 25, 47], 3 in South America [16, 37, 45], and 1 in Oceania [20]. Among the 40 included studies, 14 involved a game related to oral hygiene [9-11, 18, 22, 26, 28, 29, 34, 41-45], 10 sexually transmitted infections [21, 24, 25, 27, 33, 35, 36, 38-40], 9 hand hygiene [12, 15, 17, 30, 32, 37, 46-48], 4 vaccines [13, 14, 20, 31], 1 respiratory hygiene [16], 1 AMR [23], and 1 concerned vaccination, respiratory hygiene and AMR at the same time [19]. More specifically, 75% (3) of the studies performed on the African continent included games that would enhance participants' knowledge about STIs [21, 24, 25]. Of the 16 Asian studies, 69% (11) focused on oral hygiene [9, 10, 18, 22, 28, 29, 34, 41-44], while the remaining 31% (5) on hand hygiene [12, 15, 17, 30, 46]. The European studies were more heterogeneous: 2 concerned vaccinations [13, 31], 2 STI [27, 33], 2 hand hygiene [32, 48], 1 AMR [23], 1 oral hygiene [11], while 1 study included vaccinations, AMR and respiratory hygiene [19]. 5 of the 7 articles from North America focused on STI [35, 36, 38-40], while the remaining two focused on vaccinations [14], and oral hygiene [26]. The South American articles included games on hand [37], respiratory [16], and oral hygiene [45]. Finally, the only article published in Oceania was about vaccinations [20].

Regarding the average age of the study participants, it was planned to divide them into four age groups corresponding to the school grades: 3-5 years old for kindergarten, 6-10 elementary, 11-13 middle and 14-18 high school. Moreover, to classify the participants of each study into one of the four categories, it was considered the average age of each sample; thus, 9 studies belonged to the 3-5 year range [9, 12, 16, 37, 41, 43-45, 48], 14 into 6-10 [10, 11, 15, 17, 18, 22, 23, 26, 30, 31, 34, 42, 46, 47], 8 into 11-13 [14, 19, 20, 24, 25, 28, 29, 32, 35], and 9 into 14-18 [13, 21, 27, 29, 33, 36, 38-40]. Out of 9 studies that targeted kindergarten children, 4 concerned oral hygiene [9, 41, 43, 44], the same number of hand hygiene [12, 37, 45, 48], and only one respiratory hygiene [16]. For the 6-10 age group, most of the games dealt with oral hygiene [10,

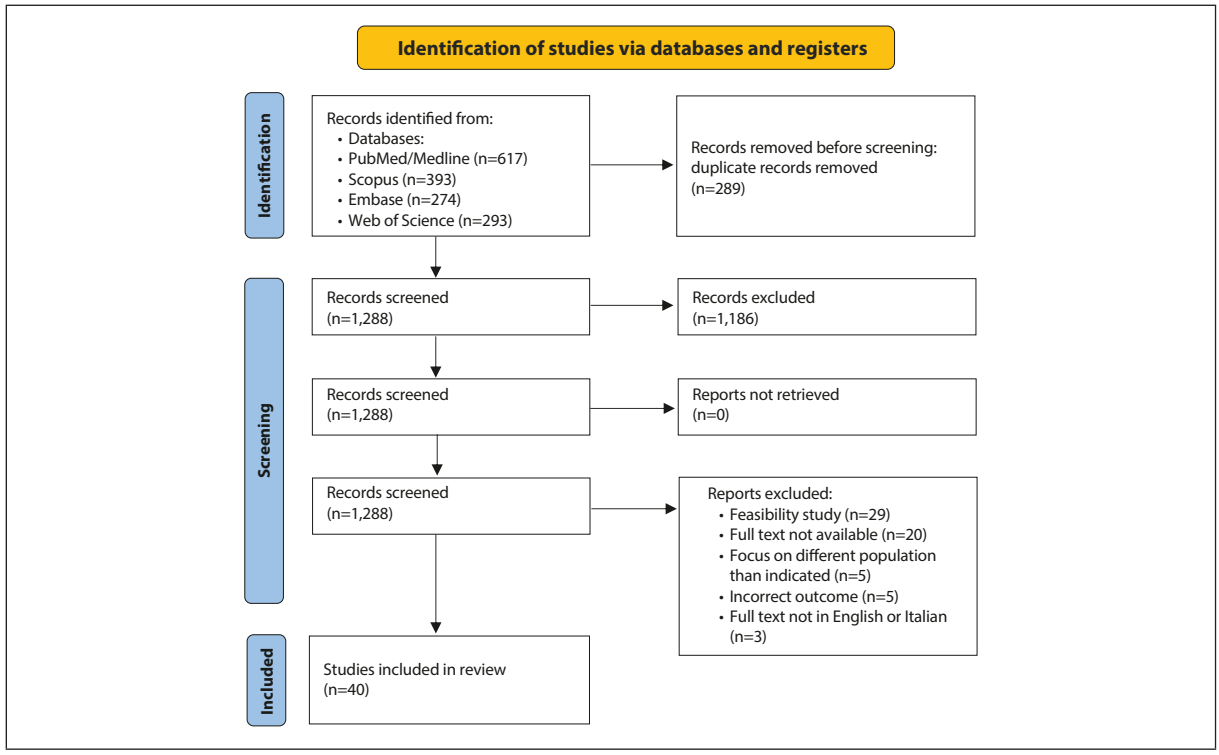

Figure 1
PRISMA flow diagram reporting the selection process.

Table 2
General characteristics of the included studies, in alphabetical order

Author and year of publication	Country	Average age	Topic	Type of game (intervention)	Sample size
Akkaya *et al.*, 2021 [9]	Turkey	5 years	Oral hygiene	Music video	n=100
Aljafari *et al.*, 2022 [10]	Jordan	6.5 years	Oral hygiene	Simulation	n=278
Aljafari *et al.*, 2017 [11]	England	7 years	Oral hygiene	Quiz	n=109
Arbianingsih *et al.*, 2018 [12]	Indonesia	5 years	Hands hygiene	Simulation	n=120
Carolan *et al.*, 2018 [13]	England	14.5 years	Vaccination	Simulation	n=63
Cates *et al.*, 2020 [14]	USA	11.5 years	HPV vaccination	Simulation	n=110
Chen *et al.*, 2022 [15]	Taiwan	8.5 years	Hands hygiene	Board game/Simulation	n=26
Costa *et al.*, 2019 [16]	Brasil	3.5 years	Respiratory hygiene	Card game/Puppets/Simulation	n=39
Devkota *et al.*, 2020 [17]	Nepal	6 years	Hands hygiene	Card game/Manual game/Music video/Simulation	n=50
Effendi *et al.*, 2021 [18]	Indonesia	7.5 years	Oral hygiene	Card game	n=54
Eley *et al.*, 2019 [19]	United Kingdom	11.5 years	Vaccination, Antibiotics, Respiratory hygiene	Role play/Simulation	n=473
Epstein *et al.*, 2021 [20]	Australia	12.5 years	Vaccination	Card game/Simulation	n=3,087
Gaughran *et al.*, 2014 [21]	Kenya	16.5 years	STI	Manual game/Role play	n=42
GeethaPriya *et al.*, 2019 [22]	India	8.5 years	Oral hygiene	Board game/Card game/Theatre	n=360
Hale *et al.*, 2017 [23]	United Kingdom	10 years	Correct use of antibiotics	Role play	n=153
Haruna *et al.*, 2019 [24]	Tanzania	13 years	STI	Role play	n=348
Haruna *et al.*, 2018 [25]	Tanzania	13 years	STI	Quiz	n=120
Jacobson *et al.*, 2019 [26]	USA	5.5 years	Oral hygiene	Music video/Puppets	n=34
Jerlström *et al.*, 2020 [27]	Sweden	15 years	STI	Role play/Theatre	n=826
Kashyap *et al.*, 2022 [28]	India	12 years	Oral hygiene	Quiz	n=160

Continues

Table 2
Continued

Author and year of publication	Country	Average age	Topic	Type of game (intervention)	Sample size
Kumar *et al.*, 2022 [29]	India	13.5 years	Oral hygiene	Music video	n=100
Kusumawardani *et al.*, 2020 [30]	Indonesia	9 years	Hands hygiene	Board game	n=126
La Torre *et al.*, 2020 [31]	Italy	7 years	Vaccination	Board game/Card game/Motion game	n=143
Larsen *et al.*, 2021 [32]	Denmark	11 years	Hands hygiene	Motion game	n=3,127
Macounová *et al.*, 2021 [33]	Czech Republic	16 years	STI	Manual game /Simulation	n=1,210
Malik *et al.*, 2017 [34]	India	10 years	Oral hygiene	Quiz	n=150
Markham *et al.*, 2020 [35]	USA	12.5 years	STI	Simulation	n=4,531
McCammon *et al.*, 2020 [36]	USA	15 years	STI	Board game	n=44
Mendes *et al.*, 2020 [37]	Brasil	3 years	Hands hygiene	Card game/Manual game music video /Puppets	n=126
Peskin *et al.*, 2019 [38]	USA	14.5 years	STI	Simulation	n=1,543
Potter *et al.*, 2016 [39]	USA	14.5 years	STI	Simulation	n=3,143
Rohrbach *et al.*, 2019 [40]	USA	14.5 years	STI	Simulation	n=4,562
Salikun *et al.*, 2021 [41]	Indonesia	4 years	Oral hygiene	Simulation	n=18
Sharma *et al.*, 2021 [42]	India	9.5 years	Oral hygiene	Board game/Card game	n=300
Shi *et al.*, 2023 [43]	China	4.5 years	Oral hygiene	Board game	n=160
Shruti *et al.*, 2021 [44]	India	4.5 years	Oral hygiene	Puppets	n=200
Sigaud *et al.*, 2017 [45]	Brasil	4 years	Hands hygiene	Card game/Music video/Simulation	n=44
Tidwell *et al.*, 2020 [46]	India	10 years	Hands hygiene	Music video/Puppets/Simulation	n=225
Winter *et al.*, 2021 [47]	Zambia	9.5 years	Hands hygiene	Board game	n=761
Younie *et al.*, 2020 [48]	England	4.5 years	Hands hygiene	Manual game/Music video/ Simulation	n=225

STI: sexually transmitted infections; HPV: human papilloma virus.

11,18, 22, 26, 34, 42], 5 with hand hygiene [15, 17, 45-47], 1 with vaccinations [31], and 1 with AMR [23]. The studies involving middle school students were much more heterogeneous: 3 concerned STI [24, 25, 35], 2 vaccinations [14, 20], one oral hygiene [28], and one hand hygiene [32]. One study dealt simultaneously with vaccinations, AMR and respiratory hygiene [19]. Out of 9 studies targeting high school adolescents, 7 articles were about STI [21, 27, 33, 36, 38-40], while only 1 was about oral hygiene [29], and 1 was about vaccinations [13].

The sample size ranges from a minimum of 18 [41], to a maximum of 4562 people [40]. Furthermore, we categorised the papers according to the type of game that had been implemented. First of all, it was evaluated whether it involved using a digital device (computer, tablet, smartphone) or not: 15 required it [10-14, 19, 23, 24, 26, 29, 35, 38-41], 24 did not [9, 15-18, 20-22, 25, 27, 28, 30-34, 36, 37, 42-47], while just one article implemented games involving both modes [48]. Then, we classified the studies according to the game type: 18 simulations [10, 12-17, 19, 20, 33, 35, 38-41, 45, 46, 48], 9 card games [16-18, 20, 22, 31, 37, 42, 45], 8 music videos [9, 17, 26, 29, 37, 45, 46, 48], 8 board games [15, 22, 30, 31, 36, 42, 43, 47], 5 games using puppets [16, 26, 37, 44, 46], 5 manual games [17, 21, 33, 37, 48], 5 role plays [19, 21, 23, 24, 27], 4 quizzes [11, 25, 28, 34], 2 theatre games [22, 27], and 2 motion games [31, 32]. Most studies have included more than one game mode. Among games that used electronic devices the most frequently were simulations [10, 12-14, 19, 35, 38-41, 48], role-playing [19, 23, 24], and music videos [26, 29, 48]. Among offline games, on the other hand, the most used were cards [16-18, 20, 22, 31, 37, 42, 45], simulations [15-17, 20, 33, 45, 46, 48], and board games [15, 22, 30, 31, 36, 42, 43, 47], while the least used were role-playing games [21, 27]. 25 studies compared the intervention group, provided with educational game-based instruction, with a control group, offered traditional instruction [9-14, 18, 20, 22, 24, 25, 27-30, 32, 34, 38-43, 46, 48]. The remaining 15 did not include a control group [15-17, 19, 21, 23, 26, 31, 33,

35-37, 44, 45, 47]. Almost all studies (37) showed an improvement in the knowledge of the health topic in the intervention group [9, 11, 12, 14-19, 21-48]. Only 3 showed no significant improvement [10, 13, 20].

DISCUSSION

This review provides a comprehensive overview about the use and evidence on the effectiveness of serious games in child and adolescent health education campaigns. Articles published between 2013 and 2023 were considered, and 10 types of games used in educational campaigns were identified. Although including four age groups, from 3 to 18 years, the most represented age group in the studies was the 6-10 years old. The findings confirm that games can be an effective tool for promoting healthy behaviors among children and adolescents. The review identified many studies that have shown the positive effects of serious games on health outcomes. Additionally, 37 out of 40 studies have found that serious games can improve knowledge and health literacy. Despite differences in study settings and other aspects, the results agree. However, each intervention had unique characteristics and structure, sometimes making direct comparisons difficult.

It should not be overlooked that there are factors that can contribute to the effectiveness of serious games, including game design, target audience and implementation [49]. The design of a game can have a significant impact on its effectiveness. Well-designed games are more likely to be engaging and motivating for children and adolescents [50]. They should also be relevant to the target audience's interests and needs [51]. Games should be designed for their target audience's specific needs and interests. Moreover, the target of a serious game, e.g., the segment of the population the game is designed for, severely influences its "technical" characteristics and educational elements [52]. Age and cultural background are key elements in building the game appropriately according to the target audience. Some other specific factors that can contribute to the game's effectiveness are narrative and graphics [53].

The implementation of a serious game is also important for its effectiveness. According to the literature, games should be implemented as part of a comprehensive health education program to have a lasting impact, and the game's effectiveness should be evaluated to ensure that it meets its intended goals [54]. Most public health interventions end with the message being conveyed to the audience. Instead, in interventions conveyed by interactive games for children and adolescents, topics must be presented in an accessible way, and the audience is challenged to examine their understanding [55]. In this way, the population is engaged in the important concepts, thereby increasing their engagement in understanding the same topic. It is known that complete immersion while performing an activity enhances learning [56]. Examples in this regard are "those occasions when we experience a sense of euphoria, a deep sense of enjoyment, which we retain for a long time and which becomes a landmark in our lives", called "optimal experiences" by [57] and before him "peak experiences" by Maslow (1964) [58] and "ecstatic experiences" by Laski (1961) [59]. Again, according to Csikszentmihalyi, these tend to occur when a person's body or mind is pushed to the limit in a voluntary effort to accomplish something difficult or useful [57].

Games are therefore very effective in increasing knowledge about the topics covered because they involve significantly more involvement than traditional teaching. Although few of the studies reviewed analyze the long-term change in knowledge, there is no question of the short-term increase in knowledge [9, 11, 12, 14-19, 21-48].

However, a common measurement tool would need to be developed to standardize the measurement of the effects of each intervention conveyed through play. The lack of a common outcome measurement tool makes it difficult to compare these interventions and determine what best educates children and adolescents and influences behavior change.

Limitations

Our study aimed to identify interventions and their benefits in educating children and adolescents with serious games about hand, oral and respiratory hygiene, immunisation, AMR and sexually transmitted infections. We had to adopt a narrative synthesis approach as each intervention had different outcome and evaluation methods, so a meta-analysis was impossible. Then, it was not possible to evaluate the interventions against each other directly using statistical analysis. In addition, only a few studies have measured long-term outcomes related to interventions, and it has not been possible to investigate the existence of effective long-term knowledge retention in all interventions.

CONCLUSIONS

New competencies may be learned through active experience with experiential learning or learning by doing or observation of others' experiences in learning by observation [60]. In fact, this review confirms findings in the literature that serious games can be a valuable tool for promoting healthy behaviors and improving health literacy among children and adolescents. We think it is important, quoting Plato: "Do not educate children in the various disciplines by resorting to force, but as by play, so that you may also better observe what the natural disposition of each one is". The key point, along with the significant increase in knowledge over the use of traditional teaching, lies in the involvement of children and young adults during learning. Indeed, there is no doubt about the improvement of knowledge through the use of games; however, we believe that the next step can be a more detailed investigation regarding the speed in changing behaviors and the assumption of virtuous behaviors following the acquisition of new knowledge through games. Indeed, the next step in educational campaigns using games is to quickly achieve a change in young people's behaviors in favor of virtuous behavior.

However, further research is needed to identify the most effective ways to design, implement, and evaluate serious games for health education. Further research is needed to identify the most effective game design

elements for promoting healthy behaviors among children and adolescents, particularly among hard-to-reach populations without Internet access. Further research is needed to evaluate the effectiveness of serious games in combination with other health education interventions. Developers of serious games should consider incorporating health behavior change theoretical frameworks into game design. Practitioners should consider the target audience, game design and implementation plan when using serious games for health education.

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Conflict of interest statement

Each Author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethics approval

Ethical review and approval were not necessary given the nature of the paper.

Authors' contributions

Conceptualization, AA and AM; methodology, AA, CL and DG; emtree terms control, DG; validation, AA; investigation, AA and CL; data curation, AA; writing-original draft preparation, AA and CL; writing-review and editing, AA, and CL and FC; supervision, AM. All Authors have read and agreed to the published version of the manuscript.

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Pandemic impact on training and mental health of medical residents: an Italian multicentre prospective study

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Abstract

Objective. To describe the mental health of Italian medical residents during COVID-19 pandemic and explore the impact of personal and work-related changes on their mental health.

Methods. A multicentre prospective study was conducted on a sample of Italian residents across five timepoints (February-October 2021). Mental health outcomes (symptoms of post-traumatic stress disorder, PTSD, depression, anxiety, poor sleep quality) were assessed. Regressions analysed the association between pandemic-related personal and professional changes and the mental health outcomes.

Results. Participants were 451. From February to October 2021, the prevalence of symptoms ranged from 21.6% to 12.7% (PTSD), 29.8% to 16.2% (depression), 36.2% to 28.8% (anxiety), 15.2% to 5.7% (sleep). Several work-related changes were significantly associated with symptoms, e.g. a perceived negative training change was associated with all outcomes; increased working hours with PTSD, depression, and anxiety; reallocation to tasks far from expertise area with PTSD.

Conclusions. Residents reported a relevant frequency of mental issues. Many work-related changes were associated with poor mental health.

Key words

- education, medical, graduate
- internship and residency
- COVID-19
- mental health

INTRODUCTION

The COVID-19 pandemic caused a public health crisis that seriously affected medical and surgical practice [1-3]. Most countries reported the disruption of at least one essential health service [4, 5]. If on the one hand the pandemic reduced many services, on the other it generated a high demand for healthcare assistance. The impossibility of working in proper conditions, with increased workloads, organizational unpreparedness, and lack of resources caused healthcare professionals (HCPs) to feel scared, anxious, and even burnout [6]. Many physicians and residents were reallocated from their activities to emergency departments or COVID-19 wards due to a shortage of personnel [7].

HCPs were exposed to psychological distress, especially those who worked with COVID-19 patients [2, 8-10]. High risk of contagion, inadequate protection, lack of experience, negative feedback from patients, social stigma, and isolation were all factors potentially influencing mental health. Working in such conditions could cause depression, anxiety, post-traumatic stress disorder (PTSD), insomnia, and fear, affecting HCP well-being and their effectiveness at work [2, 8-10].

Medical residents are particularly at risk, as they are physicians or surgeons in a formation process, and both younger age and less experience are important distress risk factors [7]. Already before the pandemic, this population reported poor mental health outcomes, both considering their previous path as medical students [11, 12] and their residency training, which is well-known to be very stressful as residents are often burdened by long working hours, high workloads, and personal time inadequacy [13]. Although without considering clinical diagnoses, many studies evaluated the pandemic impact

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on the mental health of residents [1, 14-16], mostly considering stress, anxiety, and depression symptoms and showing results consistent with other HCPs [2, 8-10]. For instance, a study on French urology residents revealed that over 90% of respondents felt more stressed during the pandemic, with senior residents particularly affected by the crisis's impact on work quality [1]. In South Korea, orthopaedic residents reported that their quality of life scores dropped significantly during the pandemic [14]. In the UK, 64% of cardiothoracic surgical trainees expressed concerns about their mental health, with significant reductions in clinical training opportunities and fears about personal protective equipment provision [15]. A US study found that nearly half of the otolaryngology residents experienced anxiety or distress, with residents reporting higher burnout rates compared to attendings [16]. Most of the data are cross-sectional and focus on specific subpopulations of residents, limiting the ability to provide a comprehensive picture of residents' mental health across different pandemic phases. As far as we know, few studies have been conducted in Italy, where the healthcare system has been widely disrupted by the pandemic [17].

Therefore, the primary aim of this prospective multicentre study was to assess the mental health of Italian residents across different pandemic periods, exploring whether pandemic-related changes in personal and working life might influence mental health symptoms. Secondarily, this work aimed to provide a glimpse of the changes in the training and work of residents during this unprecedented situation.

MATERIALS AND METHODS

Study design

A multicentre prospective study was conducted amongst a convenience sample of medical residents. The centres were 4 universities selected by convenience in different Italian regions, from North to South. The study was approved by the Ethics Committee of the University of Turin (Piedmont), which was the leading centre. First-year residents were excluded since they began their residency in November 2020, thus they worked as residents only a few months before the study began.

Residents were recruited via email thanks to university administrative offices. Informed consent was obtained. Participation was voluntary and participants received no compensation. Individuals were asked to create a nickname according to rules decided by the researchers to match data across timepoints. The researchers did not know the respondents' identity.

In 2021, the survey was repeated every two months: February (T0), April (T1), June (T2), August (T3), and October (T4). At each timepoint, the survey could be completed within two weeks.

The questionnaire

Four sections of the questionnaire were developed by the researchers after a study of literature on residents and mental health during the pandemic. The following topics were identified as relevant: economic situation [2, 18], living conditions [19], worries about the health of family and loved ones [14, 20], having a loved one belonging to a vulnerable group for COVID-19 [21], personal medical history [1], having contracted SARS-CoV-2 [21], year of residency [1, 20], worries about residency training and education [18, 21], perception of availability of personal protective equipment (PPE) [21, 22], changes in working tasks [21], treating COVID-19 positive patients [1, 2]. The fifth section included 4 validated tools to assess the outcomes.

Two versions of the questionnaire were created. A long one for T0 and a shorter one for the remaining timepoints.

The T0 questionnaire included a first section with sociodemographic and residency-related items. Items about living conditions were repeated at each timepoint. Most items from the second to the fourth section referred both to the period of the first lockdown (between March and May 2020) and to the period when the survey was conducted (considering the last two months). Items concerning the lockdown were explored only at T0. The second section investigated the pandemic impact on the private life of the residents and the third part the impact on the professional life. The fourth section explored work-related exposure to COVID-19 and the perception of PPE availability at work. In the last section, mental health was assessed. The English translation of the questionnaire developed by the Authors is *available online as Supplementary Material.*

PTSD symptoms were evaluated with the primary care (PC) PTSD screen for DSM-5 (PC-PTSD-5), adapted to ask about pandemic-related events over the last month. If participants answered "Yes" at least to 3 items the test was above the cut-off for PTSD [23]. The Patient Health Questionnaire-2 (PHQ-2) explores symptoms over the last two weeks and a score of 3 or higher represents a higher probability of having a depressive disorder [24]. The Generalized Anxiety Disorder-2 (GAD-2) assesses symptoms over the same period and a score of 3 or higher represents a higher probability of having an anxiety disorder [25]. The Single-Item Sleep Quality Scale (SQS) is one item that evaluates the quality of sleep during the last 7 days: a score of 3 or lower represents a poor/terrible quality of sleep [26].

Statistical analysis

Participants who completed only one questionnaire were excluded. To analyse possible differences in the outcomes at T0 between participants who completed only T0 and participants who completed at least another questionnaire, chi-squared tests were used. The same analysis was repeated between participants who completed only T0 and participants who completed all timepoints. To further evaluate missing outcome data, the scores of the outcomes at each timepoint were tested with the Little's missing completely at random (MCAR) test.

The main analyses were conducted on a sample composed of residents who completed at least two questionnaires. Questionnaires completed by the same resident were matched through nicknames. Each timepoint was not necessarily composed of the same participants.

Descriptive analyses were done for all variables at each timepoint. Age had a non-normal distribution

(Shapiro-Wilk test) and was described as the median and interquartile range (IQR). To compare the proportion of each variable across the timepoints, chi-squared tests were executed. To explore the variables associated with mental health outcomes, multilevel mixed-effect multiple logistic regression models were run (levels: university; participant). Overall, models were adjusted by gender and covariates were selected based on *p*-values at univariable analyses. Results were expressed as adjusted odds ratio (adjOR) and 95% confidence interval (CI).

To explore if the results were confirmed considering only participants who completed all the timepoints, a sensitivity analysis was performed in such longitudinal subsample. Descriptive analyses were repeated. The overall sample and the longitudinal subsample characteristics at T0 were compared through chi-squared tests. To compare the subsample characteristics across timepoints the related-samples Cochran's Q test was performed. The same multilevel multiple regression models were re-run on this subsample.

The analyses were executed with STATA v16 and SPSS v26 software. Significance was set at *p*-value<0.050.

RESULTS

Characteristics of the sample

A total of 451 residents completed at least two questionnaires and were analysed (Little's MCAR test *p*-value=0.778). Considering the outcomes at T0, participants who completed only T0 and participants who completed at least another questionnaire were not different (PC-PTSD-5: p=0.452; PHQ-2: p=0.803; GAD-2: p=0.228; SQS: p=0.517). A total of 97 participants completed all timepoints. Also in this case, these participants were not different from the ones who completed only T0 (PC-PTSD-5: p=0.601; PHQ-2: p=0.908; GAD-2: p=0.702; SQS: p=0.752).

Table 1 shows time-invariant variables explored at T0. The median age was 30 years (IQR=29-32). The most frequent changes during the lockdown were reallocation to tasks (very different from the usual ones but within their expertise area) and changes in working hours. *Table S1 available online as Supplementary Material* shows the descriptive analysis for the same variables in the longitudinal subsample; no significant differences between the overall sample and this subsample were revealed.

Table 2 shows time-varying variables reporting the changes related to the pandemic impact on personal, academic, and working life. The location of the university was not differently distributed across timepoints (p=0.834). Some variables significantly changed, e.g. perceived negative impact of the pandemic on training, reallocation, increased working hours, and working with COVID-19 patients were more frequent during the first timepoints. *Table S2 available online as Supplementary Material* shows time-varying variables for the longitudinal subsample. Also for these variables, no significant differences between the overall sample and this subsample at T0 were reported. Similarly to relationships reported for the overall sample, the related-samples Cochran's Q tests showed that the distribution across timepoints was significantly different for some work-related variables, e.g. holding a pandemic-related contract, reallocation of tasks, working with COVID-19 patients, having been isolated or tested positive, and having received COVID-19 vaccine.

Mental health outcomes

PTSD was present in 21.6% (T0), 24.2% (T1), 15.4% (T2), 12.0% (T3), and 12.7% (T4) of participants (p<0.001). Considering depressive symptoms, participants above the cut-off were 29.8% (T0), 29.2% (T1), 23.2% (T2), 17.5% (T3), and 16.2% (T4) of the sample (p<0.001). Anxiety was likely in 36.2% (T0), 34.5% (T1), 31.2% (T2), 22.6% (T3), and 28.8% of residents (T4) (p<0.007). Poor sleep was reported by 15.2% (T0), 13.7% (T1), 13.1% (T2), 10.6% (T3), and 5.7% of participants (T4) (p<0.009). *Table S3 available online as Supplementary Material* shows the outcomes in the longitudinal subsample (no significant differences at T0 with the overall sample). Related-samples Cochran's Q test confirmed similar relationships as reported for the overall sample considering PTSD, depressive symptoms, and sleep.

The multivariable models (*Table 3*) reported many significant relationships. Some locations of universities showed differences from the leading university for PTSD, depressive, and anxiety symptoms. Overall, participants who completed the questionnaire during the last 3 timepoints had a lower likelihood of poor mental health. Specifically, compared with T0, at T2 participants had a lower likelihood of reporting PTSD (adjOR=0.42, 95% CI 0.22-0.82) and depressive symptoms (adjOR=0.55, 95% CI 0.32-0.93). At T3, participants had a lower likelihood of reporting PTSD (adjOR=0.45, 95% CI 0.21-0.99), depressive symptoms (adjOR=0.35, 95% CI 0.19-0.67), and anxiety symptoms (adjOR=0.39, 95% CI 0.22-0.69). At T4, participants had a lower likelihood of reporting depressive symptoms (adjOR=0.38, 95% CI 0.20-0.72) and poor sleep quality (adjOR=0.23, 95% CI 0.08-0.61). Women had higher odds of PTSD (adjOR=2.38, 95% CI 1.12-5.06), depressive symptoms (adjOR=2.18, 95% CI 1.16-4.09), and anxiety (adjOR=2.58, 95% CI 1.41-4.70). Other socio-demographic characteristics were associated with worse mental outcomes, both non-COVID-19-related and COVID-19-related. Specifically, the following variables significantly increased the likelihood of reporting symptoms: worsening of the economic situation due to the pandemic (depressive symptoms: adjOR=2.87, 95% CI 1.29-6.37), loved ones suffering from COVID-19 (PTSD: adjOR=5.91, 95% CI 2.76-12.65), and having children (poor sleep quality: adjOR=5.48, 95% CI 1.46-20.45). Several specialization-related variables revealed significant associations, with higher odds of reporting symptoms: reallocations to tasks far from the area of expertise (PTSD: adjOR=3.12, 95% CI 1.2-8.09) or within the area of expertise (depressive symptoms: adjOR=1.82, 95% CI 1.04-3.20), increased working hours (PTSD: adjOR=2.59, 95% CI 1.41-4.76; depressive symptoms: adjOR=2.26, 95% CI 1.34-3.78; anxiety symptoms: adjOR=2.57, 95% CI 1.59-4.15), positive change in training due to the pandemic (PTSD: adjOR=4.77, 95% CI 1.83-12.43), and negative change

Table 1
Descriptive analysis of time invariant variables at T0

Characteristic		Sample at T0 (n=356)	
		N	%
Gender	Male	124	34.83
	Female	229	64.33
	Non-binary	3	0.84
Area of specialization	Medical area	178	50.00
	Surgical area	58	16.29
	Clinical services area	120	33.71
Specialization related to Emergency-Urgency area	No	290	81.50
	Yes	66	18.50
Location of University	Piedmont	169	47.47
	Friuli-Venezia Giulia	77	21.63
	Emilia Romagna	67	18.82
	Sicily	43	12.08
Year of specialization	2	122	34.27
	3	104	29.21
	4	85	23.88
	5	45	12.64
Nationality	Italian	354	99.44
	Other	2	0.56
Having children	No	326	91.57
	Yes	30	8.43
Belonging to a risk group for COVID-19 complications	No	348	97.75
	Yes	8	2.25
Loved ones belonging to a risk group for COVID-19 complications	No	130	36.52
	Yes	226	63.48
Change of living condition during the first lockdown due to the pandemic (e.g., to not share the house with frail individuals)	No	299	83.99
	Yes, less than one month	18	5.06
	Yes. more than one month	39	10.96
Psychological/psychopharmacological support during lockdown (not needed before the pandemic)	No	336	94.38
	Yes	20	5.62
Reallocation to tasks that, according to the participant, are too far from his/her area of expertise (during the lockdown)	No	321	90.17
	Yes	35	9.83
Reallocation to tasks that are very different from the usual ones but still within their area of expertise (during lockdown)	No	266	74.72
	Yes	90	25.28
Working hours substantially modified due to the pandemic (during lockdown)	No	127	35.67
	Reduced	119	33.43
	Increased	110	30.90
Working from home for most of the working hours (during lockdown)	No	318	89.33
	Yes	38	10.67
In the department where he/she worked, COVID-19 patients were treated (during lockdown)	No	183	51.40
	Yes	173	48.60
The department where he/she worked was entirely dedicated to the treatment of COVID-19 patients (during lockdown)	No	282	79.21
	Yes	74	20.79
The participant personally treated COVID-19 patients (during lockdown)	No	228	64.04
	Yes	128	35.96
The participant felt that the available PPE at work was enough to keep him/her safe (during lockdown)	No	203	57.02
	Yes	153	42.98

n=sample size; figures are expressed as number (N) and column percentages (%); PPE: personal protective equipment.

Table 2
Descriptive analysis of time varying variables across timepoints

Characteristic		T0 n=356 N (%)	T1 n=380 N (%)	T2 n=298 N (%)	T3 n=217 N (%)	T4 n=229 N (%)	*p*-value
Living condition	Alone	103 (28.93)	108 (28.42)	82 (27.52)	65 (29.95)	59 (25.76)	0.879
	Flatmates	42 (11.8)	42 (11.05)	27 (9.06)	24 (11.06)	25 (10.92)	
	Family	41 (11.52)	32 (8.42)	29 (9.73)	19 (8.76)	24 (10.48)	
	Partner w/wo children	169 (47.47)	195 (51.32)	160 (53.69)	109 (50.23)	120 (52.4)	
	Other	1 (0.28)	3 (0.79)	0 (0)	0 (0)	1 (0.44)	
Change of living condition	No	324 (91.01)	331 (87.11)	272 (91.28)	202 (93.09)	213 (93.01)	0.131
	Yes, less than one month	12 (3.37)	26 (6.84)	12 (4.03)	8 (3.69)	5 (2.18)	
	Yes. more than one month	20 (5.62)	23 (6.05)	14 (4.7)	7 (3.23)	11 (4.8)	
The pandemic is causing a substantial change of the economic situation of the participant's family	No	281 (78.93)	295 (77.63)	225 (75.5)	170 (78.34)	184 (80.35)	0.593
	Yes, it improved	48 (13.48)	60 (15.79)	49 (16.44)	37 (17.05)	35 (15.28)	
	Yes, it worsened	27 (7.58)	25 (6.58)	24 (8.05)	10 (4.61)	10 (4.37)	
Psychological/ psychopharmacological support (not needed before the pandemic)	No	325 (91.29)	337 (88.68)	268 (89.93)	197 (90.78)	204 (89.08)	0.784
	Yes	31 (8.71)	43 (11.32)	30 (10.07)	20 (9.22)	25 (10.92)	
Fear of personally contracting COVID-19 in relation to potential consequences on one's own health	None	43 (12.08)	60 (15.79)	53 (17.79)	40 (18.43)	30 (13.1)	0.080
	Little	165 (46.35)	194 (51.05)	147 (49.33)	108 (49.77)	134 (58.52)	
	Moderate	131 (36.8)	114 (30)	87 (29.19)	61 (28.11)	56 (24.45)	
	A lot	17 (4.78)	12 (3.16)	11 (3.69)	8 (3.69)	9 (3.93)	
Fear of personally contracting COVID-19 in relation to potential consequences on the health of one's loved ones	None	3 (0.84)	6 (1.58)	8 (2.68)	4 (1.84)	7 (3.06)	**<0.001**
	Little	17 (4.78)[b]	29 (7.63)[b]	35 (11.74)	37 (17.05)	45 (19.65)	
	Moderate	118 (33.15)[b]	158 (41.58)	140 (46.98)	104 (47.93)[a]	105 (45.85)[a]	
	A lot	218 (61.24)[a]	187 (49.21)[a]	115 (38.59)[b]	72 (33.18)[b]	72 (31.44)[b]	
A loved one has suffered serious health damage after COVID-19	No	324 (91.01)	323 (85)[b]	262 (87.92)	189 (87.1)	214 (93.45)[a]	**0.012**
	Yes	32 (8.99)	57 (15)[a]	36 (12.08)	28 (12.9)	15 (6.55)[b]	
Holder of a contract entered into following urgent provisions for the pandemic	No	296 (83.15)[a]	233 (61.32)[b]	206 (69.13)	158 (72.81)	182 (79.48)[a]	**<0.001[c]**
	Yes	60 (16.85)[b]	147 (38.68)[a]	92 (30.87)	59 (27.19)	47 (20.52)[b]	
Reallocation to tasks that, according to the participant, are too far from his/her area of expertise	No	338 (94.94)	352 (92.63)	283 (94.97)	208 (95.85)	219 (95.63)	0.382
	Yes	18 (5.06)	28 (7.37)	15 (5.03)	9 (4.15)	10 (4.37)	
Reallocation to tasks that are very different from the usual ones but still within their area of expertise	No	296 (83.15)	296 (77.89)[b]	234 (78.52)	184 (84.79)	203 (88.65)[a]	**0.005[c]**
	Yes	60 (16.85)	84 (22.11)[a]	64 (21.48)	33 (15.21)	26 (11.35)[b]	
Working hours substantially modified due to the pandemic	No	230 (64.61)	212 (55.79)[b]	195 (65.44)	147 (67.74)	164 (71.62)[a]	**0.003**
	Reduced	15 (4.21)[b]	35 (9.21)[a]	22 (7.38)	13 (5.99)	12 (5.24)	
	Increased	111 (31.18)	133 (35)[a]	81 (27.18)	57 (26.27)	53 (23.14)[b]	
Working from home for most of the working hours	No	352 (98.88)	377 (99.21)	293 (98.32)	216 (99.54)	229 (100)	0.294
	Yes	4 (1.12)	3 (0.79)	5 (1.68)	1 (0.46)	0 (0)	
Believing that the pandemic is substantially changing one's specialization training	No	81 (22.75)[b]	100 (26.32)[b]	112 (37.58)	96 (44.24)[a]	112 (48.91)[a]	**<0.001**
	Yes, positively	54 (15.17)	51 (13.42)	42 (14.09)	33 (15.21)	24 (10.48)	
	Yes, negatively	221 (62.08)[a]	229 (60.26)[a]	144 (48.32)	88 (40.55)[b]	93 (40.61)[b]	
In the department where he/she worked, COVID-19 patients were treated	No	159 (44.66)	152 (40)[b]	124 (41.61)	111 (51.15)	134 (58.52)[a]	**<0.001[c]**
	Yes	197 (55.34)	228 (60)[a]	174 (58.39)	106 (48.85)	95 (41.48)[b]	

Continues

Table 2
Continued

Characteristic		T0 n=356 N (%)	T1 n=380 N (%)	T2 n=298 N (%)	T3 n=217 N (%)	T4 n=229 N (%)	*p*-value
The department where he/she worked was entirely dedicated to the treatment of COVID-19 patients	No	279 (78.37)	280 (73.68)[b]	227 (76.17)	179 (82.49)	200 (87.34)[a]	**0.001**[c]
	Yes	77 (21.63)	100 (26.32)[a]	71 (23.83)	38 (17.51)	29 (12.66)[b]	
The participant personally treated COVID-19 patients	No	208 (58.43)	186 (48.95)[b]	159 (53.36)	126 (58.06)	154 (67.25)[a]	**<0.001**[c]
	Yes	148 (41.57)	194 (51.05)[a]	139 (46.64)	91 (41.94)	75 (32.75)[b]	
Having been in isolation due to suspicion or diagnosis of COVID-19	No	217 (60.96)[b]	284 (74.74)	251 (84.23)[a]	190 (87.56)[a]	204 (89.08)[a]	**<0.001**[c]
	Yes	139 (39.04)[a]	96 (25.26)	47 (15.77)[b]	27 (12.44)[b]	25 (10.92)[b]	
Having tested positive for COVID-19 through a swab test	No	308 (86.52)[b]	338 (88.95)	280 (93.96)	207 (95.39)[a]	218 (95.2)[a]	**<0.001**[c]
	Yes	48 (13.48)[a]	42 (11.05)	18 (6.04)	10 (4.61)[b]	11 (4.8)[b]	
The participant felt that the available PPE at work was enough to keep him/her safe	No	37 (10.39)	63 (16.58)[a]	50 (16.78)[a]	22 (10.14)	21 (9.17)	**0.005**
	Yes	319 (89.61)	317 (83.42)[b]	248 (83.22)[b]	195 (89.86)	208 (90.83)	
Having already received anti-COVID-19 vaccine	No	36 (10.11)[a]	13 (3.42)	4 (1.34)[b]	3 (1.38)[b]	2 (0.87)[b]	**<0.001**[c]
	Yes	320 (89.89)[b]	367 (96.58)	294 (98.66)[a]	214 (98.62)[a]	227 (99.13)[a]	

P-values are presented in bold for results with $p < 0.050$. All variables refer to the last two months; n=sample size; figures are expressed as number (N) and column percentages (%); *p*-value obtained via chi-squared test; [a]adjusted residual >1.96; [b]adjusted residual <-1.96; [c]significant relationships confirmed via the Cochran Q test for paired samples within the longitudinal subsample of 97 participants; PPE: personal protective equipment; w/wo with or without.

in training due to the pandemic (PTSD: adjOR=3.6, 95% CI 1.73-7.53; depressive symptoms: adjOR=3.20, 95% CI 1.86-5.48; anxiety symptoms: adjOR=2.89, 95% CI 1.78-4.70; poor sleep quality: adjOR=2.33, 95% CI 1.07-5.08). Attending the 3rd year of specialization compared with the 2nd was associated with a lower probability of reporting PTSD (adjOR=0.37, 95% CI 0.15-0.91). Unadjusted regressions are reported in *Table S4* and *Table S5 available online as Supplementary Material*.

The sensitivity analysis based on the longitudinal subsample confirmed many of the above-mentioned relationships (*Table* S6 and S7 *available online as Supplementary Material*). Considering PTSD, associations with gender, serious health damage of a loved one, and negative change of training were confirmed. Furthermore, participants who changed their living conditions due to the pandemic had a higher likelihood of PTSD. Regarding depression and anxiety, the relationships with T3 and negative change of training were confirmed. Concerning poor sleep quality, the association with T4 was confirmed and participants who treated COVID-19 patients were more likely to report this outcome.

DISCUSSION

This study primarily aimed to analyse medical residents' mental health from 4 Italian universities from February to October 2021, exploring the influence of working and personal life changes due to COVID-19. Second, it aimed to provide insights into residents' training changes across the pandemic.

Across all timepoints, the outcomes' prevalence was always at least above 12%, except for poor sleep quality, showing a substantial burden of mental health symptoms. Indeed, for instance, one of the major surveillance systems in Italy, the Passi surveillance, reported – using the PHQ-2 – a prevalence of depressive symptoms of 6.7% among young people aged 18 to 34 during the period 2020-2021 (https://www.epicentro.iss.it/passi/dati/depressione#dati). In addition, Italian pre-pandemic data from the World Health Organization (WHO) World Mental Health Surveys showed a 12-month prevalence of anxiety disorders and PTSD among trauma-exposed individuals of 6.5% and 1.3%, respectively [27, 28].

Our findings were consistent with data about residents from other countries during the pandemic [29-33]. PTSD symptoms prevalence rose in April 2021 and decreased successively. Similarly, depressive symptoms were higher in February and April, then decreased; as well as poor sleep quality decreased from February to October. Anxiety showed similar patterns but with a rise in October. Interestingly, in the longitudinal subsample anxiety symptoms were not significantly reduced in the last study phases. Consistently with descriptive analysis, regression models generally confirmed lower levels of symptoms during June, August, or October, compared with February. Overall, the outcomes' trends reflected the pandemic curve in Italy. The number of new daily confirmed cases in February and April ranged from 10,000 to 20,000 cases, while it ranged from 1,000 to 6,000 cases in summer and autumn [34]. It is possible residents benefited from the decline in cases since it led to fewer COVID-19 hospitalizations [34]. We hypothesise that the increased anxiety in October might be related to the expected rise in cases in autumn 2021. Speaking of the pandemic curve, it could only partially explain differences in outcomes found among university locations, e.g., Piedmont, which was the reference in multivariable models, had better epidemiological situations mostly in the latest phases (https://mappe.protezionecivile.gov.it/it/mappe-e-dashboards-emer-

Table 3
Multivariable logistic regression models

	PTSD		Depressive symptoms		Anxiety symptoms		Poor sleep quality	
	adjOR (95% CI)	*p*	adjOR (95% CI)	*p*	adjOR (95% CI)	*p*	adjOR (95% CI)	*p*
Timepoint: T0	Ref.		Ref.		Ref.		Ref.	
T1	1.04 (0.6-1.79)	0.893	0.87 (0.55-1.39)	0.577	0.87 (0.56-1.34)	0.528	0.75 (0.41-1.36)	0.350
T2	0.42 (0.22-0.82)	**0.011**	0.55 (0.32-0.93)	**0.026**	0.70 (0.43-1.14	0.156	0.67 (0.34-1.33)	0.258
T3	0.45 (0.21-0.99)	**0.046**	0.35 (0.19-0.67)	**0.001**	0.39 (0.22-0.69)	**0.001**	0.84 (0.36-1.85)	0.667
T4	0.58 (0.27-1.23)	0.157	0.38 (0.20-0.72)	**0.003**	0.88 (0.52-1.49)	0.647	0.23 (0.08-0.61)	**0.003**
Gender: Male	Ref.		Ref.		Ref.		Ref.	
Female	2.38 (1.12-5.06)	**0.024**	2.18 (1.16-4.09)	**0.015**	2.58 (1.41-4.70)	**0.002**	1.29 (0.55-3.06)	0.549
Non-binary[a]	-	-	-		-	-	-	-
Specialization related to Emergency-Urgency area	2.42 (0.98-5.97)	0.055						
Location of University: Piedmont	Ref.		Ref.		Ref.		Ref.	
Friuli-Venezia Giulia	1.51 (0.6-3.79)	0.385	2.14 (1.02-4.46)	**0.043**	1.58 (0.79-3.18)	0.192	1.11 (0.39-3.18)	0.834
Emilia Romagna	5.17 (2.12-12.64)	**<0.001**	3.89 (1.84-8.23)	**<0.001**	4.02 (1.96-8.23)	**<0.001**	2.18 (0.77-6.19)	0.141
Sicily	7.7 (2.55-23.26)	**<0.001**	3.06 (1.14-8.21)	**0.026**	1.30 (0.50-3.41)	0.585	1.53 (0.42-5.51)	0.508
Year of specialization: 2	Ref.							
3	0.37 (0.15-0.91)	**0.030**						
4	0.75 (0.3-1.87)	0.533						
5	0.36 (0.11-1.18)	0.091						
Change of living condition: No	Ref.							
Yes, less than one month	1.39 (0.46-4.15)	0.559						
Yes. more than one month	0.61 (0.19-1.99)	0.416						
The pandemic is causing a substantial change of the economic situation of the participant's family: No	Ref.		Ref.					
Yes, it improved	1.46 (0.65-3.29)	0.361	1.71 (0.88-3.33)	0.109				
Yes, it worsened	0.99 (0.34-2.87)	0.980	2.87 (1.29-6.37)	**0.009**				
A loved one has suffered serious health damage after COVID-19	5.91 (2.76-12.65)	**<0.001**					1.92 (0.80-4.60)	0.141
Reallocation to tasks that, according to the participant, are too far from his/her area of expertise	3.12 (1.2-8.09)	**0.020**						
Reallocation to tasks that are very different from the usual ones but still within their area of expertise	0.94 (0.48-1.85)	0.862	1.82 (1.04-3.20)	**0.035**	1.24 (0.73-2.12)	0.414		
Working hours substantially modified due to the pandemic: No	Ref.		Ref.		Ref.			
Reduced	1.13 (0.36-3.53)	0.838	1.86 (0.79-4.37)	0.152	0.86 (0.38-1.95)	0.722		
Increased	2.59 (1.41-4.76)	**0.002**	2.26 (1.34-3.78)	**0.002**	2.57 (1.59-4.15)	**<0.001**		
Believing that the pandemic is substantially changing one's specialization training: No	Ref.		Ref.		Ref.		Ref.	
Yes, positively	4.77 (1.83-12.43)	**0.001**	0.61 (0.26-1.42)	0.260	1.43 (0.69-2.93)	0.330	1.73 (0.62-4.78)	0.290
Yes, negatively	3.6 (1.73-7.53)	**0.001**	3.20 (1.86-5.48)	**<0.001**	2.89 (1.78-4.70)	**<0.001**	2.33 (1.07-5.08)	**0.033**

Continues

Table 3
Continued

	PTSD		Depressive symptoms		Anxiety symptoms		Poor sleep quality	
	adjOR (95% CI)	*p*	adjOR (95% CI)	*p*	adjOR (95% CI)	*p*	adjOR (95% CI)	*p*
The participant personally treated COVID-19 patients	1.8 (0.98-3.31)	0.059	1.40 (0.88-2.24)	0.152	1.37 (0.89-2.12)	0.147	1.72 (0.90-3.26)	0.095
Having been in isolation due to suspicion or diagnosis of COVID-19	1.26 (0.68-2.32)	0.460	1.07(0.64-1.77)	0.787				
The participant felt that the available PPE at work was enough to keep him/her safe					0.59 (0.33-1.08)	0.091		
Age							1.05 (0.92-1.19)	0.463
Having children							5.48 (1.46-20.45)	**0.011**
Loved ones belonging to a risk group for COVID-19 complications							2.02 (0.85-4.82)	0.110

P-values are presented in bold for results with $p < 0.050$; [a]omitted for low sample size; PTSD: post-traumatic stress disorder; adjOR: adjusted odds ratio; CI: confidence intervals; Ref.: reference; PPE: personal protective equipment; empty cells indicate variables that were not selected for inclusion in that specific regression model.

genze/dashboards-coronavirus/situazione-desktop/). Probably, other circumstances were involved, e.g. hospitalization rate and availability of material and human resources in the workplaces. Moreover, a selection bias could not be excluded.

From our results, women were more at risk for PTSD, depression, and anxiety, in line with previous research regarding HCPs [35, 36]. Although certain mental disorders are typically more prevalent among women than men, the impact of pandemic-related changes on women's work-life balance should also be taken into account [36]. Women may not have had the needed support in balancing work and family demands [36]. Furthermore, having children without care support has been acknowledged to be a risk factor for depression [36]. Additionally, we found that having children was linked to poor sleep quality, but it is not clear whether this result is due to the pandemic or is independent.

Concern about loved ones' health was associated with PTSD. This is not surprising: similar results were found regarding medical staff with families, who were more worried about their own risk of getting infected and of getting their families infected, if compared with their single colleagues [35].

Financial pandemic-related challenges were associated with depressive symptoms. Low-income status or economic concerns are well known for influencing depression [37, 38].

Considering pandemic-related changes in work life, long working hours were associated with PTSD, anxiety, and depressive symptoms. Long working hours are known to be a risk factor for such conditions, especially in extreme working environments, like COVID-19 wards [32, 35]. Additionally, redeployment was a risk factor for PTSD and depression. This result could be explained as residents were placed in an unfamiliar environment, without the specific experience for critical situations [39-41]. Indeed, during the pandemic, many HCPs, including residents, were reassigned to different departments or roles to meet urgent demands. This sudden shift may have placed them in new environments, exposing them to high-stress situations and responsibilities they were not accustomed to handling. It is also important to note that experiences may have varied significantly across different regions of Italy and different hospital departments. The impact of redeployment may have differed between departments; for instance, the transition from a non-critical specialty to a COVID-19 ward was vastly different compared to transitions within critical care specialties. Due to these variations, our observations can only be generalized to a certain extent.

Being in training during this situation meant that not only job activities were disrupted, but also formation was affected. Perceived negative training modifications were associated with all the outcomes. Concerns regarding formation have been linked with increased levels of stress, anxiety, and burnout [1, 15]. With exams and training courses being cancelled, not being able to progress in the training process and concerns about career progression could be very frustrating [42]. Also, academic pressure may have had a role in the worsening of mental health [43]. Interestingly, participants who perceived a positive impact on their training had a higher likelihood of PTSD symptoms too. This suggests that the higher workload and the numerous challenges might have represented an opportunity to learn but were still a stressful event. Furthermore, third-year residents had less odds of PTSD compared with second-year participants. Senior residents might be more capable of coping with the whole situation, being more experienced. These relationships should be further investigated.

The longitudinal subsample analyses confirmed the relevance of the perceived negative impact on training. They also suggested further pandemic-related changes that could influence residents' mental status, e.g., modifications in living conditions and treating COVID-19 patients. Remarkably, time was not signifi-

cant for PTSD, potentially due to the need for a longer follow-up.

Lastly, the findings shed light on the lockdown's impact on the working conditions and experiences of Italian residents. It is worth noting that many working changes that resulted associated with poor mental outcomes involved more than a quarter of participants, indicating a substantial proportion of residents experienced negative triggers for their health. The reduction of most of these issues during the last timepoints suggests that healthcare systems may have adapted to better manage the pandemic challenges.

Existing literature highlights several strategies for improving mental health among HCPs during health crisis. For instance, mindfulness-based interventions have shown effectiveness in reducing stress and improving mindfulness and mental well-being, though their impact on burnout, anxiety, and depression is less conclusive [44]. Group psychological therapies, including cognitive behavioral programs and acceptance and commitment therapy, also show promise in reducing distress symptoms, but studies often suffer from methodological limitations [45]. Multi-component prevention programs, which include staffing adjustments and psychological support, appear beneficial but need more robust evaluation [46]. Psychotherapy, psychoeducation, and mind-body interventions demonstrated efficacy in reducing anxiety, burnout, depression, and PTSD, with psychoeducation enhancing resilience and mind-body interventions improving quality of life [47]. Future research should focus on more rigorous methodologies and active involvement of healthcare workers in intervention design to enhance the effectiveness and applicability of these programs.

This study had several limitations. The sample size limited the representativeness. The survey was repeated during the summer when many potential respondents were on vacation. Additionally, there may have been survey fatigue, as respondents were involved in multiple questionnaires. Convenience sampling of both centres and participants could have biased sample selection. The self-reported questionnaire could represent itself a limitation in terms of data quality. However, this work represented one of the first prospective Italian studies about the pandemic impact on the training and mental health of residents, a population that is often overlooked, laying the foundation for further investigations. Few studies addressed PTSD in this population, so these data can be relevant to provide insights into this possible pandemic consequence.

CONCLUSIONS

Our study found medical residents' levels of PTSD, depression, anxiety symptoms, and poor quality of sleep that should not be underestimated. Many pandemic-related changes, like redeployment, increased working hours, and disrupted training, increased the odds of such mental health outcomes. Monitoring the long-lasting effects of the pressure many HCPs underwent will be crucial to provide support and prevent worst-case scenarios.

To plan strategies to address mental health issues among residents, it is important to note that there is growing evidence for interventions aimed at improving mental health among healthcare workers. Indeed, many approaches have shown promising benefits in reducing mental health symptoms, e.g., mindfulness-based interventions, psychological therapies, prevention programs that integrate psychological support with systemic changes, mind-body practices, and psychoeducation [44-47]. Future research should focus on rigorous evaluation of these interventions and encourage the involvement of healthcare workers in their design to improve both efficacy and relevance.

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Conflict of interest statement

The Authors have no conflicts of interest to declare.

Ethical approval and consent to participate

All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments. The study was approved by the Ethics Committee of the University of Turin (Prot. n. 492587, 4 December 2020). Written informed consent was obtained from all individual participants included in the study.

Availability of data and material

All relevant data are within the paper. Dataset is available upon reasonable request to the corresponding Author.

Authors' contributions

Conceptualization: GLM, GS, PL, FB, RS; data curation: GLM, GG, LFB; formal analysis: GLM, GG; investigation: GLM, GG, CAM, DA, LB, SB, MEF, WM; methodology: GLM, GS, PL, FB, RS; project administration: GLM; GG; resources: FB, RS, CAM, DA, LB, SB, MEF, WM; supervision: GS, PL, FB, RS; visualization: GLM, GG, LFB; writing-original draft: GLM, GG; writing-review and editing: PL, FB, RS, CAM, DA, LB, SB, MEF, WM.

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ORIGINAL ARTICLES AND REVIEWS

Tobacco, heated tobacco products, e-cigarette, alcohol, cannabis and other psychotropic substances. Polysubstance use during the COVID-19 pandemic in Italy

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Abstract

Objective. Psychoactive substance use is largely found to involve multiple substances. In recent years, the COVID-19 pandemic has changed psychoactive substance use patterns. Aim of this study is to investigate profiles of polysubstance and their pattern during and after the COVID-19 pandemic.

Methods. We collected information on alcohol consumption, use of tobacco, cannabis and other psychotropic substances, and nicotine-containing electronic devices (NCEDs; i.e., heated tobacco products and electronic cigarettes) on representative samples of the Italian adult population in five surveys from 2020 to 2023 (3,000≤n≤6,600). We used a Latent Class Analysis model to identify substance use profiles and their associated variables in each time period.

Results. We initially identified two profiles, "light users", characterized by a low use of tobacco and NCEDs (3%-20%) and a 40% at-risk alcohol consumption, and "polysubstance users", characterized by a large use of all psychoactive substances. After the 2020 COVID-19 lockdown, we also found the "dual users" profile, which show a large use of tobacco (90%) and NCEDs (50%), and also alcohol (50%). Being "dual users" and "polysubstance users" were associated with younger age and high economic status, with strengths of association less pronounced during lockdown but more marked immediately thereafter. Moreover, reporting anxiety or depressive symptoms as well as using psychotropic drugs were strongly associated with both profiles, especially in the last two years.

Conclusions. Heterogeneity of polysubstance users and their socio-demographic characteristics need to be considered to design tailored prevention interventions, with special attention to the new "dual users" profile, which confirmed the increasing trend in NCED use.

Key words
- polysubstance use
- COVID-19
- tobacco
- electronic-cigarette
- alcohol
- cannabis

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INTRODUCTION

Polysubstance use refers to the consumption of more than one psychoactive substance on separate occasions (sequential use) or at the same time (concurrent/simultaneous) [1]. Although substance use is often centered around individual substances, it is largely found to involve multiple substances [2, 3]. Substance-dependent individuals report using an average of 3.5 substances [4], both simultaneously and sequentially. Psychoactive substances include alcohol, nicotine, cannabis and other psychotropic substances such as opioids and stimulants, and the use of one substance often co-occurs with the use of another. For instance, tobacco smoking is strongly associated with alcohol and marijuana use [1] and cannabis is the most commonly used drug among those who drink, besides tobacco [5].

Polysubstance use leads to poor physical and mental health, including psychotic disorders, and substance use outcomes, such as increased violence and suicidal risk, and increased overdoses and mortality risks [6-8]. Most research on substance use and its consequences (i.e., substance use disorders) addresses use, control and treatment of single substances [2]. Concurrent substance use, which is more often studied in adolescents [9-12], may complicate diagnosis and treatment of substance use disorders, as well as the effectiveness of prevention and control interventions [13].

Many individuals who develop substance use disorders are also diagnosed with mental disorders, and vice versa [14]. In recent years, the COVID-19 pandemic has enhanced mental disorders and changed substance use patterns [15, 16]. Several surveys were carried out in European countries on single substance use during the COVID-19 initial phase [17-24]. In Italy, the COVID-19 pandemic was associated with an increase in anxiety and depressive symptoms and with a worsening in the use of smoking and nicotine-containing electronic devices (NCEDs), i.e., electronic cigarettes (e-cigarettes) and heated tobacco products (HTPs), especially in its initial phase [17-20].

The extent to which polysubstance use has changed during the COVID-19 pandemic was little investigated in Europe only among youths in the initial phase of the COVID-19 pandemic [12], and it needs to be studied more in depth. Moreover, profiles of polysubstance use integrating new consumption patterns, such as the increasing use of NCEDs, are underexplored.

The aim of this study is to investigate profiles of polysubstance use and its pattern in the COVID-19 pandemic and subsequent phases together with the associated risk factors. The study was carried out in the Italian adult population between 2020 and 2023, using representative samples within the study LOckdown and lifeSTyle IN ITALY (LOST IN ITALY) and its extension LOST IN TOSCANA.

METHODS

Study design and population

The LOST IN ITALY study cohort, described in detail elsewhere [25], is based on a cross-sectional survey conducted on 6,003 participants representative of the Italian adult population aged 18-74 years who completed a web-based interview during the Italian lockdown (April 27-May 3, 2020) which collected information on two time points recording changes before and during the lockdown (Time 1: pre-lockdown, February 2020; Time 2: lockdown, April-May 2020). The fieldwork was conducted by Doxa, the Italian branch of the Worldwide Independent Network/Gallup International Association.

Following surveys, mostly based on the same study participants of the first one, were carried out in correspondence with the main COVID-19 waves. Within the LOST IN ITALY study, other two surveys were conducted on about half of the initial sample (Time 3: 3,185 in November 27-December 20, 2020; Time 4: 3,000 in May 7-18, 2021). Finally, two years after the start of the COVID-19 pandemic, 6,600 participants took part to a comparable web-based survey (Time 5: February 24-March 21, 2022) within the LOST IN TOSCANA study, and lastly, a follow-up of the LOST IN TOSCANA study was conducted between April 4 and May 3, 2023 on 6,600 participants (Time 6). In each follow-up survey, some individuals were lost, therefore, to maintain the sample's representativeness, new individuals were added from the appropriate strata in each survey *(Supplementary Figure S1 available online)*. Slight differences in the age distribution between lost and new enrolled respondents were found *(Supplementary Table S1 available online)*, but the sample representativeness was maintained.

In all surveys, participants completed an online questionnaire on socio-demographic information, lifestyle habits and symptoms of mental distress. Moreover, in the first survey, changes before and during the lockdown were recorded. Distribution of individuals by socio-demographic and individual features in all time periods considered are reported in *Supplementary Table S2 available online*.

Outcome and independent variables

Current smokers were defined as respondents who reported having smoked ≥100 cigarettes during their life and who were current smokers at the time of the interview. Users of NCEDs were defined as respondents using e-cigarettes or HTPs occasionally or regularly. Alcohol drinkers were classified based on the total score obtained on the alcohol use disorders identification test-concise (AUDIT-C). Respondents with a score ≥4 for women and ≥5 for men were identified as heavy drinkers [26]. Binge drinkers were defined as respondents who drank 6 or more alcoholic beverages at one time at least once in the last month, where 1 alcoholic beverage corresponds to 1 standard unit of alcohol, i.e., 12 g of pure alcohol (approximately a 330 ml beer, a 125 ml glass of wine or a 40 ml of spirits). A dichotomous variable describing respondents with at-risk alcohol consumption was defined as 1 for those who were heavy drinkers according to AUDIT-C or binge drinkers and as 0 for those who were neither heavy drinkers nor binge drinkers. Finally, current users of cannabis and users of other psychotropic substances were defined as respondents who reported using respectively cannabis (or cannabis light) and psychotropic substances (e.g., cocaine, heroin, synthetic psychostimulants, etc.) at least once in the previous month.

Information on sociodemographic characteristics, such as age, sex, level of education and economic status was collected at the baseline. In each survey, information about mental health (anxiety or depressive symptoms, quantity and quality of sleep) and consumption of selected psychotropic drugs was collected [17, 25]. Individuals scoring higher than 3 in the 2-item generalized anxiety disorder (GAD-2) scale [27] or in the 2-item patient health questionnaire (PHQ-2) scale [28] were identified as presenting anxiety or depressive symptoms, respectively. Individuals who reported sleeping less than 7 hours per night or who rated their overall sleep as fairly poor or very poor were identified as having sleep disorders [29]. Individuals reporting the use, in the last month, of at least one drug among antidepressants, hypnotics, anxiolytics/benzodiazepine, antipsychotics and mood stabilizers were considered psychotropic drug users.

Statistical analysis

To identify substance use profiles in each time, we used latent class analysis (LCA), a statistical model-based approach for clustering individuals in unobserved groups on the basis of substance consumption [30]. In the LCA analysis we included five indicators of substance use (i.e., conventional cigarettes, e-cigarettes or HTPs, at-risk alcohol, cannabis or cannabis light, other psychotropic substances) as binary variables. We ran an iterative process to identify the best profile solutions in each time using the corresponding survey weights. In detail, we tested four different variance-covariance structures for profiles (i.e., invariant diagonal, varying diagonal, invariant non-diagonal, and varying non-diagonal) for each set of models ranging from 1 to 3 profile classes. We used five different sets of random starting points in each model selecting the one with the best log likelihood after the expected-maximization iterations. We used the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) to assess model fit. Once we identified the preferred model, we analyzed whether the profiles of the model were identified correctly by calculating the average posterior probability (AvePP), the odds of correct classification (OCC) and the entropy which provides a summary for the overall classification precision of the model. AvePP closer to 100% and OCC >5 support adequate profile separation and precision [30, 31], and entropy values <0.8 are considered high [32].

Finally, we assessed factors associated with substance use profiles from the LCA models in logistic regressions with the bias-adjusted three-step approach which consists in first identifying the underlying latent variable, then assigning individuals to latent classes, and finally analyzing class membership and covariates accordingly [33]. We reported adjusted odds ratios (aORs) for sex, age, education, economic status, anxiety or depression symptoms, sleep disorders and use of psychotropic drugs, after adjusting also for geographic area.

All the statistical models were weighted for the corresponding survey weights, applied to guarantee the representativeness of the national sample in terms of sex, age, socio-economic status, and geographic area.

All statistical analyses were performed using Stata Version 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

RESULTS

The weighted prevalence of the use of each substance at all times are displayed in *Table 1*. The use of NCEDs increased throughout the whole period, from 9% before lockdown to 14% in 2023, whereas the use of other psychotropic substances decreased from 4% to 1%. At-risk alcohol use, cannabis use and smoking showed a slight decrease during lockdown, followed by a sharp 61% increase in alcohol use, a maintenance of lockdown prevalence for cannabis use and a return to pre-lockdown levels for smoking.

In the first two times points (i.e., pre-lockdown in February 2020; during lockdown in April-May 2020) only the LCA models with up to two classes converged whereas, in the remaining times, also models with up to three classes reached convergence. The latter was

Table 1
Prevalence of substance use in the time periods (weighted proportions)

	Time 1[1] N=6,003 % (95% CI)	Time 2[1] N=6,003 % (95% CI)	Time 3[1] N=3,185 % (95% CI)	Time 4[1] N=3,000 % (95% CI)	Time 5[1] N=6,600 % (95% CI)	Time 6[1] N=6,600 % (95% CI)
Conventional cigarette smokers	23.3 (22.0, 24.7)	21.9 (20.6, 23.2)	24.5 (22.7, 26.5)	26.3 (24.2, 28.4)	24.4 (23.1, 25.7)	23.3 (22.1, 24.6)
Alcohol at risk[2] or binge drinkers	28.1 (26.7, 29.6)	25.2 (23.8, 26.6)	33.2 (31.1, 35.3)	43.7 (41.5, 46.0)	44.9 (43.4, 46.4)	45.4 (43.9, 47.0)
Cannabis or cannabis light users	7.0 (6.2, 7.9)	6.0 (5.2, 6.8)	7.9 (6.8, 9.1)	7.8 (6.6, 9.2)	4.9 (4.3, 5.7)	5.4 (4.7, 6.1)
Psychoactive substances users	4.2 (3.6, 4.9)	4.0 (3.4, 4.7)	2.0 (1.5, 2.7)	1.5 (1.0, 2.2)	0.7 (0.5, 1.0)	1.2 (0.9, 1.6)
NCEDs users	8.9 (8.1, 9.9)	9.8 (8.9, 10.8)	11.8 (10.4, 13.3)	12.1 (10.6, 13.8)	11.7 (10.8, 12.7)	13.8 (12.7, 14.9)

N: number; CI: confidence interval; NCEDs: nicotine-containing electronic devices.
[1]Time 1: pre-lockdown (February 2020); Time 2: lockdown (April-May 2020); Time 3: November-December 2020; Time 4: May 2021; Time 5: February-March 2022; Time 6: April 2023.
[2]Alcohol at risk: respondents with a total Alcohol Use Disorders Identification Test-Concise score ≥ 4 for women and ≥ 5 for men.

Table 2
Latent Class Analysis models measures of classification and accuracy for all time periods

	Model estimated class proportion % (95% CI)	AvPP	OCC	Entropy
Time 1[1]				
Class 1	90.4 (83.7, 94.6)	95.6	2.3	0.873
Class 2	9.6 (5.4, 16.3)	91.5	102.1	
Time 2[1]				
Class 1	91.7 (88.3, 94.2)	96.9	2.8	0.897
Class 2	8.3 (5.8, 11.7)	92.7	140.1	
Time 3[1]				
Class 1	81.2 (74.5, 86.4)	92.6	2.9	0.824
Class 2	6.5 (5.1, 8.3)	88.6	112.2	
Class 3	12.3 (7.8, 19.1)	85.3	41.2	
Time 4[1]				
Class 1	78.8 (51.6, 92.8)	91.3	2.8	0.812
Class 2	6.5 (4.7, 9.0)	86.7	93.1	
Class 3	14.7 (3.4, 45.8)	91.7	64.2	
Time 5[1]				
Class 1	84.5 (78.2, 89.2)	94.7	3.3	0.845
Class 2	4.6 (3.3, 6.3)	84.5	114.0	
Class 3	11.0 (6.4, 18.2)	90.3	75.7	
Time 6[1]				
Class 1	68.7 (58.4, 77.4)	91.7	5.0	0.708
Class 2	4.3 (3.4, 5.4)	82.7	106.2	
Class 3	27.0 (18.5, 37.6)	77.1	9.1	

CI: confidence interval; AvPP: average posterior probability; OCC: odds of correct classification; Class 1: light users; Class 2: polysubstance users; Class 3: dual users.
[1]Time 1: pre-lockdown (February 2020); Time 2: lockdown (April-May 2020); Time 3: November-December 2020; Time 4: May 2021; Time 5: February-March 2022; Time 6: April 2023.

reached in all times with all the variance-covariance specifications. We then chose the least restrictive variance-covariance structure, i.e., varying non-diagonal, and ran the models at all times. Fit indices suggested a better fit for the two-classes LCA model for times 1 and 2, and the three-class model for the remaining times *(Supplementary Table S3 available online)*. At all time points, the selected models returned AvPP above the desired threshold of 70% for all classes, suggesting adequate classification accuracy. The OCC showed a high classification accuracy for Class 2 and Class 3 (in times 3 to 6), for which the OCC was well above the threshold criteria of 5, whereas accuracy classification for Class 1 resulted low. Finally, the entropy was between 0.7 and 0.9 suggesting a borderline overall model classification precision *(Table 2)*.

Figure 1 displays the three profiles identified with the LCA. The first, defined as "light users", included most of the total sample at all times (from 68.7% in time 6 to 91.7% in time 2, *Table 2*) and shows proportions close to 0 for cannabis and psychotropic substance use, up to 8.8% and 20.9% for NCEDs and conventional cigarette, respectively, and up to 40.4% for at-risk alcohol use. The second class identifies the "polysubstance users" and it includes between 4.3% (in time 6) and 9.6% (in time 1) of respondents characterized by an average proportion of 23.3% and 23.7% of psychotropic substance and NCEDs users, respectively, around 44.8% of tobacco smokers and over 80% of at-risk alcohol users and cannabis users. Finally, the third class, defined as "dual users", which arises from December 2020, includes between 11.0% and 14.7% of the total sample in times 3 to 5 and up to 27.0% in time 6. In addition to the at-risk alcohol use (on average 54.2%) that characterizes all the profiles, it is mainly characterized by the dual use of tobacco cigarettes and NCEDs with average proportions of 82.3% and 59.1%, respectively *(Table 2, Figure 1, Supplementary Table S4 available online)*.

The proportion of substance use shows variations in time. At-risk alcohol users increased in the last three

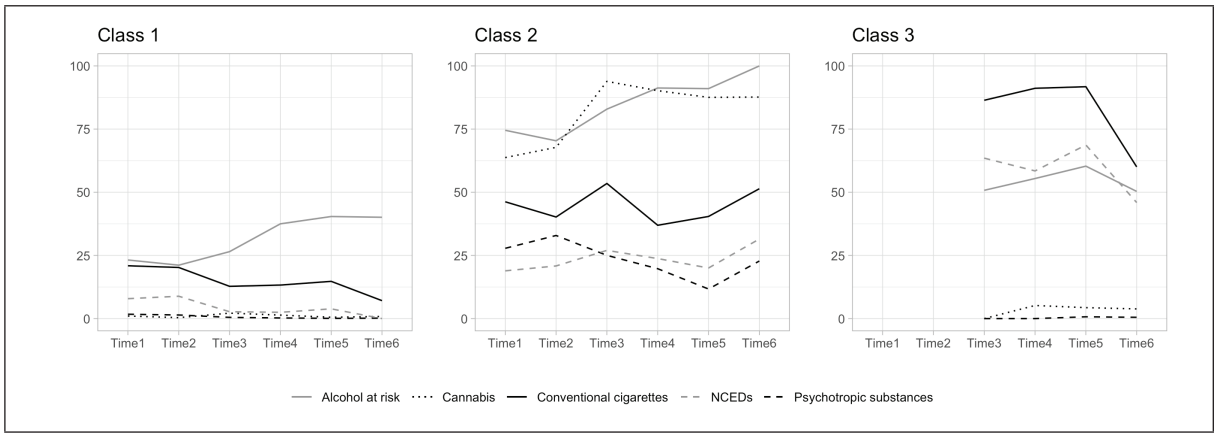

Figure 1
Expected proportions, at each time, of the population by substance use in each class identified by the Latent Class Analysis model. Time 1: pre-lockdown (February 2020); Time 2: lockdown (April-May 2020); Time 3: November-December 2020; Time 4: May 2021; Time 5: February-March 2022; Time 6: April 2023.
NCEDs: nicotine-containing electronic devices (electronic-cigarettes or heated tobacco products).

time points compared to the previous time points in both "light users" (almost doubling) and "polysubstance users". Cigarette smokers and NCEDs users in "light users" show a reduction from time 3 afterwards presumably captured in the new class of "dual users".

Tables 3 and *4* report the results of the logistic regression models for the analysis of factors *(Supplementary Table S2 available online)* associated with the substance use profiles identified with the LCA models, respectively the "polysubstance users" or "dual users" in comparison to "light users". In all the time points, males were more likely to be "polysubstance users" *vs* "light users" in comparison to females, with a strength of association that decreased from time 4, i.e., May 2021. Increasing age was associated with a decreasing odds of being "polysubstance users", with younger respondents that were up to 10 times more likely to be "polysubstance users" than older ones. During lockdown (time 2) such differences appeared slightly less pronounced and became more marked immediately afterwards. Increasing self-reported economic status was associated with an increasing odds of being "polysubstance users" *vs* "light users", with people with high economic level that were over 2 times more likely to be "polysubstance users" than people with low economic level before lockdown and immediately afterwards. During lockdown (time 2), such difference reached 3 times and, from time 4, i.e., May 2021, it increased up to 6 times. Finally, reporting anxiety or depressive symptoms

Table 3
Results of the logistic regression models for the factors associated with substance use profiles from the Latent Class Analysis models in all time points: "polysubstance users" *vs* "light users"

	Time 1[1]	Time 2[1]	Time 3[1]	Time 4[1]	Time 5[1]	Time 6[1]
	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)
Sex						
Female	ref	ref	ref	ref	ref	ref
Male	**1.60 (1.22, 2.11)**	**1.50 (1.15, 1.97)**	**1.56 (1.07, 2.27)**	1.30 (0.84, 2.01)	1.24 (0.87, 1.77)	1.26 (0.89, 1.78)
Age						
55-74	ref	ref	ref	ref	ref	ref
35-54	**2.05 (1.38, 3.04)**	**2.19 (1.51, 3.20)**	**3.82 (2.16, 6.75)**	**1.64 (0.77, 3.50)**	**2.51 (1.38, 4.58)**	**1.98 (1.18, 3.30)**
18-34	**4.23 (2.85, 6.27)**	**3.51 (2.37, 5.19)**	**7.91 (4.38, 14.31)**	**4.15 (1.93, 8.95)**	**10.43 (5.63, 19.32)**	**7.52 (4.35, 13.01)**
p for trend	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Level of education						
High	ref	ref	ref	ref	ref	ref
Medium	1.01 (0.74, 1.36)	1.10 (0.82, 1.48)	0.93 (0.64, 1.35)	0.90 (0.56, 1.44)	0.87 (0.60, 1.28)	0.83 (0.56, 1.22)
Low	1.29 (0.85, 1.97)	1.42 (0.94, 2.15)	1.01 (0.55, 1.88)	0.94 (0.49, 1.81)	1.23 (0.68, 2.23)	1.17 (0.68, 1.99)
Economic status						
Under the national mean	ref	ref	ref	ref	ref	ref
On average	1.10 (0.79, 1.53)	1.13 (0.82, 1.57)	1.34 (0.84, 2.13)	**2.09 (1.14, 3.83)**	**1.77 (1.05, 3.00)**	0.98 (0.61, 1.58)
Over the national mean	**2.34 (1.54, 3.58)**	**3.01 (1.99, 4.56)**	**2.40 (1.33, 4.32)**	**6.29 (3.43, 11.50)**	**6.12 (3.40, 11.02)**	**4.83 (2.89, 8.09)**
p for trend	*<0.001*	*<0.001*	*0.006*	*<0.001*	*<0.001*	*<0.001*
Anxiety or depression						
No	ref	ref	ref	ref	ref	ref
Yes	**2.61 (1.96, 3.48)**	**1.35 (1.01, 1.82)**	**2.48 (1.68, 3.68)**	**1.89 (1.19, 2.99)**	**3.26 (2.22, 4.78)**	**2.12 (1.39, 3.23)**
Sleep disorders						
No	ref	ref	ref	ref	ref	ref
Yes	1.13 (0.85, 1.49)	0.99 (0.75, 1.32)	0.98 (0.66, 1.45)	1.13 (0.76, 1.69)	1.13 (0.78, 1.64)	1.19 (0.78, 1.81)
Use of psychotropic drugs						
No	ref	ref	ref	ref	ref	ref
Yes	**4.25 (3.07, 5.87)**	**4.84 (3.57, 6.57)**	**4.36 (2.82, 6.75)**	**4.71 (2.92, 7.60)**	**7.62 (5.23, 11.11)**	**10.03 (6.79, 14.84)**

aOR: adjusted odds ratio; CI: confidence interval.
[1]Time 1: pre-lockdown (February 2020); Time 2: lockdown (April-May 2020); Time 3: November-December 2020; Time 4: May 2021; Time 5: February-March 2022; Time 6: April 2023.

as well as using psychotropic drugs was strongly associated with being "polysubstance users". In the last two time points, i.e., 2022 and 2023, people using psychotropic drugs resulted 8-10 times more likely to be "polysubstance users" compared to non-users *(Table 3)*.

Being "dual users" in comparison to "light users" was associated with a younger age, especially in latest time points, with a high economic status, with anxiety or depressive symptoms and psychotropic drugs use, although the association of the last two factors only reached significance at the last time points *(Table 4)*.

DISCUSSION

In the present study we found that patterns of psychoactive substance use among Italian adults in the COVID-19 pandemic period was initially characterized by two profiles, "polysubstance users" and "light users", that become three after the lockdown, with the identification of a new profile of "dual users", e.g., those who mainly smoked tobacco cigarettes and used NCEDs. At-risk alcohol use characterizes all profiles. "Light users" were characterized by no use of cannabis neither psychotropic substances, a light use of conventional cigarettes and NCEDs, which decreased after lockdown (since November-December 2020), and use of alcohol at risk, which, albeit it showed a little reduction during lockdown, it largely increased afterwards. Polysubstance use was characterized by the use of all substances, especially alcohol at risk and cannabis which showed an increase in use after lockdown. Finally, the "dual users" profile showed a constant use of conventional cigarettes, NCEDs and alcohol at risk, with a decrease, especially in smokers, in the last time point.

Results confirm findings on the use of single substances during the COVID-19 pandemic in Italy, which showed a modest reduction during the phase of first restrictions followed by an increase to values higher than those recorded in the pre-pandemic period [19, 34-36].

The emergence of the new profile of "dual users" confirms the increasing trend in NCEDs use, in particular

Table 4
Results of the logistic regression models for the factors associated with substance use profiles from the Latent Class Analysis models in all time points: "dual users" *vs* "light users"

	Time 3[1] aOR (95% CI)	Time 4[1] aOR (95% CI)	Time 5[1] aOR (95% CI)	Time 6[1] aOR (95% CI)
Sex				
Female	ref	ref	ref	ref
Male	1.06 (0.76, 1.48)	1.20 (0.81, 1.79)	1.10 (0.85, 1.43)	**1.15 (1.00, 1.33)**
Age				
55-74	ref	ref	ref	ref
35-54	1.41 (0.92, 2.17)	1.32 (0.85, 2.05)	**1.33 (1.02, 1.73)**	1.13 (0.97, 1.32)
18-34	**1.69 (1.00, 2.84)**	**1.78 (1.03, 3.07)**	**1.48 (1.01, 2.16)**	**1.26 (1.02, 1.57)**
p for trend	*0.042*	*0.039*	*0.034*	*0.028*
Level of education				
High	ref	ref	ref	ref
Medium	1.00 (0.70, 1.45)	1.08 (0.72, 1.63)	1.12 (0.87, 1.46)	**1.27 (1.08, 1.49)**
Low	1.06 (0.57, 1.97)	0.99 (0.53, 1.88)	1.07 (0.74, 1.55)	1.22 (0.98, 1.53)
Economic status				
Under the national mean	ref	ref	ref	ref
On average	1.14 (0.73, 1.79)	1.06 (0.68, 1.67)	1.17 (0.82, 1.68)	0.93 (0.79, 1.09)
Over the national mean	**1.90 (1.05, 3.44)**	**2.68 (1.30, 5.54)**	**1.67 (1.05, 2.63)**	1.01 (0.80, 1.27)
p for trend	*0.064*	*0.028*	*0.046*	*0.85*
Anxiety or depression				
No	ref	ref	ref	ref
Yes	0.91 (0.63, 1.32)	1.06 (0.70, 1.61)	**1.39 (1.07, 1.79)**	**1.23 (1.06, 1.44)**
Sleep disorders				
No	ref	ref	ref	ref
Yes	1.21 (0.87, 1.68)	1.29 (0.88, 1.88)	1.04 (0.82, 1.31)	0.99 (0.86, 1.14)
Use of psychotropic drugs				
No	ref	ref	ref	ref
Yes	1.44 (0.88, 2.35)	1.33 (0.75, 2.35)	1.10 (0.69, 1.73)	**1.39 (1.1, 1.77)**

aOR: adjusted odds ratio; CI: confidence interval.
[1]Time 3: November-December 2020; Time 4: May 2021; Time 5: February-March 2022; Time 6: April 2023.

HTPs and disposable e-cigarettes. Most use of NCEDs is accompanied by more than replacing the use of conventional cigarettes [37].

We found that men were more likely to be polysubstance users than women, confirming results from several studies [38] although a growing body of research suggests a narrowing of the "gender gap" in overall drug patterns [39]. Moreover, according to the literature, we found that polysubstance use was associated with having younger age [1, 5, 40-41] and being lower educated [41]. Our findings also highlight an association of polysubstance use with high economic status that provides greater access to a wider range of substances, potentially contributing to polysubstance use [42].

Finally, our results confirm the association between the risk of polysubstance use and the increase in symptoms of anxiety and depression, and, above all, with the use of psychotropic drugs (aOR=3.90 for ≥2 substances) [14].

Strengths and limitations

Among the strengths of the present study, there are the large samples considered in the various surveys. The selection of the samples from online panels should be considered, since this could invalidate the generalizability of the findings to the whole Italian adult population. However, our results are in line with other national studies (IPSAD, ISTAT) [43-44] confirming the good degree of representativeness obtained in the LOST samples. In order to explore the generalizability of our findings, it should be noted that the definitions of at-risk behaviours could be different among studies depending on both the questions and the scales, as well as the age size of the samples, returning in different prevalence estimates. As an example, the prevalence of at-risk alcohol users defined using the AUDIT-C score is higher in comparison to that defined form the National Institute of Health in the Report to the Parliament [45]. In addition, we did not take into account for the longitudinal structure of our data in order not to reduce sample size and to add complexity to the models, but further analyses exploring changes in time in polysubstance use could improve understanding the phenomenon. Although other studies used the same data of this work to study trends in the use of substances during the pandemic period and their associated factors [17-20, 34, 35], here we wanted to investigate a different aspect, i.e. the characteristics and trends in the concomitant use of substances, an aspect that has been little studied, especially in adults. Our analysis employed LCA models which have emerged in recent years as a modern approach to polysubstance research, especially among adolescents, emphasizing a person-centered, rather than variable-centered, approach [46]. Finally, the surveys were carried out during most of the COVID-19 pandemic waves, thus allowing us to capture the possible effect of the pandemic peaks on the population's psychological distress and lifestyle changes. Several surveys were carried out during the COVID-19 pandemic in Europe, however most of them focused on the lockdown period. The added value of this study is also to explore changes in the long term after the emergency period and the pattern of polysubstance use normalization.

CONCLUSIONS

The COVID-19 pandemic has carried changes in psychoactive substance use patterns as highlighted by the emergence of consumption profiles diversified over time. To facilitate the development and design of tailored prevention strategies, it is essential to acknowledge the peculiarities within polysubstance users, including their associated socio-demographic factors and developmental antecedents. Given the harmful health consequences of polysubstance use and since polysubstance use seems to be associated to similar characteristics as heavy users of single substances (e.g., higher psychological distress, male) a special attention of prevention should be focused on this subgroup of users. Targeting specific polysubstance use patterns and corresponding risk profiles may offer significant benefits in both prevention efforts and clinical research.

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Ethics approval

The two study protocols of the LOST IN ITALY and LOST IN TOSCANA studies were approved by the Ethics Committee of the coordinating centres (Istituto Besta, file number: 71-73, April 2020, and Comitato Etico Regionale per la Sperimentazione Clinica della Toscana, Sezione Area Vasta Centro, file number: CEAVC 19834, April 2021, respectively). All the enrolled participants provided informed consent to participate in the study.

Availability of data and materials

Data that support the findings of the present study and materials are available from the corresponding author upon reasonable request.

Conflict of interest statement

None to declare.

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Recommendations for preventing sentinel events: results of a national cross-sectional survey in Italy

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Abstract

Introduction. In 2005, the Italian Ministry of Health entrusted the National Agency for Regional Healthcare Services (Agenzia Nazionale per i Servizi Sanitari Regionali, AGENAS) with the task of monitoring the implementation of recommendations to prevent sentinel events, which are serious adverse events that can compromise patient safety. The aim is to provide Regions and healthcare facilities with a standardised method for managing these events. Currently, there are nineteen recommendations developed with the support of regional experts and other stakeholders.

Objective. This study assessed the applicability and implementation of these recommendations in Italy, also comparing data on the most frequently reported sentinel events.

Materials and Methods. The study, conducted from March to October 2023, involved all acute care, rehabilitation, and post-acute long-term care facilities, both public and private. A questionnaire was used to gather information on the applicability and implementation of the recommendations as of December 31, 2022. The data were analysed using the statistical software Jamovi.

Results. 34.7% of the facilities found no recommendations applicable, while 18.4% considered all 19 recommendations. Regarding implementation, 35.5% did not implement any recommendations, while 11.3% implemented all 19. In particular, Recommendation 4 ("Prevention of patient suicide in hospital") was not implemented by 16% of the facilities.

Conclusions. The applicability of the recommendations varies depending on the type of facility. The implementation rate is influenced by the diversity of participating facilities. The low implementation of Recommendation 4 suggests a need for further investigation to understand the challenges faced.

Key words

- recommendations
- sentinel events
- adverse events
- clinical risk
- risk management

INTRODUCTION

In 2005, the Italian Ministry of Health asked the National Agency for Regional Healthcare Services (Agenzia Nazionale per i Servizi Sanitari Regionali, AGENAS) to activate the monitoring of the implementation at the company level of the recommendations on the prevention of sentinel events to share with the Regions and Autonomous Provinces (PA) and the Health Authorities a univocal method of surveillance and management of the prevention of these events on the national territory, to guarantee the essential levels of care (*livelli essenziali di assistenza*, LEA).

The sentinel event was defined [1] in the 2009 Monitoring Protocol as an "adverse event of particular gravity, potentially avoidable, which may result in death or serious harm to the patient, and which causes a loss of public confidence in the health service. The occurrence of a single case is sufficient to trigger a fact-finding investigation to ascertain whether eliminable or reducible factors contributed to it and to implement appropriate corrective measures by the organisation".

The Joint Commission International [2] has defined a sentinel event as an event that causes death, permanent harm or serious temporary harm to a patient. For this body, sentinel events result in a loss of public confidence in the health service and major repercussions for health organisations, professionals, and local and regional administrations. The term sentinel refers to a system problem that could lead to similar events in the future. As defined by the Joint Commission Interna-

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tional, sentinel events initially included only situational events occurring in patients; since 2013, the concept has been expanded to include "harmful events" for staff, visitors, and the organisation.

To raise awareness of the potential danger of certain circumstances, to indicate the actions to be taken to prevent adverse events and to promote the assumption of responsibility by health professionals, the Ministry of Health, in collaboration with experts from the Regions and Autonomous Provinces, has been drafting and disseminating "Recommendations for the prevention of sentinel events" since 2005, and to date nineteen have been published.

Recommendations for the prevention of sentinel events (*Multimedia Appendix A available online as Supplementary Materials*) are defined [3] as: "Clinical and organisational care recommendations on conditions/situations that may cause serious and/or fatal consequences for patients. They aim to: raise awareness of the potential danger of certain circumstances; provide tools to manage clinical risk and prevent adverse events; promote the assumption of responsibility by operators and policy makers; and constitute reference documents for the evaluation of sentinel events". This study arises from multiple impulses. First, there have been significant regulatory updates. The Law of 8 March 2017, n. 24 [4], introduced provisions regarding the safety of care and the professional liability of healthcare providers. This law also established the Regional Centres for the management of healthcare risks.

Subsequently, the Decree of 29 September 2017 [5] established the National Observatory of Good Practices (Osservatorio Nazionale delle Buone Pratiche sulla Sicurezza nella Sanità). This decree defines its composition and functions, which include the collection of data on risks, adverse events, sentinel events, and those without harm [6].

Finally, the Ministerial Decree of 19 December 2022 [7] addresses the evaluation of quality, safety, and appropriateness of activities for accreditation and contractual agreements with healthcare facilities. Among the verification requirements, it mandates the application and dissemination of clinical risk recommendations.

In addition, the applicability and implementation of the recommendations on clinical risk are included in the LEA questionnaire, which contains the information necessary to verify the fulfilment of the obligations to which the regions are bound according to the regulations in force, as indicated in the State-Regions Agreement of 23 March 2005.

AGENAS, at the request of the Ministry of Health, has developed a dynamic system for monitoring the applicability and implementation of these recommendations to provide a single national platform to support the Regions and Autonomous Provinces [8] .The computerised system allows the Regions and Autonomous Provinces to start monitoring one or more times a year with the support of AGENAS and to be able to constantly observe the status of applicability and implementation of the recommendations by the public and private health and hospital companies in their respective territories. By analogy with other institutional monitoring tools, the general architecture of the system envisages an articulation on three levels: central (AGENAS and Ministry of Health), regional, and corporate. The tool on which the monitoring system is based is a questionnaire on the applicability and implementation of each recommendation.

Aim of the study

Based on the stated objective and activities, the aim of the study is to analyse in detail how the 19 recommendations for the prevention of sentinel events are applicable and implementable across all acute healthcare facilities. This includes evaluating their implementation in different healthcare contexts and comparing data related to the most frequently reported sentinel events in 2022. In summary, the goal is to enhance patient safety through the proper application of the recommendations and to identify potential areas for improvement.

MATERIALS AND METHODS

The descriptive observational study was conducted in Italy, collaborating with risk managers at both the regional level and within individual healthcare facilities. The facility risk managers participated by responding to a questionnaire between March and October 2023, using a secure online platform. To facilitate completion, the platform provided a manual, FAQs, and training modules.

Once the questionnaire was completed by the facility risk managers, the regional risk managers performed a formal review of the content and submitted the final version to AGENAS. The questionnaire, designed specifically for this study, consisted of nine questions. These questions aimed to explore how the individual recommendations were applicable and implemented within the healthcare facilities. The questions were as follows (attached image of the platform):

1. Is the individual recommendation considered applicable in the facility?
2. Has the individual recommendation been implemented, meaning there is a plan or program for its execution?
3. Has the individual recommendation been implemented? (Details per company and facility).
4. What is the total coverage and ongoing implementation for each recommendation? (Provide details per company and facility).
5. What difficulties were encountered during implementation?
6. How is the implementation of the individual recommendation monitored? (Specify the method and frequency).
7. Were one or more stakeholders involved in the implementation process of the individual recommendation?
8. What communication initiatives have been promoted by the facility? (Information, training courses, conferences, etc.).
9. Is there a PDF document referring to the individual recommendation (company procedure)?

This cross-sectional study included all healthcare facilities providing acute care, rehabilitation, and post-acute long-term care, both public and private, accred-

ited according to the Ministry of Health's dataset. The responses collected pertain to the applicability and implementation of the recommendations for preventing sentinel events, updated as of December 31, 2022.

Quality control

To reduce the risk of data entry errors, a check was carried out by the regional contact person (regional risk managers) after completion by the company contact persons. The regional contact persons conducted a formal logical check of what was declared by the company contact persons and verified the relevance of the document attached to the specific Recommendation and the content declared in the individual questions.

Population and sample

For our analysis, we determined the sample size using the dataset from the Ministry of Health, which includes the HSP (Health Service Provider) 11 and HSP 11 bis registries. A total of 1,323 healthcare facilities were anticipated, of which 865 actively participated by completing all the questionnaires for each recommendation. HSP 11 provides a list of accredited healthcare facilities, offering essential information such as type (hospitals, clinics, etc.), location, and services provided. In contrast, HSP 11 bis is an updated version that enriches this data with more specific details regarding facility management, access methods, and the professionals involved. These tools are crucial for managing and monitoring the healthcare system in Italy, as they facilitate data collection and the assessment of service quality, making them an essential reference sample for our research.

Cut-off and limitations

Currently, the implementation of the recommendations is outlined in the document "Notes for completing the documentation for 2019" from the Ministry of Health. Regions must submit information regarding the questionnaire to verify the delivery of essential levels of care (LEA), ensuring that the conditions of appropriateness are met and that the necessary resources for the National Health Service (Servizio Sanitario Nazionale, SSN) are available. To evaluate the results, Regions must complete a table (point AS 1.1. Clinical risk and patient safety) indicating how many recommendations have been implemented in their facilities. A Region is considered compliant if it has implemented at least 14 out of 18 recommendations and if at least 80% of the healthcare organisations in the Region have applied each recommendation. Unfortunately, the missing data from one Region is due to the absence of a regional clinical risk manager during the monitoring; this lack of a regional manager was a limitation of the study, as it hindered the completion of the questionnaires by the risk managers of the healthcare facilities. Another limitation to consider is the low applicability value for some recommendations, as certain recommendations, as mentioned earlier, are tied to the type of services they provide.

Statistical analysis

The data were entered and organised in a Microsoft Excel file, to allow the data of the participating structures to be entered (Structure Code; Region Code; Name of Region or Autonomous Province; Province; Province Code; Name of Health Authority; Municipality; Structure Name; Type; Applicability, Implementation) and analysed with the statistical calculation software Jamovi version 2.3.28.

RESULTS

The following cross-sectional observational study investigated how healthcare facilities reacted in terms of applicability and implementation to the recommendations for the prevention of sentinel events proposed by the Italian Ministry of Health.

There were 1,323 facilities involved in Italy, of which 865 responded, broken down by individual Region or Autonomous Province. The percentage of facilities for each Region and Autonomous Province is shown in *Table 1*.

Table 2 shows the total expected facilities and the responding facilities by type and level of care complexity. The typologies with the highest representation in the sample are: Private nursing homes – Accredited constituting 37.80% of the sample; and Directly operated hospitals constituting 45.27% of the sample, while the lowest percentage is represented by Research Institutions 0.23% of the sample and Private University Polyclinics 0.15% of the sample. The remaining types accounted for less than 16.55% of the sample.

Out of the total of 1,323 facilities involved, of which 865 responded, the percentage of recommendations that were considered applicable and/or responded to the questionnaire was analysed: 458 facilities were not considered applicable and/or responded for any Recommendation, representing 34.62% of the sample, while 18.37% of the facilities considered applicable and/or responded for all nineteen recommendations. 0.08% of the facilities considered four to six recommendations as applicable and/or responded, 0.23% considered one to three recommendations as applicable and/or responded, 0.30% considered seven to eight recommendations as applicable and/or responded, 0.53% considered ten recommendations as applicable and/or responded, 1.44% of the facilities considered nine recommendations as applicable and/or responded, and a percentage ranging from 2.95% to 4.38% considered eleven to eighteen recommendations as applicable and/or responded.

The percentage of applicability per recommendation of each facility involved was analyses, as shown in *Table 3*.

The lowest percentages of applicability of the recommendations in all the typologies in the sample are: Recommendation 6 "Recommendation for the prevention of maternal death related to labour and/or delivery" and Recommendation 16 "Recommendation for the prevention of death or permanent disability in healthy newborns weighing >2,500 grams not related to congenital disease", being recommendations that preclude types of facilities with the presence of a delivery room, while some recommendations that are applicable in any context have a high percentage of applicability.

The percentage of implementation of the recommendations out of the total number of facilities was then analysed: 470 facilities did not implement and/or

Table 1
Data on the expected and responding Italian Regions and Autonomous Provinces in monitoring recommendations for the prevention of sentinel events

Regions	Expected	Percentage of total	Respondents	Percentage respondents
Abruzzo	27	2.04	27	100.00
Basilicata	15	1.13	2	13.33
Calabria	57	4.31	37	63.16
Campania	128	9.67	91	71.09
Emilia-Romagna	102	7.71	95	92.16
Friuli Venezia Giulia	21	1.59	19	90.48
Lazio	126	9.52	88	69.05
Liguria	36	2.72	25	69.44
Lombardia	190	14.36	166	86.84
Marche	39	2.95	15	38.46
Molise	9	0.68	3	33.33
Piemonte	99	7.48	67	67.68
Provincia Autonoma di Bolzano	18	1.36	18	100.00
Provincia Autonoma di Trento	15	1.13	5	33.33
Puglia	82	6.20	38	46.34
Sardegna	40	3.02	4	10.00
Sicilia	138	10.43	0	0.00
Toscana	76	5.74	65	80.26
Umbria	24	1.81	24	100.00
Valle d'Aosta	2	0.15	1	0.00
Veneto	79	5.97	75	94.94
Total	**1323**	**100.00**	**865**	**65.38**

Table 2
Types of responding facilities by level of complexity in monitoring recommendations for the prevention of sentinel events

Types of structures	Expected	Percentage of the total	Respondents	Percentage respondents
AO integrated with the National Health Service	16	1.21	9	56.25
AO integrated with the university	27	2.04	26	96.29
Hospital	49	3.70	29	59.18
Private nursing home – Accredited	500	37.80	283	56.60
Research organisation	3	0.23	2	66.66
Institutes for hospitalization and care with a scientific character – Foundation	11	0.83	10	90.90
Scientific institute for hospitalization and treatment – Private	42	3.17	33	78.57
Institutes for hospitalization and care with a scientific character – Public	32	2.42	20	62.50
Qualified institute presidium of the USL	14	1.06	10	71.42
Directly operated hospital	599	45.27	418	69.72
Classified or assimilated hospital within the meaning of article 1 last paragraph of Law 132/1968	28	2.12	23	82.14
Private university hospital	2	0.15	2	100.00
Total	**1323**	**100.00**	**865**	**100.00**

AO: Hospital trust integrated into the National Health Service (NHS), meaning it is part of the publicly funded healthcare system, providing comprehensive healthcare services to the population; USL: Local Health Units.

Table 3
Percentage of applicability per Recommendation of each facility

N	Recommendations	Yes	No	Not filled in
1	Correct use of concentrated solutions of potassium chloride (KCL) and other concentrated solutions containing potassium	822/865 (95.03%)	34/865 (3.93%)	9 (1.04%)
2	Recommendation to prevent retention of gauze, instruments, or other material within the surgical site	658 (76.07%)	152 (17.57%)	55 (6.36%)
3	Recommendation for proper identification of patients, surgical site, and procedure	706 (81.62%)	112 (12.95%)	47 (5.43%)
4	Recommendation for the prevention of patient suicide in hospital	830 (95.95%)	25 (2.89%)	10 (1.16%)
5	Recommendation for the prevention of transfusion reaction due to AB0 incompatibility	808 (93.41%)	49 (5.66%)	8 (0.92%)
6	Recommendation for the prevention of maternal death related to labor and/or delivery	337 (38.96%)	369 (42.66%)	159 (18.38%)
7	Recommendation for the prevention of death, coma or serious harm resulting from errors in drug therapy	848 (98.03%)	5 (0.58%)	12 (1.39%)
8	Recommendation to prevent acts of violence against health workers	851 (98.38%)	12 (1.39%)	2 (0.23%)
9	Recommendation for the prevention of adverse events resulting from malfunction of medical devices/medical electrical equipment	845 (97.69%)	11 (1.27%)	9 (1.04%)
10	Recommendation for the prevention of bisphosphonate osteonecrosis of the maxilla/mandible	518 (59.88%)	245 (28.32%)	102 (11.80%)
11	Death or serious injury resulting from a malfunction of the transport system (in-hospital, out-of-hospital)	732 (84.62%)	103 (11.91%)	30 (3.47%)
12	Prevention of errors in therapy with "Look-alike/sound-alike" drugs	855 (98.84%)	5 (0.58%)	5 (0.58%)
13	Recommendation for the prevention and management of patient falls in healthcare facilities	859 (99.30%)	3 (0,35%) (0.35%)	3 (0.35%)
14	Recommendation for the prevention of errors in therapy with antineoplastic drugs	486 (56.18%)	275 (31,79%) (31.80%)	104 (12,02%) (12.02%)
15	Death or serious injury resulting from incorrect assignment of the triage code in the 118 operations center and/or within the emergency department	466 (53.87%)	324 (37.46%)	75 (8.67%)
16	Recommendation for the prevention of death or permanent disability in a healthy newborn weighing >2,500 grams unrelated to congenital disease	338 (39.07%)	362 (41.85%)	165 (19.08%)
17	Recommendation for reconciliation of drug therapy	850 (98.26%)	3 (0.35%)	12 (1.39%)
18	Recommendation for the prevention of errors in therapy resulting from the use of abbreviations, acronyms, acronyms and symbols	839 (97.00%)	15 (1.73%)	11 (1.27%)
19	Recommendation for handling solid oral dosage forms	812 (93.87%)	36 (4.16%)	17 (1.97%)

AB0: AB0 reaction refers to an immune response that occurs when there is an incompatibility between the donor's and recipient's AB0 blood groups, leading to the destruction of transfused red blood cells; N: number.

respond to any recommendations, representing 54.33%. For each recommendation, the implementation related to applicability was analysed. The recommendations that show the lowest values in terms of implementation, despite low percentages of non-applicability are: Recommendation 4 "Recommendation for the prevention of patient suicide in hospital"; Recommendation 17 "Recommendation for the reconciliation of drug therapy"; Recommendation 18 "Recommendation for the prevention of errors in therapy resulting from the use of abbreviations, acronyms, acronyms, and symbols" and Recommendation 19 "Recommendation for the handling of solid oral pharmaceutical forms".

The percentages of facilities that implemented between one and eleven recommendations were analysed, those that, by type of participating facilities, could be applicable in all the facilities involved in the study. Among the Hospital authorities integrated with the University those with <eleven recommendations implemented are 223 and 177 Directly managed hospitals. We have the lowest figure among Research Institutions and Private University Polyclinics with several implemented recommendations <11 equal to 1.

Comparing the data on the three most reported sentinel events in 2023 and 2022 [9] with the most frequently reported events in the report published by the Ministry of Health (January 2005 - December 2020) [10], the following sentinel events highlighted:

- Sentinel event number 9: "Death or serious harm due to a patient falling"
- Sentinel event number 10: "Suicide or attempted suicide of a patient in hospital"
- Sentinel event number 12: "Death or serious harm due to violence against a healthcare worker"

For each of these events, the percentage of facilities, by type, that have not implemented the related recom-

mendations for the prevention of sentinel events was analyzed. The recommendations in question are:

- Recommendation 4: "Prevention of patient suicide in hospital"
- Recommendation 8: "Prevention of violence against healthcare workers"
- Recommendation 13: "Prevention and management of patient falls in healthcare facilities".

As shown in *Table 4*, for Recommendation number 4 "Recommendation for the prevention of patient suicide in hospital", out of 855 responding facilities 720 stated that they implemented it and 135 did not (15.79%). The largest percentage of non-implementation is represented by the Institutes for hospitalisation and care with a scientific character – Public (35.00%), the Hospital companies integrated with the National Health Service (22.22%) and the Private nursing home accredited (19.93%). For Recommendation number 8 "Recommendation to prevent acts of violence against health workers", out of 852 responding facilities 794 declared to implement it and 68 did not (7.89%). The highest percentage of non-implementation is represented by the Institutes for hospitalisation and care with a scientific character – Public (30.00%), by the Hospital companies integrated with the National Health Service (22.22%) and by the Private nursing home – Accredited (13.17%).

For Recommendation number 13 "Recommendation for the prevention and management of patient falls in health care facilities", out of 862 responding to facilities 831 declared to implement it and 31 did not (3.60%). The highest percentage of non-implementation is represented by the Institutes for hospitalisation and care with a scientific character – Public for 20.00% and by the Hospital companies integrated with the National Health Service for 11.11%.

DISCUSSION

The analysis conducted showed that, out of a total of 1,323 facilities, 865 responded to the administered questionnaire. The percentage of non-respondents is prevalent in some regions and evenly distributed across the country, and it is evident in certain types of facilities without a clear distinction among different levels of complexity. This situation raises questions about the potential to optimise communication and awareness regarding the importance of participation in the questionnaire, suggesting that health authorities should intensify informational efforts in areas with lower response rates. The number of recommendations deemed applicable varies according to the different types of facilities and the services provided. However, the number of those actually implemented is influenced not only by their applicability but also by the variety of facility types. This

Table 4
Implementation of Recommendations 4, 8, 13 by type of facility

	Recommendation 4 "Recommendation for the prevention of patient suicide in hospital"				Recommendation 8 "Recommendation to prevent acts of violence against health workers"				Recommendation 13 "Recommendation for the prevention and management of patient falls in healthcare facilities"			
	A	**NI**	**I**	**%NI**	**A**	**NI**	**I**	**%NI**	**A**	**NI**	**I**	**%NI**
Hospital companies integrated with the National Health Service	9	1	8	11.11	9	2	7	22.22	9	2	7	22.22
Hospital company integrated with the University	26	0	26	0.00	26	0	26	0.00	26	1	25	3.85
Hospital company	29	1	28	3.45	29	1	28	3.45	29	2	27	6.90
Private nursing home – Accredited	280	9	271	3.21	281	56	225	19.93	281	37	244	13.17
Research organisation	2	0	2	0.00	2	0	2	0.00	2	0	2	0.00
Institutes for hospitalisation and care with a scientific character – Foundation	10	0	10	0.00	10	0	10	0.00	10	0	10	0.00
Institutes for hospitalisation and care with a scientific character – Private	33	0	33	0.00	33	4	29	12.12	33	1	32	3.03
Institutes for hospitalisation and care with a scientific character – Public	20	4	16	20.00	20	7	13	35.00	20	6	14	30.00
Qualified institute presidium of the local health unit	10	0	10	0.00	10	1	9	10.00	10	1	9	10.00
Directly operated hospital	418	16	402	3.83	410	63	347	15.37	417	17	400	4.08
Classified or assimilated hospital within the meaning of article 1 last paragraph of Law 132/1968	23	0	23	0.00	23	1	22	4.35	23	1	22	4.35
Private university hospital	2	0	2	0.00	2	0	2	0.00	2	0	2	0.00
Total	**862**	**31**	**831**	**3.60**	**855**	**135**	**720**	**15.79**	**862**	**68**	**794**	**7.89**

A: applicable; NI: not implemented; I: implemented.

indicates a need for in-depth qualitative analysis to better understand the reasons behind low implementation rates and the specific barriers faced by some facilities.

Among the recommendations that exhibit critical issues in their implementation are Recommendation n. 4 "Recommendation for the prevention of patient suicide in hospital" (13.25%) and Recommendation n. 6 "Recommendation for the prevention of maternal death related to labor" (11.57%). These data highlight the need to develop targeted training and awareness programs for healthcare personnel to improve understanding and skills in managing these critical issues.

In contrast, the remaining recommendations show an implementation rate exceeding 90%, suggesting that some practices are already well integrated into facility routines. It may be beneficial to analyse the success factors of these recommendations and consider adopting similar strategies for those that are less implemented.

Further critical issues emerge from a cross-analysis of sentinel event data and the corresponding recommendations. For instance, sentinel event number nine "Death or serious injury due to patient fall" is directly linked to Recommendation n. 13 on fall prevention. This suggests that the lack of effective implementation of such recommendations could be correlated with an increase in sentinel events. Therefore, it is essential to implement ongoing monitoring and specific intervention strategies to reduce these incidents.

Finally, the data present some limitations, as this is the first time data collection has been conducted, providing a general overview of situations that require more detailed analysis. It is suggested to establish a regular cycle of data collection and analysis to monitor progress over time and make necessary adjustments. It is crucial to conduct comparisons between facilities while considering their organisational aspects, fostering a collective reflection on the necessary changes in risk management practices in Italy.

CONCLUSIONS

There is a significant percentage of non-respondents, evenly distributed across different regions and types of facilities. This raises concerns about the effectiveness of communication and awareness regarding the importance of participation in the questionnaire, suggesting that health authorities should intensify informational efforts, especially in areas with lower response rates.

The recommendations considered applicable vary according to the different types of facilities and services, highlighting the need for in-depth qualitative analyses to understand the reasons behind the low implementation rates and the specific barriers faced by some facilities. Recommendations that present critical issues, such as those related to the prevention of suicide and maternal death, require the urgent development of targeted training and awareness programs for healthcare personnel to improve skills in managing these critical issues.

In contrast, recommendations with implementation rates exceeding 90% suggest that some practices are already well integrated into facility routines. It is essential to analyse the success factors of these recommendations and consider adopting similar strategies for those that are less implemented.

Moreover, the cross-analysis of sentinel event data and the corresponding recommendations highlights the correlation between the lack of effective implementation of recommendations and the increase in sentinel events, such as patient falls. Therefore, it is essential to implement ongoing monitoring and specific intervention strategies to reduce such incidents.

Finally, since this is the first data collection conducted, it is important to recognize certain limitations. It is advisable to establish a regular cycle of data collection and analysis to monitor progress over time and make necessary adjustments. Additionally, it is crucial to conduct comparisons between facilities while considering their organisational aspects, fostering a collective reflection on the necessary changes in risk management practices in Italy. Only through a collaborative and systematic approach will it be possible to improve the quality of care and ensure greater patient safety.

Author contributions

Conceptualization: ES; methodology: ES; software: ES, MM; validation: ES, MTL, DM; formal analysis: ES, MTL; investigation: ES, MTL; resources: ES; data curation: ES, MM, MTL; writing – original draft preparation: ES, MC, MTL; writing – review and editing: ES, MM, MTL, DM; visualization: ES; supervision: MTL; project administration: MTL, DM. All Authors have read and approved the published version of the manuscript.

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Book Reviews, Notes and Comments

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EVOLUZIONE BIOLOGICA E RIVOLUZIONI CULTURALI
Un approccio alla complessità degli esseri viventi
Filippo Belardelli, Eleonora Aricò
Trieste: Scienza Express Edizioni; 2024
300 p.
ISBN 979-12-80068-90-3
€ 27,00

[Biological evolution and cultural revolutions. An approach to the complexity of living beings]

As its first quotation, this book contains, unsurprisingly, that of the British biologist and naturalist Charles Darwin "Man in his arrogance thinks himself a great work, worthy the interposition of a great deity. More humble, and I believe truer, to consider him created from animals".

This citation is also prolegomenon to address the structurally biological perspective that leads and directs this text, which opens with an initial chapter: "*Prima del DNA: le teorie sull'evoluzione biologica*" ("Before DNA: theories of biological evolution"), just to seal its expository path. The chapter that follows is, in fact, more overtly historical: "*Il dibattito sull'evoluzione tra Ottocento e Novecento*" ("The Debate on evolution between the Nineteenth and Twentieth centuries").

The text also delves into the ideological drifts that start from Lamarckism and Darwinism, dwelling on the Lysenko case in the Soviet Union, on the long and hard-fought (never dormant) history of Social Darwinism, eugenics and physical anthropology: these disciplines both serve as sad biological bases of the "ethological" views that led to a terrible extermination operation based just on the alleged difference and "inferiority," even behavioral, of the various human "races". Thus, increasing some of the frequently nefarious effects of seemingly innocuous biomedical research: perhaps confined to the icy environments of the inquiry, conducted among laboratories, stables and sterile rooms.

The crux of the book is what the authors call the "overcoming of the geno-centric view," a detailed history of that crack in the central dogma of biology that will also profoundly influence the scientific generations of this volume's authors. Text precisely built on the careful selection of some of the most relevant "steps and passages" in recent biomedicine.

The analytical novelty sparked by Epigenetics, the pivot of Chapter 4, permeates and branches out into the whole book (which, however, represents an overview that is never overly didactic and absolutely free of conventional overtones), outlining some of the main topics in contemporary biomedical disciplines. It overviews the analysis of complex systems, which obviously invests the dynamic assemblies that make up a biological organism (with emphasis on System Biology) as well as the interaction between different organisms and individuals (e.g., social interactions), the tumultuous contemporary studies on the microbiota and consequently on the new prospective analyses on how a dietary style can profoundly affect our health. This latter issue includes a roundup on the development between nutrigenetics and nutrigenomics, also complemented by some original and vivid information on the environmental conditioning affecting gametogenesis.

The chapter editorially placed at the center of the volume, entitled: "*Epigenetica ed ereditarietà*" ("Epigenetics and heredity") represents the most lively and original contribution of the text, and not surprisingly takes its cue from the role of genes and environment in the determination of aggressive and violent behavior (in laboratory mice as in the human species).

In particular, it narrates of a study that astonished and in its own way revolutionized the style of analysis of phenomena whose regulations are even transmitted for the successive generations: this thanks to the phenotypic expression of genotypes that preserve traces of biographical events occurred during previous generations. Subtly, the discussion implies in not even a little overt form, how basically the triumph of contemporary epigenetics in some ways "compensates" for the Lamarckist viewpoint. A perspecive, this latter, very often completely obliterated by the objectively more compelling Darwinist positions: those later exalted by that long phase of contemporary neo-Darwinism that followed the mighty advance of post-Mendelian genetics, and especially by the discovery in the mid-1950s of DNA and RNA as the bases of the transmission of genotypic and therefore phenotypic characters of all living organisms.

One of the features of this text is precisely the wise ability of Belardelli and Aricò to choose a few paradigmatic studies (not surprisingly, whose authors earned Nobel Prizes), almost as if they were steps on a long ladder that gradually advanced the biomedical sciences.

However, the most original feature of this book, which really makes it a relevant publishing event, is the unusual fusion of philosophical-oriented perspectives in a text that dynamically reviews the major advances in contemporary biomedicine. The references to Spinoza, the almost surreal presence of a philosopher

who has certainly influenced generations conducting research since the late 1970s is that of Emanuele Severino. Alongside their fathers, the founders of Western philosophy emerge and accompany the biomedical discoveries, almost providing a frame of reference for the purely scientific activities that unfold over the decades. The reference to "*Il canto notturno di un pastore errante dell'Asia*," equal poem by Giacomo Leopardi, reveals the deep humanistic culture, which alongside Descartes and philosophers T. Morton or Y.N. Harari, accompany the more specifically scientific chapters in complete heuristic harmony.

This is not by chance. Indeed, senior author Filippo Belardelli has both a degree in Philosophy and in Biological Sciences: which explains this particular style of exposition, where the history of ideas produced by original human minds makes little distinction between humanistic or scientific disciplinary backgrounds: we do not forget the debate within the British intellectual community that pitted those who, in the Royal Society, preferred the designation of "*natural philosopher*" instead of "scientist" for members whom we would then call scientists tout court today. The latter prevailed, as we know.

The text cannot fail to include the authors' references to their past and actual specialized knowledge, from the lengthy studies on interferon to the reflections that a public institute dealing with cell biology necessarily exerts on industrial development, precisely due to the innovative capacities of research, especially that public research that has the ethical and moral task of making up for the lonely disciplinary areas that do not naturally attract private capital for their development. Also, the interest in advances in cellular and especially molecular bases in understanding phenomena of terrible social impact such as addiction testify to the ethical sensitivity of the authors.

Chapter 9 "*Le sfide dell'Homo sapiens per un mondo sostenibile*" ("The challenges of Homo sapiens for a sustainable world"), which encompasses the paragraphs "Who are we and where are we going?" and especially "Priority challenges for biomedical research today", actually encapsulates a concise but visionary summary of what the challenges might be today for the near future of research, essentially aimed at the psychophysical well-being of humanity. We should never forget those areas of the planet where human survival is jeopardized by hunger or disease, perhaps diseases long since eradicated or effectively controlled in the wealthy parts of the planet. Hints of the interactions between sustainability management choices and their reflections on health conditions also touch on a topic as topical as it is burning. They demonstrate the authors' deep sensitivity to sensitive issues as well.

The Preface to the book, written by Umberto Agrimi (veterinarian and executive at the Italian National Institute of Health), re-proposes an absolutely non-anthropocentric view; not coincidentally, it concludes with a fine quote from sociobiologist Edward O. Wilson who praises the structural unity of all living beings with the species *Homo sapiens*. Agrimi therefore emphasizes, as a militant researcher, the growing importance of One Health perspectives, those that see in the complex and multifaceted world of animal and plant beings and in their environments, the analytic key to the future of biomedical sciences and global terrestrial health as well as its protection.

Very usefully, the text is rich with a voluminous glossary, which starts from a few general headwords to list highly specialized terms as well. It should be emphasized that throughout the text, glossary included, the humanistic flavor of this volume infuses the treatment through clever and regular reflections about the etymological origins of the individual scientific terms, another element that in its own way makes the volume a rather rare example of a successful fusion of C.P. Snow's "Two cultures" ("*Due culture*").

Finally, thanks to quotations or explicit acknowledgments, the book contributes also to reconstruct historiographically the Istituto Superiore di Sanità (the Italian National Institute of Health) that hosted and hosts the authors. This text leaves an editorial trace of the scientific activities of the presidents and directors who guided the Institute: on which stands out the unforgettable figure of the virologist Giovanni Battista Rossi, mentor of Belardelli (as of many of the best researchers of his generation) who, in a still in some respects marginal Italy, knew how to make the ISS a leader in the management of the "Aids emergency," leaving a scientific, but also managerial, example that Belardelli himself, in his activity as head of complex and diversified structures, was able to continue and make flourish.

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INCONTRI CON GLI ASINI
Percorsi educativi, formativi e terapeutici
Damiano Biscossi,
Elena Mignosi, Birgit Winther
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[Meeting with donkeys. Educational, training and therapeutic courses]

Animal-Assisted Therapy (AAT), often referred to as Pet therapy, is presently considered a therapeutic approach that involves domestic animals with the aim of promoting emotional, psychological, and physical health and well-being in humans. AAT interventions are often led by qualified professionals who facilitate structured interactions between patients and animals, with clearly defined therapeutic objectives [1]. It is important to distinguish AAT from Animal-Assisted Activities (AAAs), which do not have specific therapeutic goals,

as well as from the use of service animals, such as guide dogs for the visually impaired.

Although species like horses and donkeys have been increasingly employed in various contexts, dogs have long been regarded as the preferred species for pet therapy due to their long-standing evolution alongside humans, as well as their sociability and trainability. For example, therapeutic strategies that leverage the emotional connection between children with autism spectrum disorders and dogs may possibly be an effective complementary way to reduce social withdrawal. The simple, easily interpretable movements of dogs can help facilitate engagement in straightforward social actions that do not rely on verbal communication and are highly repeatable and predictable (e.g., throwing a ball for the dog to fetch, walking the dog on a leash, or giving hand commands) [2, 3]. However, it is important to recognize that while non-human animals are increasingly acknowledged for their ability to provide unique opportunities for positive social interaction, the evidence supporting the use of AAT in clinical populations is still limited by several methodological challenges, including a scarcity of randomized controlled trials and poor replication.

Italy is one of the few countries to have implemented national regulations for Animal-Assisted Interventions (AAI). In 2015, an agreement was formalized between the Italian Government and regional authorities, establishing official guidelines for AAI. These guidelines specify the training requirements for each single professional type involved in the design and delivery of AAI (i.e., veterinarians, animal handlers, health professionals), set behavioral standards for the animals involved, and outline actions to ensure the welfare of the animal involved and ongoing assessment of benefits for participants.

As part of the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) activities, the team led by psychobiologist Francesca Cirulli contributed in the years to the development of the national guidelines and has spent over a decade conducting research to evaluate the actual benefits of AAIs for different populations [2-6]. The group also produced a technical-scientific report on the methodologies for assessing the suitability of the animals involved in AAIs and their welfare, edited by Nadia Francia [7]. In addition, in 2019, Francesca Cirulli and Marta Borgi edited the book *Che cos'è la pet therapy* (What is Pet Therapy) to provide the general Italian public with scientifically grounded insights into this complex topic.

According to the current Italian guidelines, only five specie — dogs, horses, donkeys, cats, and rabbits — are allowed for AAT at the national level. A 2017 Italian survey found that donkeys were the third most commonly involved species in AAI [8]. However, despite some potential of these approaches, scientific evidence on the benefits of donkey-assisted interventions remains scarce [9, 10], especially when compared to the growing body of research supporting the positive effects of dog- and horse-assisted approaches on human health.

The present book provides the Italian public with an overview of interventions employing donkeys both in Denmark (Section 1) and in Italy (Section 2). The authors are all from the educational science field; therefore, inevitably this small volume exudes a humanistic aroma. The book is organized into chapters, each focusing on different facets of the human-donkey relationship. Chapter 1 offers an historical overview of donkeys in therapeutic settings, while the subsequent chapters delve into their potential to ameliorate mental health and support physical recovery in humans. The final chapter provides a compelling exploration of the bond formed between humans and donkeys, highlighting how this connection can also be applied in educational contexts. The text draws from a rich tradition of emotional bonding between humans and equines, featuring real-life, narrative-type stories and heartwarming anecdotes that illustrate the transformative power of animals in our lives. However, it lacks scientific evidence from international peer-review journals to substantiate its claim.

This essay has some limitations. The passionate approach taken by the faithful authors likely represents a minor flaw for a more rigorous scientific audience. Rather rich in content and accessible to a broad audience, the book may though provide a few valuable insights for healthcare professionals, veterinarians, and anyone interested in the emotional and behavioral traits of this somehow surprisingly complex animal species, whose ethological characteristics and behavioral changes have been shaped by a long domestication process, likely influenced by scattered selective actions from different and diversified human populations.

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Publications from International Organizations on Public Health

Edited by
Annarita Barbaro

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS (FAO)

The State of Food Security and Nutrition in the World 2024. Financing to end hunger, food insecurity and malnutrition in all its forms. Rome: FAO, IFAD, UNICEF, WFP and WHO 2024; 286 p. ISBN 978-92-5-138882-2. The theme of this year's report focuses on the financing to achieve Sustainable Development Goal (SDG) Targets 2.1 and 2.2 (financing to end hunger, food insecurity and malnutrition in all its forms). The report provides a definition of financing for food security and nutrition and the guidance to implement it. To support such implementation, the five participating organizations commit to advocate for, and support, data development for a better global accounting system of financing for food security and nutrition. There are also recommendations regarding the efficient use of innovative financing tools and reforms to the food security and nutrition financing architecture. Establishing a common definition of financing for food security and nutrition, and methods for its tracking, measurement and implementation, is an important first step towards sustainably increasing the financing flows needed to end hunger, food insecurity and all forms of malnutrition, and to ensure access to healthy diets for all.

Pesticide residues in food 2023 Evaluation part I – Residues. Joint FAO/WHO Meeting on Pesticide Residues. Rome. Rome: Food and Agriculture Organization of the United Nations and World Health Organization 2024; 2933 p. ISBN (FAO) 978-92-5-138770-2 ISBN (WHO) 978-92-4-009018-7 (electronic version) ISBN (WHO) 978-92-4-009019-4 (Print version). The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) comprises the FAO Panel on Pesticide Residues and the WHO Core Assessment Group. The WHO Core Assessment Group is responsible for reviewing pesticide toxicological data and estimating acceptable daily intake (ADI) and acute reference doses (ARfDs) and characterizing other toxicological criteria. The FAO Panel on Pesticide Residues reviews the results of a range of studies including residue field trials and processing studies. These studies, called evaluations, are conducted for each individual pesticide and published in this report for the benefit of national governments who may use the information while undertaking national assessments.

Residue evaluation of certain veterinary drugs. Joint FAO/WHO Expert Committee on Food Additives, 98th Meeting 20-29 February 2024. Rome: Food and Agriculture Organization of the United Nations and World Health Organization 2024; 120 p. ISBN (FAO) 978-92-5-139126-6 ISBN (WHO) 978-92-4-010141-8 (electronic version) ISBN (WHO) 978-92-4-010142-5 (print version). This volume of FAO JECFA Monographs contains residue evaluation of certain veterinary drugs prepared at the 98th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), held from 20 to 29 February 2024. This JECFA meeting was convened specifically to consider residues of veterinary drugs in food-producing animal species. The tasks for the Committee were to further elaborate principles for evaluating the safety of residues of veterinary drugs in food and for establishing acceptable daily intakes (ADIs) and/or acute reference doses (ARfDs), and to recommend maximum residue limits (MRLs) for substances when they are administered to food-producing animals in accordance with good veterinary practice (GVP) in the use of veterinary drugs. The present volume contains monographs on the evaluations of residue data of substances scheduled for evaluation at the request of the Codex Committee on Residues of Veterinary Drugs in Food. A summary of the recommendations on compounds is also presented in this report. The enclosed monographs provided the scientific basis for the recommendations of MRLs.

INTERNATIONAL SCIENCE COUNCIL (ISC)

Snapshots of Reform. Researcher Evaluation within Science Organizations. Paris: International Science Council 2024; 33 p. ISBN: 979-8-9859206-3-5. This report is a joint publication by the Global Young Academy (GYA), the InterAcademy Partnership (IAP) and the International Science Council (ISC). Derived from desk-based research, surveys, and interviews, this report provides insights into the current state of researcher evaluation. The diverse perspectives captured highlight both the challenges and opportunities that lie ahead and recognize that a one-size-fits-all approach is neither feasible nor desirable. The report finds that our organizations can play a role in supporting the reform of researcher evaluation through: championing missing voices, lending the credibility needed to put reform on the agenda, supporting interventions that have reached

their "tipping point", protecting researcher mobility within the global system and promoting the exchange of ideas and lessons.

UNITED NATIONS ENVIRONMENT PROGRAMME (UNEP)

Navigating New Horizons: A global foresight report on planetary health and human wellbeing. Nairobi: United Nations Environment Programme 2024; 108 p. ISBN: 978-92-807-4166-7. This report, made jointly by the United Nations Environment Programme (UNEP) and the International Science Council (ISC), identifies and assesses the so-called "signals of change" – early symptoms or indications of changes that could result in potential disruptions or important developments on the horizon for which the world may need to prepare. It also discusses eight critical shifts (or emerging phenomena) that are accelerating the triple planetary crisis of climate change, nature and biodiversity loss, and pollution and waste, and some of the interconnections between them. These shifts include humanity's degradation of the natural world, the rapid development of technologies such as AI, competition for natural resources, widening inequalities and declining trust in institutions. Eighteen accompanying signals of change – identified by hundreds of global experts through regional and stakeholder consultations that included youth – offer a deeper glimpse into potential disruptions, both positive and negative, that the world must prepare for.

Emissions Gap Report 2023: Broken Record. Temperatures hit new highs, yet world fails to cut emissions (again). Nairobi: United Nations Environment Programme 2023; 108 p. ISBN: 978-92-807-4098-1. The Emissions Gap Report (EGR) is UNEP's spotlight report launched annually in advance of the annual Climate negotiations. The EGR tracks the gap between where global emissions are heading with current country commitments and where they ought to be to limit warming to 1.5°C. This year's report finds that there has been progress since the Paris Agreement was signed in 2015. Greenhouse gas emissions in 2030, based on policies in place, were projected to increase by 16 per cent at the time of the agreement's adoption. Today, the projected increase is 3 per cent. However, predicted 2030 greenhouse gas emissions still must fall by 28 per cent for the Paris Agreement 2°C pathway and 42 per cent for the 1.5°C pathway. As things stand, fully implementing unconditional Nationally Determined Contributions (NDCs) made under the Paris Agreement would put the world on track for limiting temperature rise to 2.9°C above pre-industrial levels this century. Fully implementing conditional NDCs would lower this to 2.5°C. The EGR report calls for all nations to accelerate economy-wide, low-carbon development transformations. Countries with greater capacity and responsibility for emissions will need to take more ambitious action and support developing nations as they pursue low-emissions development growth.

EUROPEAN FOOD SAFETY AUTHORITY (EFSA)

EFSA Scientific Committee, More S.J, Benford D, Hougaard Bennekou S, et al. **Guidance on risk–benefit assessment of foods.** EFSA Journal 2024, 22(7), e8875. The EFSA Scientific Committee has updated its 2010 Guidance on risk–benefit assessment (RBA) of foods. While it retains the stepwise RBA approach, it provides additional methods for complex assessments, such as multiple chemical hazards and all relevant health effects impacting different population subgroups. The updated guidance includes approaches for systematic identification, prioritisation and selection of hazardous and beneficial food components. It also offers updates relevant to characterising adverse and beneficial effects, such as measures of effect size and dose–response modelling. The guidance expands options for characterising risks and benefits, incorporating variability, uncertainty, severity categorisation and ranking of different (beneficial or adverse) effects. The impact of different types of health effects is assessed qualitatively or quantitatively, depending on the problem formulation, scope of the RBA question and data availability. Additional approaches are presented, such as probability of all relevant effects and/or effects of given severities and their integration using severity weight functions. The update includes practical guidance on reporting results, interpreting outcomes and communicating the outcome of an RBA, considering consumer perspectives and responses to advice.

EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Turck D, Bohn T, Castenmiller J. et al. **Guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283.** EFSA Journal 2024, 22(9): e8961. The European Commission requested EFSA to update the scientific guidance for the preparation of applications for authorisation of novel foods, previously developed following the adoption of Regulation (EU) 2015/2283 on novel foods. This document provides advice on the scientific information needed to be submitted by the applicant towards demonstrating the safety of the novel food. Requirements pertain to the description of the novel food, production process, compositional data, specifications, proposed uses and use levels and anticipated intake of the novel food. Furthermore, information needed in sections on the history of use of the novel food and/or its source, absorption, distribution, metabolism, excretion, toxicological information, nutritional information and allergenicity is also described. The applicants are also required to integrate and interpret the data presented in the different sections to provide their overall considerations on how the information supports the safety of

the novel food under the proposed conditions of use. Where potential health hazards have been identified, they are to be discussed in relation to the anticipated intake of the novel food and the proposed target populations.

WORLD HEALTH ORGANIZATION (WHO)

Manual for plague surveillance, diagnosis, prevention and control. Geneva: World Health Organization 2024; 92 p. ISBN 978-92-4-009042-2 (electronic version) ISBN 978-92-4-009043-9 (print version). This manual provides comprehensive information on plague epidemiology and recommendations for surveillance, diagnosis, clinical management, and prevention. It also aligns with WHO's proposals from the 75th World Health Assembly to enhance global health emergency preparedness and response. Key revisions include the use of rapid diagnostic tests in varied contexts, the inclusion of fluoroquinolones as a first-line treatment option, and updated protocols for personal protective equipment when handling plague-infected corpses. These recommendations were published in 2021 and are based on evidence reviewed during an international expert meeting in 2020. This manual is developed for clinicians and public health professionals who may be tasked with ensuring preparedness or response. This manual is also developed to inform the policy- and decision-makers responsible for developing national policies and guideline documents as well as for making purchasing arrangements and implementing training programmes.

Clinical practice guidelines for influenza. Geneva: World Health Organization 2024; 241 p. ISBN 978-92-4-009775-9 (electronic version) ISBN 978-92-4-009776-6 (print version). This WHO Clinical practice guideline for influenza is an update and expansion from the previously published WHO guideline on the clinical management of patients with severe influenza or at risk of severe influenza. These updated guidelines provide recommendations on the management of both severe and non-severe influenza and include recommendations on the use of antiviral medications to prevent influenza virus infection in individuals exposed to the virus in the previous 48 hours. This update applies to patients with seasonal influenza viruses, pandemic influenza viruses and novel influenza A viruses known to cause severe illness in infected humans. This update also includes baseline risk estimates for hospitalization and death and proposed definitions of patients at high or extremely high risk of developing severe influenza, to enable the recommendations to be targeted appropriately. The guidelines are designed primarily for health care providers who manage patients with influenza virus infection. The guidelines can be applied at all levels of the health system including community-based care, primary care, emergency departments and hospital wards. These guidelines will also serve as a reference source for policymakers, health managers and health facility administrators to support the development of national, regional and local guidelines for epidemic and pandemic preparedness.

Guidance on wastewater and solid waste management for manufacturing of antibiotics. Geneva: World Health Organization 2024; 79 p. ISBN 978-92-4-009725-4 (electronic version) ISBN 978-92-4-009726-1 (print version). The purpose of this guidance is to provide an independent scientific basis for the determination and inclusion of targets in the binding instruments of different target audiences to prevent the emergence and spread of antibiotic resistance. The scope of this Guidance covers human health-based targets to reduce the risk of emergence and spread of antibiotic resistance as well as targets for ecotoxicological risks for aquatic life caused by all antibiotics intended for human, animal or plant use. It covers all steps from the manufacturing of active pharmaceutical ingredients (APIs) and formulation into finished products, including primary packaging. Guidance applies to both liquid and solid waste with a focus on liquid effluent, run-off and discharges to land. Assessment covers risks for selection of resistance by antibiotics before and after dilution in recipient water bodies and also release of resistant bacteria. Separate assessments are needed for manufacturing sites producing more than one API or finished product. The target audiences for this guidance are: regulatory bodies (national or regional) responsible for the regulation of pharmaceutical product manufacturing or wastewater and solid waste (in countries or regions that manufacture), procurement teams or agencies of antibiotics for human, animal and plant use, entities responsible for generic substitution schemes and reimbursement decisions, third-party audit and inspection bodies, industrial actors in all stages of the antibiotic production chain and their collective organizations and initiatives, investors in the sector, and waste and wastewater management services that handle antibiotic waste.

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Godlee F, Jefferson T. Peer review in health sciences. London: BMJ Books; 1999.
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US Social Security Administration. Evidentiary require-

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