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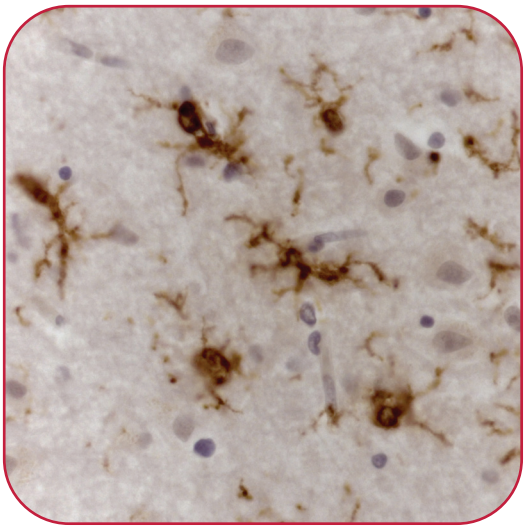
The photograph on the cover is an immunohistochemical staining of activated microglial cells expressing MHC class II molecules in the mouse brain cortex (counterstaining with hematoxylin). The image is provided by Barbara Serafini, Department of Neuroscience, Istituto Superiore di Sanità, Rome, Italy.



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EDITORIAL
The long journey of people with rare diseases: from darkness to the UN Resolution 2021

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Rare diseases (RD) occur globally, affecting 6-8% of the population worldwide; they include 6000-8000 different conditions of either genetic (80%) or multifactorial (20%) origin. RD may involve any organ or system, often are multisystemic, arising at any age, mainly during infancy and childhood. RD are defined by the European Union (EU) as life-threatening or chronically debilitating diseases, with low prevalence (not more than 5 persons per 10 000) [1]. Their rarity, numerosity and heterogeneity pose a major hurdle to timely diagnosis and to provisions of appropriate care to patients.

Individual RD are known since ancient times and are part of history of medicine and culture, for example the achondroplasia of the Egyptian god Bes [2] or neurofibromatosis depicted in works of Hellenistic art [3].

However, only few decades ago RD have been recognised as public health issue as a whole, with specific features. US started in 1983 with the Orphan Drug Act and the EU in 2000 with the European Commission's (EC) Orphan Medicinal Products regulations to incentivize research, development and marketing of new treatments. Similar legislative mandates exist in many Countries worldwide [4].

Tackling RD goes beyond the development of treatments. Severe knowledge gaps still exist on many conditions, due to the combined effects of low prevalence, scarce awareness and weak commitment by funding bodies and enterprises. Hence, uncertainties often burden the evidence basis for action [5], from prevention to treatment and social inclusion. Diagnosis and care require multidisciplinary expertise: prompt diagnosis is crucial for reducing the severity of outcomes, including morbidity and early mortality. Moreover, undiagnosed conditions are estimated to affect around 10%-30% RD patients.

These specific characteristics require special solutions in both healthcare and research. RD-tailored public health plans or strategies should include, e.g., primary prevention actions to reduce risk factors, newborn screening programmes and medical management. Besides, patients and their families often experience stigma, discrimination, and lack of active participation and visibility in society.

Several initiatives have been implemented at EU level as well as in many Countries, within as well as outside the EU. In particular, the EU, recognizing that combined efforts are needed to address the above challenges, has singled out RD as a unique domain for European added value. In 2017, the EC launched 24 European Reference Networks (ERN) encompassing all RD groups. ERN are virtual networks connecting healthcare professionals and centres of expertise in different countries to share knowledge and resources. They aim to tackle complex or rare diseases and conditions that require high competences. ERN allow experts to discuss patients' diagnosis and care, with their consent, via an online IT platform, the Clinical Patient Management System. Hence, knowledge travels instead of patients.

At Member States level, Italy recognized RD as a public health challenge since 2001, establishing the National Network for RD for their prevention, surveillance, diagnosis and treatment. The National Network is articulated in regional networks with Centres of expertise; it includes the National Registry for RD, a pivotal scientific tool for collecting and analysing epidemiologic and clinical patients' data, at the National Centre for Rare Diseases (NCRD) of the Istituto Superiore di Sanità (ISS). The ISS, is the technical and scientific body of the Italian National Health Service; its mission includes promotion and protection of public health through activities carried out on several groups of diseases, including RD (www.iss.it/en/web/guest/home).

The NCRD formally established in 2008 at the ISS is the national and international reference point for RD, its activity includes scientific research, prevention, surveillance of RD and monitoring of the National Network through the National Register. NCRD activities span from scientific research through to patents' empowerment. Accordingly, priority topics encompass translational research, including undiagnosed RD,

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promoting high-quality diagnosis and care, training of health care professionals, providing information on relevant services, promoting empowerment of patients and their social inclusion, health humanities, as well as the proactive contribution to European and international programmes and networks on RD (www.iss.it/web/iss-en/rare-diseases).

In November 2021 the Italian Parliament approved an innovative law on RD [6]. The law's objectives include: uniformity of RD patients care across the Country; educational, social and work inclusion; strengthening the activities of the NCRD and the National network, including ERN Centres; coordination of actions, and incentives to research. Research is vital to reduce the main knowledge gaps on RD, and beyond. Already in 1657, William Harvey highlighted "…; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease" [7].

The long journey of people with RD made recently an important leap forward. On December 2021 the United Nations (UN), during the 76th session of the General Assembly, recalling the *Universal Declaration of Human Rights* and the *Convention on the Rights of Persons with Disabilities*, adopted the first Resolution – "Addressing the Challenges of Persons Living with a Rare Disease and their Families" – which recognizes the need to promote and protect the human rights of all persons, including the estimated 300 million persons living with a RD worldwide, many of whom are children, by ensuring equal opportunities to achieve their optimal potential development and to fully, equally and meaningfully participate in society [8].

Importantly, the Resolution was promoted by patients' organizations such as Rare Diseases International in partnership with EURORDIS and NGO Committee for Rare Diseases. The Resolution places RD at the top of the agenda of the UN Secretary General, identifying five main objectives: 1) to encourage social inclusion and participation of people with RD and their families, taking into account major equality issues such as gender and poverty; 2) ensure equal and universal access to quality health services; 3) promote national and international strategies and actions; 4) integrate RD among the programs and priorities of the UN agencies; 5) publish periodic reports to monitor progress in the implementation of the Resolution itself.

The UN Resolution is a form of "soft law" binding on the UN secretariat and the UN budget and programs. The Resolution therefore serves as a basis for further integration of RD into the UN agenda, actions and priorities. The motto *Leave no one behind* is at the core of the UN Agenda 2030 Sustainable Development Goals (SDGs), and it fits for persons living with a RD. For instance, for children with RD, discrimination may strike very early in life with access to education, while in adulthood it may be difficult to find, maintain or return to work or to pursue lifelong learning, relevant to SDGs 4 ("quality education") and 8 ("decent work and economic growth"). Women are disproportionately discriminated in society, either as patients or as mothers of RD patients (SDG5 "Gender inequality"). Families with a member living with a RD are at greater risk of impoverishment, as they have more expenses and less income (SDG1 "No poverty").

In conclusion, the impact of going through life with a RD goes beyond health issues, and involves the whole family, affecting the place, role and perspectives in society.

The Resolution becomes a reference point to support the RD community at national and international levels. A major point is encouraging the development of national strategies and international collaborations to address the challenges and barriers faced by patients and their families.

Conflict of interest statement

The Author declares that there are no conflicts of interest.

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COMMENTARY
SARS-CoV-2 variants: what have we learnt so far?

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Abstract
Besides the timely detection of different SARS-CoV-2 variants through surveillance systems, functional and modelling studies are essential to better inform public health response and preparedness. Here, the knowledge available so far on SARS-CoV-2 variants is discussed from different perspectives, in order to highlight the relevance of a multidisciplinary approach in countering the threat posed by this insidious virus.

Key words
- SARS-CoV-2 variants
- mutations
- surveillance
- vaccines
- classification systems

The remarkable capacity of viruses to adapt rapidly to new hosts and environments is highly dependent on their ability to generate genomic diversity in a short period of time. RNA viruses introduce and select mutations in their genome faster than DNA ones, thus evolving rapidly [1]. This high evolutionary rate causes accumulation of mutations over time. While most of these mutations are expected to be either deleterious and get rapidly eliminated, or relatively neutral with no detectable effects, some of them confer a selective advantage to the viruses [2]. The potential epidemiological consequences of novel mutations are closely related to their impact on viral replication and transmission and on the competition between co-circulating strains.

In the case of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), modern high throughput sequencing technologies have been applied to obtain millions of viral genome sequences in near real time, providing the unprecedented opportunity to identify and track most of the novel mutations as they accumulated in the genome. This allowed the development of effective "genomic surveillance" systems for monitoring viral variants associated with changes in transmissibility, disease severity and immune evasion.

At the time of writing, more than 233 thousand mutations have been independently identified for SARS-CoV-2 genome [3]. However, while surveillance systems succeeded in compiling an extensive catalogue

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of viral diversity, our understanding of all the possible functional implications is ongoing.

Most efforts to identify and characterize epidemiologically relevant mutations, in particular those potentially associated with immune escape, have been focused on the spike protein (S) gene and specifically its receptor-binding domain (RDB), defining the portion that mediates the recognition of ACE2 receptor on human host cells and representing the main target of neutralizing antibodies [4]. However, considerable efforts have been made also to investigate the effects of different mutations on viral proteins targeted by antiviral therapies, e.g., the catalytic subunit of the RNA-dependent RNA polymerase (RdRp), non-structural protein 12 (nsp12) [5], or by molecular diagnostic assays based on real-time reverse-transcriptase polymerase-chain-reaction (rRT-PCR), e.g. nucleocapsid protein (N) [6].

Although the role of several mutations in conferring a selective advantage to SARS-CoV-2 has been established [7], some important limitations persist. First of all, while genetic/phylogenetic approaches have been successfully applied for the identification of genomic sites and mutations potentially under positive selection, these do not provide direct mechanistic insights and the inferred estimations may be confounded by genetic drift, founder effect and sampling bias [8]. Moreover, decipher the impact of novel mutations, or identify potential epistatic interactions (*i.e.*, the combined effect of two or more mutations), through functional studies typically requires a time frame not always compatible with the rapid spread of successful variants [9].

Significant advances in viral population genetics and *in silico* protein structure prediction will be required in the future to develop novel and more accurate tools for predicting the fate of viral mutations and variants. The application of population genetics theory and models is not straightforward for SARS-CoV-2 dynamics, due to the inherent complexity of the viral population structure, transmission mechanisms and a continuous alteration of viral population size. Methods based on artificial intelligence have been recently developed [10], but the extent to which such methods can be applied for the prediction of the structural and functional effects of single or multiple amino acid substitutions, also in relation to protein-protein interactions, is not completely clear.

With the aim to facilitate the monitoring of the virus evolution, and the tracking of variants of potential epidemiological relevance, different nomenclature and classification systems have been proposed by the scientific community to classify clusters of SARS-CoV-2 strains with common sets of defining mutations. Among these systems, the most common ones are:

1. Nextstrain, which labels clades that persist for several months and have significant geographic spread with an *ad hoc* number-letter combination (*i.e.*, the estimated year of appearance, followed by a letter). As of January 2022, it includes 24 clades (the complete list is available at https://nextstrain.org/ncov/gisaid/global [11]).
2. Global Initiative on Sharing All Influenza Data (GISAID), based on marker mutations within high-level phylogenetic groupings corresponding to clades, from the early split of S and L to the further evolution of L into V and G, and later of G into GH, GR and GV, and more recently GR into GRY [12]. In late 2020, a new clade split from base clade G forming clade GK. The recent emergence of the Omicron variant (November 2021) caused the introduction of the GRA clade in GISAID.
3. Phylogenetic Assignment of Named Global Outbreak Lineages (Pangolin, introduced in April 2020) [13], which combines considerations based on evolutionary history, geographic spread and overall prevalence to define coherent groups of genomic sequences or "lineages" (the full list of lineages is available at cov-lineages.org, [13]). As of January 2022, the Pango nomenclature includes more than 1550 distinct lineages.

While the Nextstrain and GISAID nomenclature system provide a large-scale overview of the clade trends, Pangolin captures a more fine-grained representation of local/regional outbreaks/clusters of SARS-CoV-2 [12].

In addition to these classification systems, the World Health Organization (WHO) has introduced a simplified nomenclature based on the Greek Alphabet (*i.e.*, Alpha, Beta, Gamma, Delta, Omicron) that appears to be easier and more practical also for experts from different disciplines [14].

International health authorities have established a series of guidelines for the identification of SARS-CoV-2 variants associated with relevant changes in epidemiological features. According to the European Centre for Disease Prevention and Control (ECDC) [15], SARS-CoV-2 variants are classified as Variants of Concern (VOCs), Variants of Interest (VOIs) or Variants under Monitoring (VUMs), based mainly on their possible association with increased transmissibility, more severe disease and/or reduced serum neutralization. Variants can also be de-escalated from the status of VOC/VOI/VUM when at least one of the following criteria is satisfied: (i.) the variant is no longer circulating; (ii.) the variant has been circulating for a long time without any impact on the overall epidemiological situation; (iii.) scientific evidence demonstrates that the variant is not associated with concerning traits [15].

Different approaches have been applied to quantify the transmissibility of VOCs, and in particular of the Alpha and Delta variants, from household studies analysing secondary cases generated by different variants, to mechanistic transmission models and statistical inference methods applied to population prevalence data on circulating lineages [7, 16]. These studies suggested that Alfa was 45-66% more transmissible than previously dominant variants [16] and that the increased transmissibility of Delta with respect to Alfa may be around 50-60% (*i.e.*, 76-120% more transmissible than lineages circulating in the 2020) [7, 16]. Estimates for the Gamma variant suggest that the increased transmissibility of this variant compared

to historical lineages may range from 3% to 56% [7], depending on different factors. However, the analysis of the emergence of the Delta variant in India, where the observed immunity was, at the time of the Delta appearance, mainly ascribed to natural infection, suggested that this variant may have been associated with a reduced sensitivity to immune responses generated against previous variants.

Regarding Omicron variant, a modelling study highlighted that its emergence in South Africa quickly shifted the SARS-CoV-2 reproduction number from below one to values around 1.7 in about two months since the seeding [17]. In early December 2021, the daily growth rate of Omicron cases in Denmark was associated with a doubling time between 1.8 and 3.2 days [18]. At the same time, a report from United Kingdom described a 20-45% reduction of the risk of hospitalization for Omicron relative to Delta infections [19].

Overall, the replacement of previous lineages by a new emerging variant (*i.e.*, from near 0% to over 50%) may occur in a short period of time and the epidemiological consequences of the progressive spread of a new VOC could markedly differ across distinct geographical areas due to heterogeneous co-circulation of different lineages and/or vaccine uptake [20-22].

It should be also noted that lineages characterized by a shorter generation time (i.e., the interval between infection of primary and secondary cases) or an increased transmission occurring before symptom onset could hasten its spread and drastically reduce the effectiveness of contact tracing operations in interrupting SARS-CoV-2 transmission chains.

The timely detection and interpretation of trends regarding the circulation of SARS-CoV-2 variants are key to trigger the public health response to COVID-19.

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Retroviruses: a broad view of SARS-CoV-2 and its relatives, with a narrative essay on the current state of biomedical sciences

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Abstract
The actual "pandemic" times, beside their burden of sorrow in terms of both victims, destruction of societal links and economic consequences, are an unprecedented occasion to give a closer look to the status of biomedical research. Beside the undoubted technological advances, the general impression is alarming: the fragmentation of science culture prevents any wise synthesis of the many aspects involved in a global phenomenon as SARS-CoV-2 epidemics. Here we try to acquire a "detached" view to some evolutionary and physiological aspects of the human-virus interaction highlighting the need to revitalize science by a strong departure from ultra-specialization toward a real integration of different fields of investigation.

Key words
- SARS-CoV-2
- retroviruses
- cancer
- ecoevolution
- exosomes
- integrative medicine

INTRODUCTION

The crisis triggered by the COVID-19 pandemic that has brought health systems to their knees is an alarming sign of the fragility of our way of living and thinking. It should not be thought that COVID-19 – just as the SARS and MERS epidemics that in 2003 and 2012 respectively kept the international health agencies in suspense – is an accidental phenomenon. Evidence of severe deterioration of environmental matrices and the collapse of ecological systems have been known for decades. Therefore, the pandemic crisis due to SARS-CoV-2 has deep roots and has to do with the crisis of an unsustainable development model that produces environmental damage, social inequalities and obscure ideologies, but still today receives support in most of the world. Within this framework, we cannot fail to turn our gaze towards the cultural stasis in which medical science navigates, as will be illustrated in more detail below.

In the 19th century and up to the 1970s, the natural sciences made remarkable progress in terms of discovering the fine structure of both living and non-living matter. These developments have had important effects on medicine, paving the way for so-called scientific medicine. These events made it very clear that medicine, as an applied discipline that absorbs the essential elements of its theories and practices from the natural sciences, became more and more dependent on new acquisitions coming from outside its sphere of influence [1].

The close relationship between medicine and natural sciences should today constitute the backbone of biomedical science and the heart of the philosophical thought that characterizes its normative principles. Unfortunately, the inter-disciplinarity that should solicit the current biomedical thought seems to have slowly dissolved. The new knowledge produced by the natural sciences has lost its power to feed the cognitive tools useful for exploring and understanding diseases [2]. This turning point in scientific medicine, which increasingly appears to be a privatized sector governed by financial interests, does not foreshadow good promises. Modern medicine increasingly makes use of advanced technologies for diagnosis and treatment (artificial intelligence, bioengineering, imaging devices, etc.), but at the same time progressively loses interest in protecting the health of citizens by promoting the primary prevention of diseases. The mere technological (and therefore instrumental) use of contributions from other sciences has made biomedical scientists to forget the scientific basis and tools they used in their day-to-day practice. Up until three decades ago, every neurologist knew the meaning of a Fourier analysis of an EEG and all experimental researchers had a clear understanding of the meaning of statistical significance, but today this is no longer the case [3]. Many influential members of the scientific community raised alarms regarding this cultural decay. One of the most acute and concise con-

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tributions, in our opinion, is that of Geman and Geman who compare the sense of wonder at the scientific progress perceived by a hypothetical scientist who travels in time between 1915 and 1965, with the much more modest excitement of another traveler moving between 1965 and 2005 [4].

The exaggerated emphasis on "technological-translational" aspects of medicine had a deleterious effect on the "tacit knowledge" dimensions of medicine by which physicians face the complexity carried by a patient in his/her wholeness [5]. This loss of complexity also highlights a dangerous detachment of modern medicine from its social dimension in an era, such as the current one, in which medicine increasingly needs to integrate conceptually and ethically with the natural and human sciences [6]. The thought and language of medicine have surrendered to the trivialization of its essential meanings and values, accepting the rules of media and breaking that important bond capable of reconciling tradition and innovation in an inseparable *corpus* of rules and knowledge. The time of the COVID-19 pandemic has led the general public to come into contact (very often for the first time and without much explanation) with a rather obscure jargon made up of "spike protein", "natural immunity", "RNA viruses", "epidemic curves" and many other technical terms. There is a general perception of a subtle threat that, in contrast to the main current threats to human health like cancer and cardiovascular accidents, directly affects habits as well as societal and inter-personal relations with an impact never experienced before. The fragmentation of knowledge in hyper-specialized fields has made it very difficult to grasp the essential issues of the various research areas that would allow a global synthesis understandable to public opinion. The lack of context awareness is at the basis of many forecasting errors impinging on the actual management of pandemics [7]. An "infodemics" made up of millions of papers dealing with SARS-CoV-2 has invaded all scientific and popular media from all fields of investigation. A recent paper by John Ioannidis [8] reported that mechanical engineers also had something to say about the SARS-CoV-2 highlighting a profound distortion of science's freedom of judgment by political and economic instances.

This puzzling situation prompted us to try a different approach completely detached from the day-to-day news: to look at SARS-CoV-2 from a broad perspective, taking into consideration some general ecological, evolutionary and cell biology implications raised by RNA viruses, with particular reference to retroviruses. Retroviruses are those viruses whose genetic material is a single-strand RNA molecule, which occasionally, after being "retro-transcribed" into the DNA of a cellular organism, can integrate into the host genome. Strictly speaking, SARS-CoV-2 is just an RNA virus and not a retrovirus. Its genetic material is not integrated into the host genome by reverse transcription; however, the true retroviruses whose genetic information is actually embedded in our DNA are the echoes of very ancient viral invasions in some respects not so different from SARS-CoV-2. Adopting a million-year perspective is, in our opinion, a potentially fruitful way to put in context the close integration among different aspects of the human-virus relations.

TWO SIDES OF THE SAME COIN

Evolution and ecology are two sides of the same coin. Evolution concerns biological change and genealogical relationships among organisms over time, while ecology is about the interaction networks among organisms and between organisms and the abiotic environment.

Although viruses lack a complete biological nature due to the absence of an autonomous metabolism and reproductive capacity, they exhibit evolutionary and ecological properties that determine much of their infectious behavior and the relationships they establish with host organisms. In the following, we will adopt a purely "operational" view focused on the human/viruses relations in both time and space, without entering into the debate of their living/non living character.

In the contemporary world, infectious diseases are a very important cause of suffering and death. Their incidence and geographical spread increased in recent decades, although scientists and politicians in the 1960s and 1970s believed that infectious diseases could be progressively neutralized thanks to economic and scientific progress (hygiene, better life conditions, medical advances, vaccination, technological development, etc.). This belief was formalized by the so-called "epidemiological transition theory" proposing that infectious diseases would decline in importance over time [9]. This was not the case, and since the mid-1980s the percentage contribution of infectious diseases to total mortality has increased even in developed countries and even excluding AIDS from estimates. Proponents of the epidemiological transition theory ignored the complex epidemiological patterns that characterize the waves of rise and fall of human diseases. Furthermore, they failed to clarify the disease profiles of other species, with particular reference to zoonotic diseases. In other words, they overlooked the ecology of diseases, especially the deep alterations that changes in land use, vegetation, climate, man-made environment, economy and technology cause in our relationships with pathogens (and possibly with vectors). These alterations can be appreciated, for instance, looking at the rapidly evolving resistance of pathogens to antibiotics and pesticides or considering the growing vulnerability of highly socially and economically stratified populations [10, 11]. The SARS-CoV-2 pandemic should remind us that our unbalanced interaction with the biosphere [12] raises many troubling challenges that healthcare systems around the world will face in the decades to come.

As we are realizing by examining the space-time evolution of SARS-CoV-2, any evolutionary process involving viruses and other infectious agents is the product of multifactorial dynamics and contingent events [13]. Health transitions are not linear and irreversible changes but complex processes involving possible re-emergence of diseases considered under the way of progressive reduction: many infectious diseases have an old cosmopolitan history of emergence, disappearance and recurrence [13]. The number of potentially infectious

contacts has exploded as global trade and travel bring goods, organisms and humans closer together than ever before. Nowadays, the longest intercontinental flight is shorter than the incubation period of any known infectious pathogen [13]. Meanwhile, the unexpected emergence and re-emergence of drug-resistant infectious diseases, the incidence of which is rapidly increasing, will change the global epidemiological scenario in the near future [14, 15].

Interestingly, RNA viruses, whose transmission cycles involve complex dynamics due to their evolutionary histories and their interaction with ecological factors, are the most frequent cause of emerging viral diseases [16]. A largely overlooked aspect of retroviruses is that they influenced the evolution of a large number of organisms, including our own species [17]. Evolutionary investigations suggest that retroviruses that infect vertebrates shared the biological history of their animal hosts for hundreds of millions of years [18]. In some ways, this is also consistent with the remarkable spread of retroviruses among modern vertebrates, which supports the hypothesis that their emergence dates back to around 450 million years ago. In other words, retroviruses could be contemporary infectious agents of the most ancestral animal lineages that appeared in the oceans of the Ordovician period [19]. We can safely say that viruses are an integral part of natural history – including, as we will see shortly, that of human beings – and therefore they do not represent only a "threat" of the natural world. The long evolutionary track we shared with retroviral sequences embedded in our genetic makeup had very important effects on physiological and pathological traits of our present lives [20].

RETROVIRUSES: A HISTORY OF SYMBIOSIS AND THE NEED TO RECONSIDER SOME FUNDAMENTAL PILLARS OF EVOLUTIONARY BIOLOGY

As first we need to go back from the very beginning, namely the definition of "what is life", this problem is with us at least from the time of Aristotle that basically defined a life being something that grows, maintains itself and reproduces, linking this definition to the concept of "purposed motion" or change [21]. After more than two thousand years and many heated philosophical debates, we are not so far from there, as the most popular definition of life stems from the presence of a metabolic activity (growing and maintaining itself as in Aristotle's definition) [22].

According to the above definition, a virus is not a living entity given it is neither capable of autonomous metabolism nor replication; on the other hand, viruses undergo mutation-based selective processes adapting their "phenotypes" to interaction with a host. Still more important, their relation with host presents the classical features to a parasitism-to-symbiosis transition often encountered in the natural world. This parasitism-to-symbiosis dynamic is particularly relevant in the case of retroviruses and contributed (together with other molecular biology evidences) to open a deep crisis of the still prevalent "modern synthesis" paradigm of biological evolution.

In a recent paper [23], Shapiro and Noble state:

"The common belief that the neo-Darwinian Modern Synthesis (MS) was buttressed by the discoveries of molecular biology is incorrect. On the contrary, those discoveries have undermined the MS".

In the paper they make a long list of last decades discoveries in molecular biology that undermine the basic pillars of the so called Modern Synthesis; they describe the impact on MS of these new discoveries by a metaphor borrowed by informatics.

"These 21st Century concepts treat the evolving genome as a highly formatted and integrated Read-Write (RW) database rather than a Read-Only Memory (ROM) collection of independent gene units that change by random copying errors".

In other words, organisms can change their genome in response to stress and the genotype-phenotype relationship is not only complex and far to be a one-to-one interaction, but can go the other way with phenotype that actively acts to modify genotype. The many experimental evidences of heritable phenotypic changes, what is most important in the case of retroviruses, is the falsification of the existence of an impenetrable Weismann Barrier separating somatic and germ line cells [23-27]. This means that viral genetic material integrated into somatic cells can be transmitted to the germline. Once the genome of cells that give rise to gametes (eggs and sperms) has been colonized by viral sequences, copies of the pro-viral DNA can be further amplified due to germline re-infection events [28]. These sequences are ubiquitous in vertebrates and in human genome accounting for around 8% of the genetic material (so largely outnumbering protein-coding genes) [29, 30]. For the most part, the sequences belong to the group of long-terminal repeats (LTRs) which also include the mammalian apparent LTR retro-transposons. Just like structural genes, ERVs (Endogenous Retro Viral sequences) undergo epigenetic regulation by histone methylation/demethylation and have a tissue specific expression level [30]. The term "endogenous retrovirus" does not refer to a biological entity distinct from other retroviruses, but simply describes any DNA of retroviral origin that has found its way into a host germline. This is probably the most intimate degree of symbiosis detectable in Nature: genes coming from retroviruses become part of the host genome at the same level of integration than the other genes. In this manner, the spread of ERVs may have accelerated the evolution of the host genome in largely unpredictable ways falsifying the necessity of the continuity of evolution through the slow accumulation of mutations and the consequent lack of any sharp distinction between micro- and macro-evolution, that is one of the main tenets of MS [23]. Phylogenetic analyses show that retroviruses cluster into five major groups with different host distributions, providing important insights into the classification and diversification of retroviruses [31]. Retroviruses underwent frequent host switches including many independent water-land transmissions, showing that the water-land interface is not a strict barrier for retrovirus transmission [31] and highlighting horizontal between species genetic transfer as an important factor in evolution.

The current debate on the natural/artificial origin of SARS-CoV-2 implicitly equates the consequences of an "artificially" engineered system to what normally happens in the natural world. The horizontal transfer of genetic information creates unexpected "shortcuts" between phylogenetically distant species that question the existence of a well-ordered "tree of life" in which evolutionary innovations (i.e. new species) emerge exclusively as a result of new ramifications.

ERVs are mainly regulatory sequences playing a crucial role in many biological processes like immunity, embryo development, tissue organization [32-34]. The way in which this role is exerted is very intriguing even from a pure "system science" perspective: ERVs exert a "digital control" that is more resistant to noise than analogic control. This digital control involves the so-called genetic "toggle-switches" (*Figure 1*).

The most common example of genetic toggle-switch is a bi-stable gene circuit consisting of two genes A and B which repress each other by imposing two different attractor states on the system of the two elements corresponding to: 1) A expressed at its typical level, B totally silenced; 2) A totally silenced, B expressed at its typical level [35].

Panel A reports two genes X1 and X2 represented as the poles of a feedback circuit: the edges represent the inhibitory action that one gene exerts on the other; these two inhibitory interactions have the same strength and are proportional to the concentration of the gene products. Panel B describes the dynamics of such a circuit in the X1/X2-concentration space. The point Sc, corresponding to an equal concentration of the two gene products, is a "saddle" i.e. a very unstable condition: if a small perturbation impinges on the system (e.g. slightly favouring A), the negative feedback exerted by A over B is greater than the one exerted by B on A. This initial asymmetry will grow up at each iteration until the system has only A-derived products. The opposite state (only B-derived products) occurs if we start with a little asymmetry favouring B.

Panel C adds to the X1/X2 space a third dimension called "quasi potential", a semi-quantitative estimation of the energy (and therefore of the instability) associated with each point in the X1/X2 concentration space. The same information is reported in the lower right panel which shows the presence of two minimum energy states favored by the two extremes of prevalence "A" and "B". This dynamic holds true at the single cell level and we can expect that for billions of cells in a culture or a tissue, a perfect overall balance of A and B products will be achieved due to the symmetrical character of the deviations.

Now let us look at the graph reported in *Figure 2* [36], in which the X and Y axes correspond to the cell expression profile of the same cell culture in two different instant of time. The vector points in the graph correspond to the expression levels of 23,000 genes; the evident linear arrangement of the graph is a natural consequence of the existence of a typical gene expression profile specific for cell type.

The scattering across the identity line is mainly due to Intrinsic (linked to the cell internal fluctuations in expression) and Extrinsic (caused by external noise) variability, some genes are in the so-called DE (Differentially Expressed) sub-space. They are single genes that by the effect of unknown stressors largely deviate from their ideal profile. The DE space is the preferred viewpoint for looking at possible phenotypic effects of drugs, diseases, genetic conditions. The DE space is continuous (i.e. analogical) because a gene can have a smaller or greater distance from the identity line. On the contrary, the long "whiskers" of *Figure 2* are made of On/Off "toggle" genes: in this case the variability is no more analogic but digital: a single toggle gene can be *off* (its expression is equal to zero) or *on* (and its expression level corresponds to its typical value). The puzzling point is that here we are not analyzing a single cell but populations of millions of cells in which we expect a

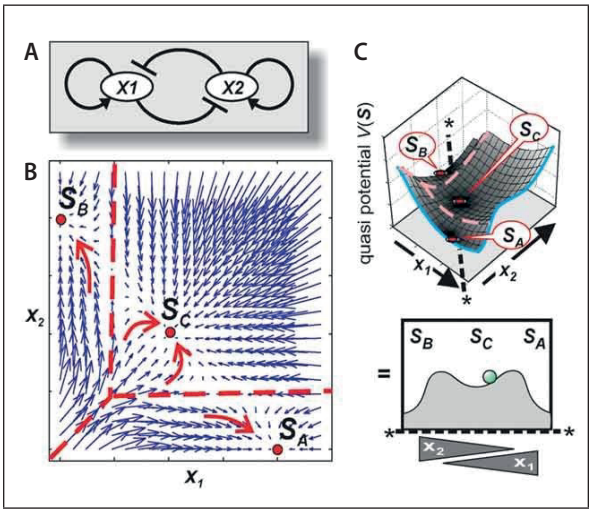

Figure 1
Toggle-switch behaviour (modified from Huang [35]),

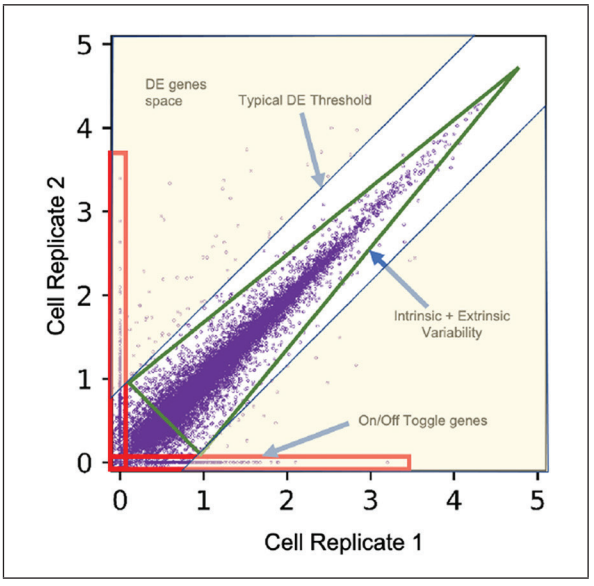

Figure 2
Whole genome expression space (from Giuliani *et al.* [36])

random distribution of the two alternative A and B solutions, with a consequent absence of the two "whiskers". The presence of hundreds of "single state" conditions tells us that the switches are tuned so to exert a digital yes/no control on the entire cell population. It is not by chance that the number of such "coordinated" toggle switches is extremely high in most critical conditions as embryo development and in general in multi-cellular organization. This digital control has a very ancient origin dating back to phages, viral particles infecting bacteria that switch between two discrete "lysogenic" and "lytic" stages corresponding to a host genome integrated and actively replicating behaviours of the viral genome [37].

The toggle-switch control, thus, appears as a main component of the dynamic regulation of gene expression, allowing for a more robust and accurate digital control with respect to continuous (analogic) variability. This kind of regulation is much more relevant in multicellular than unicellular systems pointing to a link between evolution of multicellularity and the need of a more reliable control to keep alive the physiological integrity of the tissues. It is worth noting the prevalence of ERVs in toggle switches, so highlighting the deep nature of virus-host symbiosis.

This as for the "sunny side": the above-sketched interactions describe the establishment of an unavoidable vital link between the expressions of genes due to the virus-host shared very long evolution track. On the other hand, the "dark side" concerns the involvement of ERVs in cancer (*Table 1*) and auto-immune diseases, that in turn are both "tissue-based" pathologies and in a sense can be considered as the price we pay for being complex and very finely integrated organisms [38]. Although the carcinogenesis mechanisms induced by ERVs have not yet been fully elucidated, the role of the viral sequences in the transformation of normal tissues into neoplastic tissues is widely recognized. Investigations of the past few decades suggest a broad association of different human ERVs with several cancers.

Extracellular Vesicles (EVs) are lipid bilayer-enclosed entities often containing proteins and nucleic acids. EVs resemble enveloped viruses in both structural and functional aspects. In full analogy with viral biogenesis, some of these vesicles are generated inside cells and, once released into the extracellular milieu, are called exosomes. Others bud from the plasma membrane and are generally referred to as micro-vesicles. The role of EVs as potent vehicles of intercellular communication stems from their ability to carry a wide range of biological macromolecules such as proteins, lipids, and nucleic acids. Regarding nucleic acids, DNA fragments, single and double-stranded DNAs, mitochondrial DNA and RNA species, such as mRNAs, miRNAs and a great variety of small non-coding RNAs have been detected in EVs [39]. Beside the still debated on common origin of retroviruses and exosomes [40], it is well established that a crucial factor in the control of infections is the accessibility of immune system cells to the foreign material. Exosomes – for their role in intercellular communication – play a key role in the dissemination of pathogens as well as host-derived molecules during infection either promoting or inhibiting host immunity [41]. The close interaction between exosomes and viral infections (including coronaviruses) is reviewed in Giannessi and colleagues [39]. In general, it is worth noting that exosomes are particularly rich in ERVs [38] and the demonstration of their transit from soma to germ line (so overcoming the Weismann barrier) [24] sheds light on the virus-host co-evolution.

All in all, a closer look at retrovirus-host interaction is telling us a very different and much more intriguing story than the one freezed in the central dogma of biol-

Table 1
Overview of the human ERVs detected in several cancers. The lack of X only means that there is no record of the human expression of that ERV for that cancer, and not necessarily that it is not present (from Vergara Bermejo *et al.* [28]).

	HERV-K	HERV-E	HERV-W	HERV-H	HERV-W	HERV-FRD	HERV-R	HERV-P
Breast	X		X	X	X		X	X
Lymphoma	X		X	X				
Leukaemia	X						X	
Endometrial	X	X	X			X	X	
Prostate	X							
Seminoma	X		X					
TCC			X					
Ovarian	X	X			X		X	
Melanoma	X							
Lung	X			X	X		X	X
Colon	X		X	X				X
Pancreas	X							
Sarcoma	X							
Urothelial/Renal	X	X	X	X	X		X	
HNSCC	X						X	

ogy and modern synthesis, endowed with many implications for human pathology [42].

CONCLUSIONS

Between the seventies and the nineties of the last century, some interesting essays were published on the fundamental definitions of health and disease, a subject of not so obvious interest within the scientific community but rather intriguing for sociologists, philosophers and historians of medicine [43-47]. Many authors argued that a true scientific discussion of health should start with the recognition of the relevance of complexity in human biology, medicine and psychology, clearly alluding to the systems theory of Ludwig von Bertalanffy [48]. The notion of health is closely connected to the notion of life: another thorny question that the biomedical community has historically avoided addressing, relegating it to philosophical reflection.

According to systems theory, distinct phenomena emerge at different hierarchical levels of biological complexity: atomic, molecular, cellular, individual, population (or social), ecosystem. Implicitly, the systemic perspective introduced the idea that biological and epidemiological exploration of the relationship between health and disease belong to the scientific realm of ecology, so that an exclusive focus on the molecular level as the ultimate causative organization layer does not allow to predict what happens at higher levels [48].

Today we know that the emergence of new detectable properties due to combination of many elements occurring at a given hierarchical level of complexity is fundamental to elucidating most of the biological dynamics. A very simple example of how reductionism is absolutely inadequate to explain the myriad of collective phenomena occurring in the natural world is offered by the so-called "herd immunity" (one of the many cases of obscure jargon mentioned in the first part of this contribution and abused by most mass media in relation to COVID-19). Indeed, herd immunity operates at the population level and clearly not at the individual level (according to the Edition 2020 of the Oxford English Dictionary, "Herd immunity is defined as resistance to the spread of a contagious disease within a population that results if a sufficiently high proportion of individuals are immune to the disease, as a result of vaccination against it or natural immunization").

In this paper, by taking retroviruses as case history (here we again stress that SARS-CoV-2 is not a retrovirus but only a RNA virus) we tried to give a glimpse to the intermingled status of biological knowledge. We tried to clarify how apparently heterogeneous issues like evolution, gene regulation, viral infections, ecology, and cell-biology are mutually consistent and ask for a global appreciation. For this and other reasons that can be coarsely defined as "attention to the context" we argue that an effort to seek new approaches is strongly needed in the health sciences and these new approaches must encompass the "serendipity" linked to the tacit knowledge of physicians [49].

Our goal was not to follow a blatantly "programmatic assertive" style of reasoning; on the contrary, in dealing with apparently very specialized problems such as RNA virus infections, we let the logical line be established by the need to simultaneously consider issues borrowed from a wide range of disciplines. The recent case of COVID-19 pandemics, at least in our opinion, made very evident the lack of a shared inter-disciplinary scientific culture and the urgent need to foster such a culture. The solutions that arise from strict reductionist approaches were in many cases unsuccessful and responsible for high costs for the health system [50]. We cannot forget that some alternative strategies have demonstrated a positive impact on the healthcare systems principally by implementing prevention and health promotion. Some other strategies have shown several advantages, like in the cases where different medical traditions are integrated to help patient engagement and compliance to self-care, reduced reliance on pharmacotherapy, and enhanced symptom control [51]. Particularly in the treatment of heart failure, the combination of traditional Chinese medicine with allopathic medicine has shown several benefits such as reduction of side effects and others [52]. Many biomedical scientists observed that these models have the potential to reduce the burden of both chronic and infectious diseases, lower the cost of healthcare, and offer a sustainable healthcare financial paradigm [53].

In conclusion, as aptly stressed by Georges Canguilhem [54], the complexity of human society and its current health and social needs require a systemic framework in which diseases are considered as the result of a negative interaction between multiple factors that characterize the human being as an individual and as a community. These approaches derive largely from a systemic view of human life and values, which highlights the fundamental principles of the organization of living beings from a perspective of well-being, equity and resilience.

Authors' contribution

The Authors contributed equally to this work.

Conflict of interest statement

No conflict of interest to declare.

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Self-reported compliance with drug therapy during the first SARS-CoV-2 Italian lockdown in patients with respiratory disease

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Abstract

Background. Low compliance with drug therapy in patients with chronic respiratory diseases was a well-known issue even before the coronavirus pandemic, but its causes are not yet fully defined.

Objective. To verify the adherence to drug therapy in patients with respiratory disease during the COVID-19 pandemic.

Methods. From June to September 2020, about 700 patients of the Forlanini Hospital who had been unmonitored during the March-May 2020 lockdown in Italy received a questionnaire during the pneumological check-up based on self-reported information on compliance with therapy during lockdown.

Results. 284 out of the 418 returned questionnaires could be used in this study: 179 patients (63.0%) responded positively to the continuation of therapy, 18 (6.3%) reduced the dosage of their medication and 82 (28.9%) interrupted the therapy.

Conclusions. The low percentage of patients that reduced their drug dosage may be due to an increased awareness of drug treatment benefits, and may also be ascribed to the Government healthcare strategy during lockdown.

Key words

- compliance with therapy
- lockdown SARS-CoV-2
- patients with respiratory disease

INTRODUCTION

In Italy, the proportion of patients with obstructive airway disease that comply with their medical treatment for 3 months is 27.3%, while those who continue the correct treatment for 6 and 12 months represent only 13.0% and 8.2% of patients, respectively; these are the lowest compliance rates of all chronic conditions [1]. Although OsMED (the institution that monitors the use of medicines in Italy) has highlighted the low adherence to drug treatment in chronic conditions, especially respiratory conditions such as asthma and COPD (chronic obstructive pulmonary disease), this problem seems not to be a priority of the healthcare community, thus negatively impacting the effectiveness of the respective drug therapy regimes [2]. The option of a single daily inhalation therapy, currently available for asthma and COPD, may lead to an improvement in compliance, but this remains to be confirmed [3]. Treatment failure of this kind is not solely attributable to patient behavior [4], but it represents a significant risk factor for successful treatment and needs to be investigated.

In general, patient adherence to medication is considered "full adherence" if more than 80% of the prescribed drug is taken, "partial adherence" if the patient takes from 20 to 70%, and "non-adherence" if the patient takes less than 20% of the drug [5]. However, such thresholds are set arbitrarily and proved in any context [6]. In the context of routine clinical practice, assessment of adherence is usually performed with a self-report from patients about their drug therapy [7, 8]. This evaluation is totally subjective and widely influenced by doctor-patient relationship, with a possible overstatement by 20% of the true level of compliance.

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Anonymous, yet self-reporting, surveys may help mitigating such overstatement and may deliver aggregated, helpful information from samples of outpatients. This study exploited such an assessment tool to investigate the adherence to drug therapy in patients with respiratory disease presenting as outpatients after the first Italian lockdown of March-May 2020 due to the COVID-19 pandemic. Main aim of the study was to explore those patients' behavior with respect to therapy adherence during the health crisis that forced many pulmonary divisions to accept only COVID-19 patients. As in many others clinical centers, at the San Camillo-Forlanini Hospital in Rome, the pandemic and accompanying lockdown caused a drastic interruption in both pulmonary outpatient visits and diagnostic examinations for all external users with conditions other than COVID-19. In June 2020, when normal business was resumed with a backlog of nearly 700 check-ups and 400 instrumental examinations, outpatients voluntarily filled in anonymous questionnaires. This study examines compliance with drug therapy during the pandemic as a means of assessing how Government health strategies influenced patient behavior.

MATERIALS AND METHODS

During the 3-month Italian lockdown due to the COVID-19 pandemic, hospital personnel did a telephone selection of all already booked patients together with a selection of indispensable physical or instrumental examinations. With the approval of the San Camillo-Forlanini Hospital Ethical Committee (Prot. n. 888/CE Lazio 1), in June 2020, soon after the end of the lockdown, a voluntary questionnaire was offered for pneumological check-up to booked patients who could not be seen during the lockdown. Questionnaires were anonymously completed by patients, having given informed consent to participate in the research, and handed to nurses before the check-up at the ambulatory clinic at the day hospital for interstitial lung disease (ILD), asthma, COPD, respiratory sleep disorders, smoking cessation and respiratory physiopathology.

The questionnaire included personal data, as well as multiple-choice questions about respiratory disease, continued treatment, respiratory therapy interruption or reduction during lockdown, the reasons for interruption, the medications affected, presence or absence of disease recurrence, the type of the referring physician (whether general doctor, pneumologist, or other clinical professionals), tobacco abuse and the result of a SARS-CoV-2 test, if done.

The completed questionnaire data were digitized and collected in a database after two-step verification of the information. Basic non-parametric statistics tests were applied to all variables: the only continuous variable (age) was analysed using the Mann-Whitney test (with significance set at $p<0.05$); a chi-squared test ($p<0.05$, properly adjusted for multiple comparisons) was applied to all other variables. All data management and processing was performed using the R open-source integrated suite, version 4.0.4 (the R Foundation, (https://www.r-project.org).

RESULTS

In total, 418 questionnaires were collected from June 2020 to September 2020: 39 (9.3%) were not filled out; 33 (7.9%) had been completed by Stop Smoking Clinic patients with or without respiratory disease or tobacco-related symptoms; 58 (13.9%) had been answered by first access patients; and 4 (1%) had been filled out by patients that do not take any medication. The remaining 284 (67.9%) had been completed by patients with respiratory disease who were undergoing drug treatment before lockdown, and these represent the subject of this study.

Since some patients with respiratory disease are still tobacco addicted, we investigated whether there were significant differences between these patients and the smokers without respiratory conditions with respect to the main investigated variables, detailed in *Table 1*. Briefly: Stop Smoking Clinic patients (33 questionnaires/patients) were significantly younger than respondents with respiratory disease (284); there were no statistically significant differences between percentages of women and men in the two groups; the percentage of Stop Smoking Clinic patients who were still smokers (87.9%) was significantly greater than the percentage of smokers within the respiratory disease group (23.6%), the latter including a high percentage of ex-smokers (38.0%), who had stopped for more than one year, and patients who have never smoked (35.6%); out of 67 smoker patients with respiratory conditions, 35 (52.2%) had tried to stop smoking, 31 (88.6%) by themselves, i.e. without any external help, and 4 (11.4%) with the support of the Stop Smoking Clinic.

The analysis on adherence to therapy was conducted on the subgroup of patients with respiratory conditions who were undergoing drug therapy before the lockdown. 284 questionnaires were returned in total from this groups of patients; of these, 5 (1.8%) did not contain information about the follow-on of treatment; 179 (63.0%) reported a positive response to therapy; 18 (6.3%) reported a partial response to therapy; 82 (28.9%) reported the interruption of therapy. Therefore, overall adherence was around 70%, with 63.0% showing full adherence and 6.3% a reduction of drug therapy.

We then proceeded with the characterization of the three groups of patients who CONTINUED (179 patients), INTERRUPTED (82) or REDUCED (18) their treatment.

There were no significant differences between groups as for their age, as well as between women and men.

Statistically significant differences were found between the three groups with respect to tobacco addiction. In particular, among those patients who continued the therapy, there was a greater percentage of ex-smokers than never-smokers, with smokers being the smallest group. The never-smokers represented the highest proportion of those patients who interrupted therapy, followed by a similar percentage of smokers and ex-smokers. Among patients who reduced their therapy, there were no smokers; they were either ex-smokers or never-smokers.

In terms of recurrence of acute episodes of the dis-

Table 1
Main variables self-reported by Stop Smoking Clinic patients and Respiratory disease patients of the San Camillo-Forlanini Hospital, Rome, Italy

Age (years)					
	25° percentile	**Median**	**75° percentile**	***Mean***	***Standard Deviation (SD)***
Stop Smoking Clinic patients	52.8	59.0*	66.3	*59.4*	*11.4*
Respiratory disease patients	58.5	69.0*	75.0	*66.2*	*14.1*
Tobacco addiction					
	Smokers	**Ex-smokers**	**Never smoked**	**NA**	
Stop Smoking Clinic patients	29 (87.9%)**	4 (12.1%)**	-	-	
Respiratory disease patients	67 (23.6%)**	108 (38.0%)**	101 (35.6%)	8 (2.8%)	
Adherence to drug therapy during lockdown among Respiratory disease patients (grouped according to tobacco addiction)					
	Smokers	**Ex-smokers**	**Never smoked**	**NA**	
Continued	40 (22.3%)	78 (43.6%)	55 (30.7%)§	6 (3.4%)	
Interrupted	24 (29.3%)	19 (23.2%)§	37 (45.1%)	2	
Reduced	-	10 (55.6%)	8 (44.4%)	-	
Reasons for interruption among Respiratory disease patients who interrupted or reduced the drug therapy					
	"I felt good"	**"Difficulty with GP"**	**Expired treatment plan**	**Other**	
Interrupted	42 (51.2%)**	2 (2.4%)	8 (9.8%)	3 (3.7%)	
Reduced	7 (38.9%)**	4 (22.2%)	2 (11.1%)	3 (16.7%)	

*statistically significant difference (Mann-Whitney, $p<0.05$).
**statistically significant differences (chi-squared test, $p<0.05$).
§statistically significant different from the other two groups among the three groups of continued, interrupted and reduced drug therapy (chi-squared test, adjusted $p<0.05$).
NA = not available.

ease, there were no significant differences between the three groups during lockdown: in all groups the highest proportion of patients showed an absence of recurrence, although this was not statistically significant. Despite this, we noted that the absence of recurrence was most likely found among patients who continued the therapy (79.9%), slightly less in patients who interrupted the treatment (74.4%) and lower in patients who reduced the therapy (66.7%).

With respect to the reasons for interruption, examined in patients who either interrupted or reduced their drug treatment, the two groups showed significant differences in terms of the reported reasons, chosen from those proposed namely: good perception of self-assessed health ("I felt good"), difficulty in interaction with the general practitioner ("difficulty with GP"), expired treatment plans – even though the period of validity had been extended during lockdown – and other or not-reported reasons. The "I felt good" reason was the main justification for interrupting the therapy in a significantly greater proportion of patients than those reporting "difficulty with GP". With respect to an appeal to a healthcare professional during lockdown, up to 80% of questionnaires did not contain information.

Finally, although the questionnaire was self-reported, thus entailing a possible bias, we also aimed at exploring whether the type of disease or the coexistence of more than one respiratory disease correlated with adherence or with the reasons for therapy interruption *(Tables 2 and 3)*. Greater compliance was found in patients who reported two concurrent diseases, in particular chronic bronchitis and asthma (85.7%), and COPD and emphysema (83.3%). Among patients who reported a single respiratory pathology, adherence was 79.4% for COPD, 65.8% for asthma, and 65.4% for pulmonary fibrosis; lower adherence was registered in patients with referred chronic bronchitis (53.9%), emphysema (36.4%), and bronchiectasis (28.6%). Among patients with pulmonary fibrosis, interruption of therapy occurred in 23.1% of cases and reduction in 11.5%. The most frequent reason for an interruption or reduction of therapy was "I felt good" for all pathologies, except for the group with COPD, where the prevailing reason was the reported non-renewal of the treatment plan. Finally, in groups with just one pathology, adherence showed good positive correlation with the lack of recurrence (coefficient of determination of the linear regression $R^2 = 0.62$), which is an intuitive although not obvious result in self-reported data.

DISCUSSION

We found no evidence of a reduction in the compliance with drug therapy during the first SARS-CoV-2 Italian lockdown in patients with respiratory disease. To our knowledge, neither similar studies nor previous data collected at the same clinical center (San Camillo-Forlanini Hospital in Rome, Italy) were available to compare the outcomes of the present study. We could however observe that our findings confirmed what has been published by Kaye *et al.*, even though based on much larger cohorts than ours and on data collected through digital surveys on drug use [9]. Our conclusions are in

Table 2
Respiratory patients of the San Camillo-Forlanini Hospital, Rome, Italy, grouped by type and number of coexisting respiratory pathologies: 19 patients out of 284 did not report on this question, and thus were not included in the Table

Pathologies			Age (years)		Sex (%)		Adherence (%)			Reasons for interruption (%)				Exacerbations (%)		Smoking (%)		
#	type	N. of patients	mean	SD	M	F	yes	no	partially	good health status	troubles with GP	expired TP	other	yes	no	smoker	former smoker	never smoked
1	Asthma	38	52.1	18.0	34.2	65.8	65.8	26.3	5.3	21.1	0.0	5.3	0.0	5.3	84.2	10.5	21.1	60.5
1	COPD	34	70.7	11.9	52.9	41.2	79.4	17.6	2.9	5.9	2.9	8.8	0.0	2.9	94.1	23.5	47.1	29.4
1	Emphysema	33	68.0	12.3	51.5	45.5	60.6	36.4	3.0	21.2	0.0	6.1	0.0	6.1	81.8	42.4	39.4	18.2
1	Chronic bronchitis	26	72.6	10.0	46.2	50.0	42.3	53.8	3.8	42.3	0.0	0.0	0.0	3.8	76.9	38.5	34.6	26.9
1	Pulmonary fibrosis	26	70.0	14.3	73.1	26.9	65.4	23.1	11.5	11.5	0.0	7.7	3.8	7.7	76.9	15.4	46.2	38.5
1	Bronchiectasis	14	67.8	12.0	21.4	78.6	50.0	28.6	21.4	21.4	7.1	7.1	14.3	14.3	64.3	14.3	21.4	64.3
1	Other	37	65.8	12.2	35.1	56.8	48.6	37.8	5.4	18.9	0.0	8.1	2.7	0.0	73.0	18.9	35.1	37.8
2	Chronic bronchitis & asthma	7	68.7	10.4	28.6	71.4	85.7	14.3	0.0	14.3	0.0	0.0	0.0	14.3	85.7	14.3	14.3	57.1
2	COPD & emphysema	6	69.3	3.8	66.7	33.3	83.3	16.7	0.0	0.0	0.0	16.7	0.0	0.0	100.0	50.0	33.3	16.7
2	Chronic bronchitis & emphysema	5	70.2	9.1	80.0	20.0	60.0	20.0	20.0	0.0	20.0	0.0	0.0	20.0	40.0	40.0	60.0	0.0
2	COPD & asthma	4	64.8	8.8	25.0	75.0	50.0	25.0	25.0	25.0	25.0	0.0	0.0	25.0	75.0	0.0	100.0	0.0
2	Chronic bronchitis and COPD*	2	59; 69		1	1	1	1						1	1		2	
2	Emphysema & pulmonary fibrosis*	2	75; 86			2		2			1			1	1			2
2	Bronchiectasis & pulmonary fibrosis*	2	69; 63		1	1	2							1	1		1	1
2	Chronic bronchitis & pulmonary fibrosis*	1	71			1			1		1			1				1
2	COPD & pulmonary fibrosis*	1	58			1	1							1			1	
2	Emphysema & bronchiectasis*	1	60			1		1						1		1		
2	Chronic bronchitis & bronchiectasis*	1	63			1	1							1			1	
>2	All combinations	14	68.0	11.0	42.9	57.1	71.4	28.6	0.0	0.0	7.1	7.1	7.1	35.7	50.0	35.7	28.6	35.7
>2	At least COPD, asthma & emphysema	6	66.5	9.5	50.0	50.0	83.3	16.7	0.0	0.0	0.0	16.7	0.0	16.7	50.0	50.0	33.3	16.7
>2	At least chronic bronchitis, COPD & asthma	5	64.8	12.0	40.0	60.0	80.0	20.0	0.0	0.0	0.0	20.0	0.0	20.0	40.0	40.0	40.0	20.0

*group formed by 1 or 2 patients only: absolute values are reported instead of percentages.
GP: general practitioner; TP: treatment plan; COPD: chronic obstructive pulmonary disease.
For the sake of space, not available (NA) cases have not been reported.

Table 3
Details of pathologies in respiratory patients of the San Camillo-Forlanini Hospital, Rome, Italy, who self-reported more than two respiratory pathologies

Pathologies			Pathology (%)						
Number	Type	N. of patients	Chronic Bronchitis	COPD	Asthma	Emphysema	Bronchiectasis	Pulmonary fibrosis	Other
>2	All combinations	14	50.0	71.4	64.3	85.7	35.7	35.7	35.7
>2	At least COPD, asthma & emphysema	6	66.7	100.0	100.0	100.0	66.7	16.7	16.7
>2	At least chronic bronchitis, COPD & asthma	5	100.0	100.0	100.0	80.0	60.0	20.0	40.0

COPD: chronic obstructive pulmonary disease.

line with the OsMED report for the 2020 lockdown period too [10], although relevant differences between the studies must be kept in mind: our study was limited to 284 patients, focussed on the lockdown period Mar-May 2020, and used self-reporting questionnaires including – but not limited to – questions on the use of medicines; the OsMED report, instead, analyzed the use of medicines – on the whole Italian territory – in chronic diseases such as COPD and asthma only, and calculated the national per capita consumptions per 10,000 inhabitants per day relating to the pre and post COVID-19-period. More in detail, the OsMED report found no statistically significant differences in drug use between the pre- and during-COVID-19 periods (Jan-Feb 2020 and Mar-Apr 2020 respectively). OsMED attributed this success to the health strategy used to support continuity of care for chronically ill patients, which involved: extending the period of validity of treatment plans; encouraging access to medication by the use of electronic prescriptions; continuously updating relevant information on institutional sites.

Our study findings seem to confirm that, at least within the small sample of outpatients referring to our pulmonary disease division, those measures allowed the continuous delivery of high-quality assistance to patients, proving that an appropriate health strategy can improve patients' awareness of their condition and help maintain an adequate adherence to therapy even in an emergency context. In particular, we were especially interested to know, in view of other possible lockdowns or emergency periods, whether the telephone selection of all the visits already booked during the lockdown period to identify the urgency of performance in presence had proven useful for therapeutic purposes, when used in conjunction with the actions implemented by the Italian National Health Service through digitalization for the continuation of drug therapies.

By analyzing the ex-smokers group, we found that the highest compliance with treatment regimes occurred in those patients with two associated disease conditions (COPD and asthma), as well as in patients with COPD alone. The most common reason for interruption of therapy was "I felt good"; this demonstrates limited knowledge of the patients with respect to the chronic nature of their condition. This problem is already known in the literature, especially in asthmatics, who often interrupt their therapy and show levels of adherence between 16% and 50% [11]. It is important to note the reduction in adherence rates in patients with pulmonary fibrosis, a rare condition monitored in dedicated centers such as the San Camillo-Forlanini Hospital Pulmonology Service, in which medical counseling is only performed in urgent cases using a telephone counseling service organized in conjunction with the Patient Association.

We noted that the smokers in our study were younger than other groups, thus highlighting the importance of greater visibility of the Stop Smoking Clinic set in the Hospital, which is run in collaboration with the pulmonary healthcare service; it has a crucial role in the prevention of smoking-related diseases, and at the same time it is also an integral part of the treatment of pulmonary conditions. Our data revealed that 23.6% of individuals in the group of patients under treatment for pulmonary conditions were still smoking. This finding is similar to those published in an OsMED 2019 report [1] in which 28.5% of patients with asthma and 40.4% of those with COPD were reported as still smoking. Other relevant literature shows that many patients are smokers at the time of diagnosis of a chronic pulmonary disease, and a relatively high percentage of them keep smoking despite their condition, without receiving any therapy for tobacco addiction [12, 13]. Our study revealed that more than half of smokers wanted to try to stop smoking, but without any support. The treatment of tobacco abuse should always be prescribed as an integral part of the respiratory therapy. Further, it should be well kept in mind that, within the still existing context of COVID-19 pandemic, smoking increases the probability of severe disease in those who contract COVID-19 [14]. For the National Health Systems, reduction of tobacco abuse would thus mean a significant improvement in clinical outcomes, in reducing lethality and in the optimization of healthcare expenditure. The fact that tobacco abuse increases the impact of COVID-19 should persuade governments to expedite plans to reduce tobacco consumption.

Last on the methodology used in our study, it is worth observing that, despite its intrinsic limitations, the anonymous, self-administered questionnaire used in this study reached a high percentage of respondents

(90.7%) and represented the fastest way to gather data associated to patients usually belonging to our respiratory service: the data on drug consumption, in fact, which are detectable by local health facilities, would not have allowed us to identify the group of patients of the specific service.

CONCLUSIONS

This investigation confirms that the healthcare strategy applied during the first 2020 SARS-CoV-2 Italian lockdown successfully contributed to maintain the pre-existing level of adherence to drug therapy in patients with respiratory disease. Despite its limitations – among which the small sample of outpatients, the self-reported nature of the data and the relatively short period of the Mar-May 2020 lockdown – the study was helpful to highlight possible improvements in the patients' care. Among emerged criticalities, there remains the need to improve healthcare education in patients, who need to adopt increasingly conscious approaches to chronic disease during the whole pandemic period and afterwards. One helpful means to those approaches might be the use of new digital systems that include a role for pharmacists in the treatment and monitoring of patients with chronic conditions [15].

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Consent for publication

The manuscript has not been published or presented elsewhere in part or in entirety, and it is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. All Authors read and understood the Journal's policies, and confirm that neither the manuscript nor the study violate any of these. All Authors read and approved the final manuscript.

Ethics approval and consent to participate

The study has been performed with the approval of the Ethics Committee at S. Camillo-Forlanini Hospital and with the participants' informed consent in compliance with the Helsinki Declaration.

Data statement

All relevant data are reported in the manuscript. Raw data from the survey can be made available by the first Author.

Authors' contribution

Conceptualization and methodology: RP, LDM, AS, DS, CP, GG, CG. Investigation: RP, LDM, AS, DS, CP, GG. Formal analysis: RP, CG. Data interpretation: RP, LDM, AS, DS, CP, GG, CG. Writing – original draft: RP, CG. Writing - Review & Editing: RP, LDM, AS, DS, CP, GG, CG. Project administration: RP.

Conflict of interest statement

The Authors have no conflicts of interest to declare.

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Prevalence of breastfeeding and birth practices during the first wave of the COVID-19 pandemic within the Italian Baby-Friendly Hospital network. What have we learned?

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Abstract

Background. At the beginning of the COVID-19 pandemic, healthcare workers were faced with difficult decisions about maternity care practices. The evidence-based practices recommended by the WHO/UNICEF Baby Friendly Hospital Initiative (BFHI) were confirmed by Italian national guidance.

Aim. To describe, in a number of facilities that are part of a national Baby-Friendly network, the adherence to some steps of BFHI standards during the COVID-19 emergency.

Methods. We conducted a cross-sectional online survey, inviting all hospitals interested in the Initiative, to fill out a semi-structured questionnaire.

Results. Out of the 68 participating hospitals, 30.9% were hubs and 69.1% spokes. During May 2020, 61.8% of hospitals had COVID-19 and non-COVID-19 clinical pathways, while 38.8% were only non-COVID-19. None was dedicated exclusively to COVID-19 pathways. The BFHI was effective in guaranteeing ≥80% exclusive breastfeeding, the presence of companion of mother's choice, skin-to-skin and rooming-in. The type of accreditation was associated with the presence of a companion of the mother's choice during labour (p=0.022) and with skin-to-skin (p<0.001). According to the narratives, increased interpersonal distance made interactions with mothers difficult and the absence of a birth companion was reported as a major issue.

Discussion and conclusions. The BFHI is a highly-structured, evidence-based care model. Investing in strong collaborative care approaches contributes to hospitals' preparedness.

Key words

- baby-friendly initiative
- baby-riendly hospitals
- breastfeeding
- COVID-19
- skin-to-skin contact
- rooming-in

INTRODUCTION

During the initial phase of the COVID-19 pandemic when international and national guidelines were either conflicting or non-existent, Italy was the hardest-hit country in Europe [1], and healthcare workers were faced with difficult decisions about maternity care

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practices in the absence of consolidated guidelines for women with suspected or confirmed COVID-19 infection. Both the World Health Organization [2] and the United Nations Children's Fund [3] published interim guidance in early March recommending that mothers continue breastfeeding according to standard infant feeding guidelines, using precautions for infection prevention and control (IPC). This interim guidance confirmed the importance of the evidence-based practices outlined in the WHO/UNICEF Baby Friendly Hospital Initiative (BFHI) [4]. These included having a companion of the mother's choice (CMC) present at the birth, holding her baby skin-to-skin immediately after birth, breastfeeding and rooming-in with her baby within arms' reach, and were summarized through a series of WHO infographics and frequently asked questions for health care workers published at the end of March 2020 [5, 6]. In the same period, the Italian National Institute of Health (Istituto Superiore di Sanità – ISS) organized and coordinated an initiative to examine and disseminate the updates of the scientific literature on COVID-19 in pregnancy, childbirth and breastfeeding that involved the major national scientific organizations: the Italian Society of Neonatology (SIN), the Italian Society of Perinatal Medicine (SIMP), the Italian Society of Pediatrics (SIP), the Associazione Culturale Pediatri (ACP), the Association of Italian Hospital Obstetricians and Gynecologists (AOGOI), the Association of Italian University Gynecologists (AGUI), the Italian Society of Anesthesiology and Intensive Care Medicine (SIAARTI), and the National Federation of Midwives (FNOPO) [7]. The objective was to provide national clinical practice guidance for health professionals caring for pregnant women and assisting during labor and delivery, and disseminate it through scientific webinars for health providers and infographics for the general population [8].

From 27th February to 7th May 2020 the updates were published weekly on the EpiCentro website of the ISS [9]. The Italian National Center for Disease Prevention and Health Promotion (CNaPPS) of the ISS was responsible for querying PubMed, Scopus, Embase and CINAHL databases for available literature on studies of any design and published in any language beginning in January 2000. It was also responsible for finding and reviewing literature and documents on COVID-19 in pregnancy, childbirth and the puerperium produced by international government agencies and specialist scientific societies. At the end of May, the ISS published "Interim indications for pregnancy, childbirth, breastfeeding and the care of very young children 0-2 years in response to the COVID-19 emergency", and a subsequent update at the beginning of February 2021 [10].

During those months, the Italian National Committee for UNICEF (UNICEF Italy), which is responsible for the BFIs in Italy, including the BFHI, the Baby-Friendly Community Initiative (BFCI) and Breastfeeding-Friendly University Program Initiative (BFUP), was collaborating on translating and/or disseminating information from these sources [2, 3, 5], as well as organizing webinars to offer support and opportunities for networking and sharing solutions for maintaining Baby-Friendly standards. All hospitals, community health services and university programs that were Baby-Friendly accredited or in the accreditation process were invited to participate in the free weekly or biweekly webinars to create the conditions for knowledge sharing and exchange of experiences, documents and procedures.

At that time, information was missing on how hospitals were dealing with the emergency, what practices had been adopted for maternal and newborn care (i.e., skin-to-skin at birth, rooming-in, breastfeeding, presence of a companion of mother's choice), if and how Baby-Friendly Hospitals (BFHs) were applying the BFHI standards and what were the main barriers and facilitators.

In this scenario, our study, undertaken by the CNaPPS-ISS and UNICEF Italy, aimed to describe, in a number of facilities that are part of a national Baby-Friendly network: 1) the adherence to some steps of BFHI standards during the COVID-19 emergency; 2) the differences in adherence to the recommended practices by BF accreditation; 3) how practices changed and what the challenges and strengths in applying some of the steps of the BFHI were.

METHODS

Design

The study was a cross-sectional online survey.

Setting and relevant context

The BFHI is a strategy launched by WHO and UNICEF to protect, promote, and support breastfeeding in maternity facilities [11]. Several investigators have found that BFIs have a positive impact on breastfeeding rates and outcomes [12, 13]. In Italy, the BFHI and BFCI are promoted together by UNICEF Italy as "Together for Breastfeeding: Baby-Friendly Hospitals and Communities – United for protecting, promoting, and supporting breastfeeding" [14].

Sample

All the accredited Baby-Friendly Hospitals (n 30), those in the process of accreditation (n 22), those who had sent the online manifestation of interest for the Italian Baby-Friendly Initiative (n 54) were invited to participate to the study. The BFHI accreditation process involves a three-staged series of assessments regarding the facility's policies and procedures, staff training on the BFHI steps, and interviews with mothers and pregnant women to ensure they are receiving care consistent with BFI standards. Passing all three assessments leads to BFH accreditation. Facilities that have officially enrolled in the process and are working with a UNICEF tutor are considered "in the process of becoming a BFH", while those who have compiled an online form requesting information about accreditation are considered "interested in becoming a BFH".

Measurement and data collection

An online semi-structured questionnaire was used, based on the BFHI standards that were most negatively impacted during pandemic (e.g., presence of a CMC,

skin-to-skin contact, rooming-in 24/7 with the infant within arms' reach). The tool consisted of 65 quali-quantitative items and was divided into 6 sections. The first provided information on the hospital, the prevalence of exclusive breastfeeding (EBF) and hospital organization and services during the pandemic. The other 4 sections included items on provision of care in vaginal births and caesarean sections (CS) to women who were SARS-CoV-2 positive and negative. The last section assessed the perceived evolution of practices during pandemic and included some open-ended items on professionals' opinions. The questionnaire also included questions to evaluate how the guidance provided by the CNaPPS-ISS and UNICEF Italy was used to support clinical practice. At the end of the questionnaire, there was a space for a contact person's email or telephone address, in case of incomplete answers. Ethical approval was obtained from the Ethics Committee of the Italian National Institute of Health (Protocol n AOO-ISS 14/05/2020 0017295). The respondents were informed of and agreed to the use of anonymous data in accordance with Italian and European Data Protection legislation.

The study was conducted between May and July 2020 and the questions referred to the period March-April 2020. Only one questionnaire was permitted for each hospital. The respondent, usually the reference person for the BFHI, replied on behalf of the hospital. A letter of invitation to participate in the survey, explaining the purpose of the survey and giving information on its compilation, was sent via the UNICEF BFI Network. Before sending invites to all hospitals, our team tested the survey with three respondents whom we recruited from three hospitals not included in the survey. This test aimed to assess the functionality and clarity of the questions and was useful for rewording some of them. Follow-up contacts with respondents were carried out during June and July 2020 to obtain missing data and improve the quality of information.

Data analysis

Categorical variables of greater interest were reported as frequency and percentage, continuous variables were summarized by median and interquartile range (IQR). Bivariate analysis was performed by creating two main categories, according to an increasing level of engagement in the BFHI. Accredited BFHs and those in the process of BFH accreditation (having successfully passed stage one of UNICEF evaluation) were compared to hospitals interested or "other" categories using the chi-square test. Statistical analyses were conducted using SPSS v. 26. Significance was set at a p-value < 0.05. Open-ended questions were treated for qualitative categorical analysis. Two researchers separately coded the narratives on an inductive basis, according to emerging categories, and created a shared codebook. The coding process was done using NVivo 12 software.

RESULTS

Quantitative results

At the time of the survey, the Italian Baby-Friendly Hospital Network was composed of 30 accredited BFHs, 22 BFHs working toward accreditation, and 54 that had expressed interest in working to become BFHs in the past five years (*Table 1*).

Sixty-eight hospitals, mainly from northern Italy, participated to the survey. Of these, 38.5% (n = 26) were accredited BFHs, 20.6% (n = 14) were in progress, 32.4% (n = 22) had expressed interest toward the accreditation process in the previous five years, 8.8% (n = 6) had expressed interest before 2016 (coded as "other"). The respondents' geographical distribution was consistent with the Italian BFH network: 26.5% northwestern Italy, 36.8% northeastern, 29.4% central, 4.4% southern, 2.9% islands (*Figure 1*).

In 2019, the total number of births in the participating hospitals was 77,088, with a median value of 925 (range 78-5,400), including some small and highly specialized services (e.g., only for births of newborns needing cardiac surgery). According to the level of intensive care, 30.9% of hospitals were hubs (higher) and 69.1% spokes (lower). During the month of May 2020, 61.8% of hospitals had both COVID-19 and non-COVID-19 clinical pathways, while 38.8% were only non-COVID-19. None of the hospitals was dedicated exclusively to COVID-19 clinical pathways.

In the middle of the first wave of the pandemic in March 2020, the number of health personnel was the same in 72.1% of health facilities, 17.6% had had a reduction in personnel, while 5.9% had increased the workforce. At the time of the survey data collection, 88.2% of healthcare facilities tested all pregnant women at hospital admission for SARS-CoV-2 using a nasal swab. During the lockdown, up to the beginning of May 2020, online prenatal group meetings were offered by community services (Consultori Familiari) in

Table 1
Composition of the Italian BFH Network and Hospital enrolled in the survey in March-April 2020

		Accredited BFH (n)	In progress (n)	Interested (n)	Other (n)
BFH Italian Network (n 106)		30 (28.3%)	22 (20.8%)	54 (50.9%)	–
Hospitals enrolled in the survey (n 68)		26 (38.2%)	14 (20.6%)	22 (32.4%)	6 (8.8%)
Level of intensive care	High (HUB)	6 (23.1%)	3 (21.4%)	10 (45.5%)	2 (33.3%)
	Low (SPOKE)	20 (76.9%)	11 (78.6%)	12 (54.5%)	4 (66.7%)
COVID-19 clinical pathway (COVID-19+/non-COVID)	Both	18 (69.2%)	8 (57.1%)	13 (59.1%)	3 (50%)
	Non-COVID-19 only	8 (30.8%)	6 (42.9%)	9 (40.9%)	3 (50%)

Note. The figure shows the national distribution of BFHs participating to the survey: North-West, North-East, Centre, South, Islands.

Figure 1
Distribution of participating hospitals.

27.9% (19/68) of cases, in 17.6% (12/68) by hospitals, in 13.2% (9/68) by integrated hospital and community services, 11.8% (8/68) by others (e.g., individual video calls using instant messaging applications for smartphones where no web applications for computers were available), mother-to-mother support associations independently (1.5%, 1/68) or integrated with community services (1.5%, 1/68). Among the 68 health facilities, 25.0% (17/68) had stopped all prenatal group support or educational activities, whether online or face-to-face. After hospital discharge, support group meetings via web were offered in 25.0% of cases by community services (17/68), in 11.8% by hospitals (8/68), in 13.2% by others (9/68), in 4.4% were integrated hospital and community services (3/68), in 1.5% (1/68) by mother-to-mother support associations independently or integrated with the community services (1.5%, 1/68). Among the 68 health facilities, 32.4% (22/68) had stopped all types of postnatal group support or education activities, whether online or face-to-face. During the same period, hospital respondents reported that individual support after birth was offered by a midwife at home (n = 12), at a community clinic (n = 29) or via web (n = 15). The family pediatrician, which every baby in Italy in entitled to as a part of the National Health Service, was available for a home visit (n = 5), in a community clinic (n = 17) or via web (n = 4). The lengths of hospital stay in non-COVID-19 care pathways (n = 68) were either 1-2 days (50.0%) or 3-4 days (50.0%) for vaginal birth. After a CS, 16.2% (11) of facilities kept mothers for 1-2 days, while 79.4% (54) did for 3-4 days and 4.4% (3) ≥5 days. In the facilities with clinical pathways for COVID-19 positive women (n = 42), 4.8% (2) of hospital discharges occurred within 24 hours after vaginal births, 35.7% (15) at 1-2 days, 40.5% (17) at 3-4 days and 19.0% (8) ≥5 days. In COVID-19 positive women with CS (n = 42), hospital stays were generally longer: only 14.3% (6) were discharged at 1-2 days, 61.9% (26) at 3-4 days and 23.8% (10) stayed ≥5 days.

EBF prevalence is reported only for those facilities that were accredited BFHs and provided all the required data: yearly data for 2019, monthly for March and April 2020. This choice was driven by the need to present data collected according to international standards [15]. *Figure 2* shows the prevalence of EBF in BFHs dedicated both to COVID-19 and non-COVID-19 clinical pathways or only non-COVID-19. The EBF prevalence is represented in relation to the 80.0% prevalence standard required by the WHO/UNICEF accreditation system.

In 2019, most of the BFHs, except for 2, presented an EBF rate above 80.0%. During the first wave of the pandemic, in March 2020, 9/15 had an EBF prevalence ≥80.0% while in April 2020, 11/15 were compliant with the BFH standard. There was a decrease from 2019 with a median value of 85.0% (IQR 83-88) to March 2020 (median value 82.0%, IQR 76-90), while there was a slight increasing from March 2020 to April 2020 with a median value of 83.0% (IQR 78-90).

In *Table 2*, the frequencies of different BFI practices are presented, according to the type of BFH accreditation and COVID-19 status.

In accredited BFHs (n = 18) women who tested positive to SARS-Cov-2 (COVID-19+) and were asymptomatic or paucisymptomatic could have a CMC during labor in 35.3% (6/17) of cases and 37.5% (6/16) during childbirth. Skin-to-skin contact for at least 1 hour was possible in 43.8% (7/16) of cases, while rooming-in 24 hours a day in close contact was practiced by 100.0% (26/26) of hospitals. When maternal conditions were severe, 1/14 hospitals allowed a CMC during the hospital stay. In CS in COVID-19+ mothers, skin-to-skin contact for at least 1 hour was practiced in 42.9% (6/14) and rooming-in in 100.0% (13/13) of health facilities. One hospital allowed the presence of a CMC inside the operating theatre, even when the mother's conditions were severe, and during the hospital stay.

The type of accreditation (BFH accredited/in progress vs interested/other) showed a statistically significant association with the presence of a CMC during labor ($p = 0.022$) and with the provision of skin-to-skin contact according to the WHO/UNICEF standard of at least one, uninterrupted, hour at birth ($p < 0.001$).

Provision of evidence by ISS and UNICEF

The evidence provided by the ISS through its web portal was known to 89.7% (n = 61) of the responding health facilities. Out of these, 55.7% used this evidence to inform their professional practice and clinical protocols, 59.0% for updating the professional team, 47.5% for personal enrichment; 1.6% did not use them and 1.6% did not find this means of provision of care useful for operational purposes. UNICEF updates were known to 88.2% (n = 60) of respondents; out of

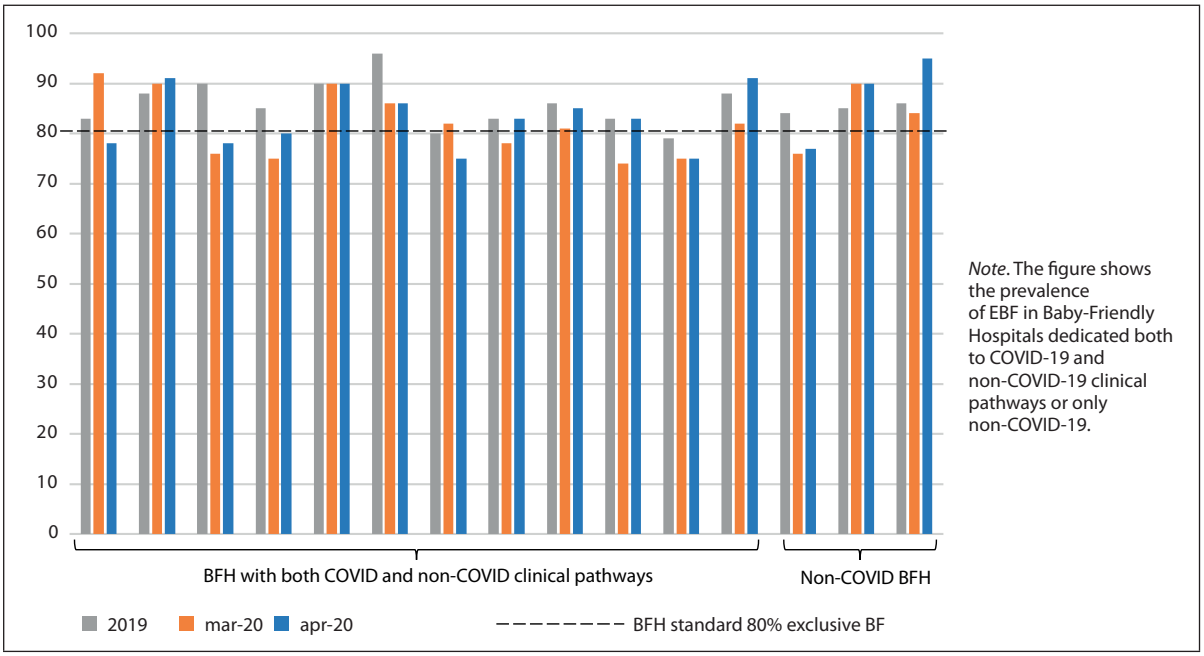

Figure 2
Prevalence of EBF in accredited BFH providing 2019, Mar-2020 and Apr-2020 data.

these, 48.3% used this evidence to inform professional practice and clinical protocols, 70.0% for updating the professional team, 48.3% for personal enrichment; 1.7% did not use them and 1.7% did not find this means of provision of care useful for operational purposes.

Qualitative analysis of the open-ended questions provided by the respondents for the BFH

Two open-ended questions explored how healthcare had changed and what the emerging demands and needs of women, fathers and health professionals were. According to a categorical analysis of the narratives, care provision had become more complex since the beginning of the pandemic, due to several aspects of care, e.g., the need to manage oral swabs and waiting areas, even in the absence of symptoms suggestive of COVID-19, especially in women admitted to a hospital in advanced labor. Wearing and managing Personal Protective Equipment (PPE), together with organizational, logistic and bureaucratic aspects of care, had become more time consuming and took precious time away from direct care to women. Furthermore, the increased interpersonal distance made normal interactions with mothers more difficult as no facial expressions were visible (e.g., smiling). The hospitals where "warmth and affection" were part of normal mother-partner-baby care felt penalized by the need to use PPE, which affected communication and relationships. Healthcare provision rapidly adapted to changing needs, including reinforcing one-to-one care for women who had been isolated from their partners and relatives in a moment where community services were also in transition from in-presence to online provision of support. Nevertheless, mothers' care was "more standardized, less personalized". Different communication tools were adopted, such as telephone and video calls, to help women keep in touch with their relatives. In a time of scarce or controversial evidence, the accredited BFHs attempted to maintain the WHO/UNICEF standards while applying COVID-19 precautions for professionals, mothers, fathers and babies.

Rooming-in increased and most of the newborn care took place in the mother's room. One COVID-19-hospital where partners were admitted for labor, childbirth and during the hospital stay felt penalized by a significant increase in deliveries by women from other areas, that are normally served by other hospitals.

Hospital discharge was moved up by about 24 hours, both in vaginal birth and CS, and this impacted breastfeeding as hospital professional care was missing in a time where community services were not available, as they were re-organizing from in person to remote support. On the other hand, women themselves were asking to go home as soon as possible when their partners and the baby's siblings were not allowed to enter and share in the early parenthood experience with them. Another reason to ask for early discharge was fear of contracting the virus during the hospital stay. According to respondents, in some cases, this could have led to early use of formula or failure to recoup EBF, when post-discharge breastfeeding clinics in hospitals and community healthcare services, or peer support groups were not available at that time. In other cases, early discharge, within 24 hours from birth, for non-COVID-19 mothers was accompanied by home visit from a midwife. The absence of a CMC was reported as a major issue for those facilities that did not allow the father/partner access during labor, childbirth or hospital stay. This latter, together with the partner's absence during antenatal visits, has been described as "devastating". Women who had a CS complained of an increased difficulty in managing pain as a result of their partner's absence and the full

Table 2
Frequencies of WHO/UNICEF recommended practices provided by type of BF accreditation

Vaginal birth in non-COVID-19 women (n = 68)	**BFH accredited (n = 26)[a]**	**In process (n = 14)[a]**	**Interested/Other (n = 28)[a]**
Companion of the Mother's Choice (CMC) during labor	25/26 (96.2%)	11/14 (78.6%)	19/28 (67.9%)
CMC during childbirth	26/26 (100%)	14/14 (100%)	25/28 (89.3%)
Skin-to-skin contact (at least 1 hour)	26/26 (100%)	14/14 (100%)	26/28 (92.9%)
24 hrs rooming-in, close contact	26/26 (100%)	14/14 (100%)	27/28 (96.4%)
CMC during hospital stay	17/26 (65.4%)	6/14 (42.9%)	12/28 (42.9%)
Vaginal birth in COVID-19+ women[b] (n = 42)	**BFH accredited (n = 18)[a]**	**In process (n = 8)[a]**	**Interested/Other (n = 16)[a]**
CMC during labor	6/17 (35.29%)	4/8 (50.0%)	6/16 (37.5%)
CMC during childbirth	6/16 (37.5%)	5/8 (62.5%)	6/16 (37.5%)
Skin-to-skin contact (at least 1 hour)	7/16 (43.8%)	3/8 (37.5%)	6/15 (40.0%)
24 hrs rooming-in, close contact	13/13 (100%)	7/8 (87.5%)	14/15 (93.3%)
CMC during hospital stay	1/17 (5.9%)	1/8 (12.5%)	2/16 (12.5%)
CMC during hospital stay, if severe conditions of mother	1/14 (7.1%)	0 (0)	1/15 (6.7%)
Caesarean section in non-COVID-19 women (n = 68)	**BFH certified (n = 26)[a]**	**In process (n = 14)[a]**	**Interested/Other (n = 28)[a]**
CMC in operating theatre	8/25 (32.0%)	2/12 (16.7%)	2/25 (8.0%)
Skin-to-skin contact (at least 1 hour)	25/25 (100%)	13/13 (100%)	19/27 (70.4%)
24 hrs rooming-in, close contact	26/26 (100%)	14/14 (100%)	26/28 (92.9%)
CMC during hospital stay	17/25 (68.0%)	6/14 (42.9%)	11/27 (40.7%)
Caesarean section in COVID-19+ women[a] (n = 42)	**BFH certified (n = 18)[a]**	**In process (n = 8)[a]**	**Interested/Other (n = 16)[a]**
CMC in operating theatre	1/16 (6.3%)	0/8 (0)	0/15 (0)
CMC in operating theatre, if severe mother's conditions	1/16 (6.3%)	0/8 (0)	0/15 (0)
Skin-to-skin contact (at least 1 hour)	6/14 (42.9%)	2/8 (25.0%)	7/15 (46.7%)
24 hrs rooming-in, close contact	13/13 (100%)	7/8 (87.5%)	13/15 (86.7%)
CMC during hospital stay	1/16 (6.3%)	0/8 (0)	3/16 (18.8%)
CMC during hospital stay, if severe conditions of mother	1/16 (6.3%)	0/8 (0)	2/15 (13.3%)

[a]% calculated using as denominator the Yes/No answer, excluding "Other" (e.g. transferred) or "Not applicable".
[b]Asymptomatic or paucisymptomatic.

responsibility for taking care of the baby, especially in the first 48 hours. Respondents also reported from their perspective that fathers and partners felt excluded and missed sharing the difficulties and emotions of the first days of their baby's life. Some professionals reported both women and their partners having a sense of solitude and what they called "fear of separation", following the early pandemic restrictions. In health facilities with a higher prevalence of foreign-born women, the absence of the partner compounded communication difficulties and language comprehension issues. Once hospital protocols allowed partners in, this was perceived as a relief for mothers, partners and professionals.

Restrictions to visitors, such as relatives, including grandparents, and friends, was reported as both a strength and a weakness. Women seemed more concentrated on the mother-baby relationship and received less unsolicited advice about motherhood and breastfeeding. Insecurity, anxiety, worry and fear were reported as "new" pandemic-induced feelings that needed to be addressed by health personnel with one-to-one counselling and clear and consistent information. In the very beginning of the first wave of the pandemic, the baby's safety and protection was a major issue for parents: breastfeeding was perceived as a way to protect the baby, acting as a motivator.

On the other hand, during the very first phases of the pandemic, health professionals experienced fear of contagion, when the evidence on the use of PPE was not clear and the most suitable PPE was out of stock. This quickly changed as women underwent molecular tests for COVID-19 and PPE become available on a large scale. In some cases, a decrease in health personnel was reported, due to forced leave for professionals at increased risk of contagion (e.g., for chronic diseases). The physical, as well as the emotional, workload increased. Health professionals reported "quickly defining clear and shared clinical pathways" as useful, in order to act with "deeper awareness and knowledge". Nevertheless, "we were in a constantly changing process and all of us, mothers, fathers and professionals, lived through this experience with difficulty".

DISCUSSION

To our knowledge, this is the first study assessing how BFHs faced the outbreak of pandemic. The respondents' distribution is consistent with the Italian BFI network, which is concentrated mainly in the northern and the central areas of the country. These data are also consistent with EBF prevalence at 4-5 months of age, whose rates decrease from northern (34.0%-44%), to central Italy (22.4%-40.7%), to southern Italy (16.6%-39.8%) [16, 17]. This geographical distribution is probably due to the combined effect of a stronger investment in breastfeeding policies along with healthcare provision and community networks supportive of breastfeeding. Other reasons of these regional differences are various individual and context inequalities [18] and the limited training on breastfeeding by health professionals [19]. Moreover, lack of professional support negatively impacts on breastfeeding outcomes and maternal satisfaction [20-21]. Consequently, the use of breast-milk substitutes is a widespread practice, sometimes already during the hospital stay and at discharge [22]. WHO and UNICEF suggest 80.0% as being the gold standard for EBF at hospital discharge that is the newborn receives only mother's milk [14]. The Italian national, population-based, prospective cohort study ItOSS reports 79.6% of infants receiving any mother's milk, whether exclusive BF, predominant BF or complementary (BF + formula feeding). No data is available on EBF prevalence [23]. In our study, the BFHs were able to comply with the WHO/UNICEF exclusive BF standard even during the first wave of the pandemic.

Given the small sample, it is not possible to make inferences regarding the different practices and their association with the hospital characteristics. However, the prevalence of some practices in accredited BFHs and those in the designation process seems to better comply with WHO/UNICEF standards, especially in provision of care for non-COVID-19 women during the first wave of pandemic, compared to the other facilities. It should be highlighted that accredited hospitals and those "in the process" need to have a structured data collection system on WHO/UNICEF standards, that others hospitals may not have. Data from the BFH network could thus be more reliable. The BFHs have demonstrated the capacity to adapt to the new emerging needs, in times where evidence was scarce, health professionals themselves were worried for the number of contagions occurring in the workplace, and the decision-making process demanded rapid adaption. Some facilities maintained the presence of a CMC during labor, childbirth and post partum, both for COVID-19 and non-COVID-19 mothers. In these hospitals, security measures were increased, e.g., providing antigenic o molecular screening to the partner/caregiver. It should be emphasized that the Italian universal healthcare system promptly extended the tests to caregivers, free of charge. Keeping the mother-newborn dyad in rooming within at arms' reach was a consolidated practice in BFHs, even during the first wave of the pandemic wave, in line with WHO/UNICEF recommendations and national guidelines [10]. The crucial role of a close mother-newborn relationship and the effects of mother-baby separation during the COVID-19 pandemic was described in the CovidMotherStudy, where nearly 60.0% of mothers who experienced separation reported feeling "very distressed" and 29.0% who tried to breastfeed were unable to [24]. The same study showed that infants who were not directly breastfed, did not experience skin-to-skin care, or who did not room-in within arms' reach, were significantly less likely to be exclusively breastfed in the first 3 months, adjusting for maternal symptoms [24]. Early hospital discharge was related both to organization of care and to women's demands to re-join their partners, siblings and relatives. This study focused on hospital practices, so it is not possible to speculate on the effects of early discharge on EBF rate and to mothers' self-confidence; nevertheless, in the qualitative analysis health professionals reported this was a concern.

In February-April 2020, little evidence was available on SARS-CoV-2 transmission according to different birth practices. Since then, "physical distancing" was singled out as one of the main prevention measures. The debate was focused on the importance of maintaining social and emotional closeness while being physically distanced. With the good intention of preventing infection transmission, the "separation paradigm" was applied pervasively to the mother-partner-newborn triad all along the care pathway, negatively affecting their experience of childbirth, the bonding process and early parenthood. This phenomenon is also reported by other studies [25]. Within the BFHs, decision makers and health professionals were urged to keep together what could not be separated, if not at the cost of mental and physical health outcomes affecting both parenting and early child development [26-28]. WHO and UNICEF affirmed the BFH standard as being, still, the most appropriate and effective way to ensure maternal and newborn health, as the benefits of breastfeeding, bonding and closeness outweighed what was subsequently demonstrated to be a low risks of virus transmission [10, 23]. Despite the provision of evidence, respondents in our study reported that COVID-19+ mothers were often left alone during labor and childbirth, were not allowed to bond with their babies and could not be supported by a partner during their hospital stay. The same separation paradigm affected their partners' experience of childbirth, the bonding process and early parenthood. While no official data are available, the experiences of parents and health professionals that were reported directly to the Italian National Institute of Health and UNICEF Italy, as well as through social media, still outline a general exclusion of the partner, women's solitude and newborn separation, especially for SARS-CoV-2 positive mothers and in specific areas of the country. This phenomenon is also reported by other studies [25], and confirms that policy alone is not sufficient, and more efforts need to be enacted to translate policy into clinical practice.

The limitations of this study include the small sample (68 hospitals, mainly based in Northern-Central Italy) and the fact that the high prevalence of BFHs primary outcomes of interest doesn't allow for the comparison of group characteristics. In "ordinary times", more at-

tention would certainly have been paid to the response rate in order to avoid selection bias. We need to go back in time to the first lockdown in the spring of 2020 and remember that, in Italy, hospitals had to completely revolutionize the way they operated, given the shortage of PPE and SARS-CoV-2 tests, and the substantial uncertainty of the available evidence.

CONCLUSIONS

The study explored the prevalence of breastfeeding and birth practices care in pregnancy, childbirth and breastfeeding during the first COVID-19 pandemic wave in some facilities involved in the Italian BFH network. BFHs performed better in some of the WHO/UNICEF standards and according to the Italian national guidance, compared to other hospitals. The BFHI is a structured organizational and clinical model, evidence-based, highly demanding in terms of collaboration, cohesion and creation of a common vision of mother-father-newborn centered care. The authors support the idea that investing in strong collaborative care, including all relevant stakeholders, contribute to the *governance* and *preparedness* which are essential for facing unforeseen situations, such as emergencies. Furthermore, the authors found that COVID-19+ mothers suffered solitude, even in the absence of sound evidence. This confirms that policy alone is not sufficient, and more efforts are needed to translate policy into clinical practice.

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Authors' contributions

AG, EC and FZ conceived and designed the study. FZ and FM acquired the data. AG, FZ and SSA analysed the data. All Authors interpreted the results. AG, EC, FZ drafted the article and all Authors read and approved the submitted version.

Authors' note

Angela Giusti and Elise M. Chapin contributed equally to this study.

Conflict of interest statement

The Authors have no conflicts of interest to declare.

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Monitoring cardiovascular diseases and associated risk factors in the adult population to better orient prevention strategies in Italy

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Abstract

Introduction. Cardiovascular disease (CVD) is the first cause of death in Europe and over the world. This study analyses health-related behaviours in adults referring doctor-diagnosed CVDs.

Materials and methods. We used data from the Italian cross-sectional Behavioural Risk Factor Surveillance System PASSI gathered in 2015-2018. Complex survey design analyses included the Taylor series method for variance estimation and Poisson regression for associations between socio-demographic characteristics and CVD.

Results. Among 132,598 respondents, the prevalence of doctor-diagnosed CVD was 5%. Higher percentages are observed among: men, older individuals, socioeconomically disadvantaged people. Compared to the general population, people with CVD have greater risk and aggravating factors, and a worse health status overall. All protective behaviors and lifestyles shall be improved.

Discussion and conclusions. In Italy, adults with CVD are more likely to be exposed to aggravating modifiable risk factors: it represents a valuable information for increased preventive interventions, even more in the light of the COVID-19 pandemic scenario.

Key words

- cardiovascular diseases
- risk factors
- surveillance
- epidemiology
- prevention

INTRODUCTION

Nowadays, in Europe and other world regions, lengthening of average life and constant increase of population ageing on the one hand and a constantly decreasing natality on the other hand have determined an increasing relative weight of causes for morbidity and mortality most associated with the decline of the organism, such as chronic noncommunicable conditions. Thus, despite the huge scientific and technology advances in their prevention, diagnosis and treatment, cardiovascular diseases (CVDs) are by far the leading cause of death worldwide [1].

In Europe, slightly over 1.8 million people died from diseases of the circulatory system, mainly corresponding with heart attacks and strokes. These conditions were the two major causes of deaths in the European Union (EU) responsible for 36% and 26% of all deaths respectively, despite large decrease in CVD mortality [2]. In Italy, since 1990, a significant decline of CVD burden, particularly in the age-standardised prevalence (-12.7%), mortality rate (-53.8%), and disability-adjusted life years rate (-55.5%) has been observed. In spite of such a success in reducing disability, premature death and early incidence of CVDs, their burden is still high: all-age prevalence CVD increased from 5.75 to 7.49 million residents in Italy and CVDs confirm to be the first cause of death (34.8% of total mortality). Additionally, more than 80% of the CVD-related burden could

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be attributed to known modifiable risk factors such as high systolic blood pressure, dietary risks, high low density lipoprotein cholesterol, and impaired kidney function [3].

Given projections by 2030 of more than annually 22.2 million deaths from CVDs, the World Health Organization (WHO) introduced a global prevention agenda, which emphasizes the role of cardiovascular prevention and control, and aims to increase research capacity in the field of preventive cardiology to meet the reduction of one-third of premature deaths [4]. CVDs are associated with a relevant burden on healthcare systems, and on society as well. Overall, the impact of CVD on population health could be improved by addressing behavioural risk/aggravating factors, such as tobacco smoking, physical inactivity, overweight and/or obesity, along with the implementation of preventive measures that are weight loss and smoking cessation or involving appropriate treatments for hypertension, and diabetes mellitus among at risk population. Additionally, CVDs relate to a low socioeconomic status (SES): they do not in fact equally distribute in the population and mostly affect deprived groups [5]. Lifestyle-based preventive cardiology aims to combat the CVD burden by behavioural interventions [6].

We used data from the Behavioural Risk Factor Surveillance System (BRFSS) PASSI (Progressi delle Aziende Sanitarie per la Salute in Italia) to estimate CVD in the adult population (18-69 years) in Italy and describe their health profile. More in detail, the specific objectives are: (i) to estimate the CVD prevalence, overall and in different groups; (ii) to assess the occurrence of CVD behavioural risk factors in people with and without CVD. Such these figures are relevant to identify gaps in prevention and plan effective preventive policies and better-tailored health promotion interventions.

MATERIALS AND METHODS

Data source and study population

PASSI is an ongoing cross-sectional Italian BRFSS that originated by express commitment of the National Centre for Disease Prevention and Control of the Italian Ministry of Health: the National Institute of Health (Istituto Superiore di Sanità; ISS) is in charge of its central coordination, but it is carried on by Regions and Local Health Units (LHUs) [7, 8]. Since 2008, PASSI has been monitoring the prevalence of the major behavioural risk factors for chronic noncommunicable diseases and compliance level to the main preventive measures among the adult population (18-69 years of age) living in Italy. PASSI represents a useful tool for Regions and LHUs to describe the general population health profile, in order to plan health promotion and prevention interventions and monitor their effectiveness over time towards the objectives of the National Prevention Plan (NPP) [9].

In each LHU participating in the surveillance, the PASSI monthly sample is extracted by a random modality from an enrolment list of residents and is stratified by gender and age (18-34, 35-49, 50-69 years) in the same proportion than the reference population. Specially trained personnel from the LHUs' public health departments administer telephone interviews using a standardised questionnaire. Eligibility PASSI criteria are: falling within the target age range (18-69 years), being reachable on a telephone number (landline or mobile), not being hospitalised nor institutionalised, understanding the Italian language (in the autonomous province of Bolzano the interviewees have the option of being interviewed in German), and having the ability to participate in the interview. The PASSI operational protocol encompasses the field-substitution technique. Once data are collected, they are anonymised and electronically recorded in a national database, and an annual dataset is created by aggregation of the interviews, which are finalised in the calendar year. Furthermore, four-year datasets are combined to ensure adequate sample size for allowing population subgroups explorations. By the way, PASSI methods for data collection have been described more in detail elsewhere [10].

In the period 2015-2018, 133,070 people (almost 90% of adult population overall) were interviewed in more than 90% LHUs (89 out of 101 in 2018). Adults aged 18-69, resident in Italy, totalled 40,769,022 individuals on January 2017, 1st. The outcome rates are calculated according to the guidelines of the American Association for Public Opinion Research and the Response Rate is 80% in 2018 [11].

Indicator definitions

Information on CVDs are retrieved by asking the interviewees if a physician has ever diagnosed or confirmed any of the following: (i) myocardial infarction, cardiac ischaemia or coronary disease; (ii) other heart diseases such as heart failure or valvulopathy; (iii) stroke or cerebral ischaemia. The analysis considered people who referred at least one of these health conditions. PASSI collects also data on socio-demographic characteristics such as: gender, age, educational level (none or primary school, middle school, high school, university), economic difficulties in making ends meet by the available financial resources (many, some or not at all), nationality (Italian or other) and geographic residence area as categorised by the National Institute of Statistics criteria (North, Centre, South and major islands).

This study focuses on four cluster topics related to CVD prevention. Two groups of indicators related to health and risk profile of people with CVD: (i) health status (number of unhealthy days), depressive symptoms screened by the Patient Health Questionnaire 2 (PHQ-2) [12], referred diagnoses of any chronic disease, (ii) cardiovascular risk factors (CVRFs) as diabetes, hypertension, raised blood cholesterol, overweight/obesity, and modifiable lifestyle risk factors (tobacco smoking, higher risk alcohol consumption, physical inactivity, poor daily consumption of fruit and vegetable). The other two variable categories concern preventive measures of CVD risk: (iii) compliance with protective factors; (iv) advice by healthcare professionals on correct lifestyles promotion (such as to quit smoking, lose weight, engage in regular physical activity, reduce salt and alcohol consumption).

Statistical analysis

Different analyses of the 2015-2018 dataset included, first, estimation of prevalence, and relative 95% confidence intervals (95% CI), of CVD burden and as per types: (i) ischaemic heart disease, that is myocardial infarction, cardiac ischaemia or coronary disease; (ii) other heart diseases, such as heart failure or valvulopathy; (iii) stroke or cerebral ischaemia. We estimated CVD prevalence overall in subgroups by socio-demographic characteristics. Secondly, we described the health profile and quality of life, the occurrence of modifiable risk/aggravating factors for CVD, protective behaviours and to what extent General Practitioners (GPs) and healthcare workers advice CVD-diagnosed people on healthy lifestyles in comparison with people without CVD [13]. Prevalence estimates are weighted (at regional and national levels) by assigning each record a probability weight equal to the inverse of the sampling fraction in each LHU stratum.

The statistical package STATA 13 software (StataCorp LP) supplied data analysis.

Complex survey design analyses were conducted, using the Taylor series method for variance estimation. To estimate prevalence for principle indicators from PASSI data, the function of STATA required specification for the strata, primary sampling units, sampling weights or probabilities. Standard errors are computed using Taylor series linearisation.

A Poisson regression with robust variance was used first to estimate adjusted prevalence ratios for evaluating the association between CVD and socio-demographic characteristics and then to compare health and risk profile of people with CVD versus people without CVD. Cross-sectional studies with binary outcomes analysed by logistic regression are frequent in the epidemiological literature. However, the odds ratio can importantly overestimate the prevalence ratio. On the contrary, Poisson models with adjusted variances provide correct point and interval estimates, and the advantage being the prevalence ratio as the measure of association, it therefore represents not only a viable model other than logistic regression to analyse cross-sectional data with binary outcomes, but also more interpretable and easier to communicate, especially to a non-epidemiologist audience [13].

All prevalence ratios are adjusted for gender, age, educational level, perceived economic difficulties, nationality and geographic area of residence.

RESULTS

A total of 133,070 people was interviewed from 2015 to 2018; the analysis considered 132,598 records actually, because 472 were missing in CVD items. The distributions of the sample by age and gender closely reflect those of the resident population for the years and geographical areas considered [14]. The CVD prevalence in the adult population in Italy was 5% (stroke and ischaemia 0.82%, myocardial infarction, cardiac ischaemia or coronary disease 1.89%, and other heart diseases 2.97%) *(Table 1)*. The CVD prevalence was significantly higher in the following subpopulations: older persons *vs* 18-34 years (35-49 and 50-69 years; adj. PR=2.75, p<0.001 and adj. PR=9.69, p<0.001), people with lower educational level *vs* graduates (high school adj.PR=1.11, p=0.032; compulsory school adj.PR 1.26, p<0.001; and primary school or none adj. PR=1.81, p<0.001), individuals who referred some or many economic difficulties (adj. PR=1.18; p<0.001 and adj. PR=1.62; p<0.001, respectively *vs* people without difficulties), residents in the North *vs* in the Southern Italy (adj. PR=1.08; p=0.029). Women result to be less affected by CVD than men (4.2% *vs* 5.9%; adj. PR=0.67; p<0.001) as well as foreign citizens in comparison with Italians (2.8% *vs* 5.1% adj. PR 0.73; p<0,001) *(Table 1)*.

The *Table 2* compares health status, quality of life, cardiovascular risk and modifiable risk/aggravating factors in people with and without cardiovascular diseases. Data show a worse perceived health and quality of life profile among people diagnosed with CVD than the rest of the sample: they state to feel unwell, bad or very bad, three times more (68.5% *vs* 27.5%; adj. PR=3.3, p<0.001) and to have lived more than 14 unhealthy days in the last month, both related to physical (19.1% *vs* 5.3%; adj. PR=3.3 p<0.001) and psychological health (16.4% *vs* 6.3%; adj. PR=2.6 p<0.001), as well as per daily activity limitations (12.2% *vs* 2.6%; adj. PR=3.4 p<0.001). People affected by CVD reported to suffer from these health issues two times more frequently than others: depressive symptoms (14.1% *vs* 5.5%; adj. PR=2.0, p<0.001) and at least one chronic disease among cancers, respiratory diseases, renal failure, diabetes or liver diseases (40.1% *vs* 13.8%; adj. PR=2.4, p<0.001). The CVD group refers CVRFs more frequently than others: diabetes diagnosis (18.6% *vs* 4%; adj. PR=2.4, p<0.001), hypertension (55.9% *vs* 17.8%; adj. PR=3.0, p<0.001), high cholesterol (44.2% *vs* 21.3%; adj. PR=1.9, p<0.001) and overweight/obesity (61.1% *vs* 41.5%; adj. PR=1.3, p<0.001). Individuals with CVD have never abandoned unhealthy habits such as smoking, alcohol use at risk, physical inactivity and low consumption of fruit and vegetables that, as well as CVRF, represent aggravating factors for the progression of CVD they are affected by, for the onset of new cardiovascular events and other noncommunicable diseases (NCDs). Compared to people without CVD, among people with CVD we observed slightly lower prevalence for tobacco smoking (22.3% *vs* 25.9%; adj. PR=0.9, p<0.001) and at-risk alcohol consumption (12.1% *vs* 17.4%; adj. PR=0.9, p=0.002), even if the figure is not significant for usual high drinking (4.0% *vs* 3.0%; adj. PR=0.9, p=0.233); whereas physical inactivity is very more frequent (43.3% *vs* 34.0%; adj. PR=1.2, p<0.001), but low fruit and vegetable consumption is nearby comparable (52.5% *vs* 48.9%; adj. PR=1, p=0.149).

With regard to protective behaviours, people with CVD show to be much more compliant than CVD-free group, except for engaging in leisure-time physical exercise; there is not instead significant difference in reaching out the "five a day" formula for fruit and vegetable consumption *(Table 3)*. The compliant behaviour in CVD-diagnosed individuals is verified for: attempts to quit smoking in the previous 12 months (45% in CVD group *vs* 32.9% among those without any CVD; adj. PR=1.8, p<0.001), being on diet to lose weight if obese

Table 1
Distribution and prevalence of cardiovascular diseases, association with socio-demographic characteristics by Adjusted Prevalent Ratios (Poisson Regression Model). PASSI 2015-2018 (n = 132,598)

Characteristics	All sample (n=132,598)	Cardiovascular disease-diagnosed people (n=6,545)				
	Distribution	Prevalence		Adjusted Prevalence Ratio[a]		
	%	%	(95% CI)	Adj.PR	(95% CI)	p value
Age group						
18-34	26.5	0.9	(0.8-1.0)	1.00	-	-
35-49	33.4	2.6	(2.4-2.8)	2.75	(2.38-3.17)	p<0.001
50-69	40.0	9.8	(9.5-10.2)	9.69	(8.49-11.1)	p<0.001
Gender						
Male	48.9	5.9	(5.6-6.1)	1.00	-	-
Female	51.1	4.2	(4.0-4.4)	0.67	(0.63-0.71)	p<0.001
Education level						
University	17.3	3.1	(2.8-3.4)	1.00	-	-
High school	48.0	3.9	(3.7-4.1)	1.12	(1.01-1.23)	p=0.032
Middle school	28.8	6.4	(6.1-6.7)	1.26	(1.13-1.39)	p<0.001
Primary school or none	5.9	12.9	(12.0-13.9)	1.81	(1.60-2.04)	p<0.001
Economic difficulties*						
None	46.7	4.2	(4.0-4.4)	1.00	-	-
Some	39.9	5.1	(4.9-5.4)	1.18	(1.10-1.26)	p<0.001
Many	13.4	7.7	(7.2-8.2)	1.62	(1.49-1.77)	p<0.001
Geographic area of residence[§]						
North	37.1	5.1	(4.9-5.3)	1.08	(1.01-1.16)	p=0.029
Centre	22.7	4.5	(4.3-4.8)	0.97	(0.90-1.05)	p=0.472
South	40.1	5.2	(4.9-5.5)	1.00	-	-
Nationality						
Italian	95.4	5.1	(5.0-5.3)	1.00	-	-
Other	4.6	2.8	(2.4-3.3)	0.73	(0.62-0.86)	p<0.001

[a]Adjusted prevalence ratio for: gender, age, educational level, perceived economic difficulties, nationality and geographic area of residence).
*Self-reported difficulties in making ends meet by the available financial resources.
[§]The Southern Italy includes the two major islands (Sardinia and Sicily) as per census criteria by the Italian National Institute of Statistics.

or overweight (34.7% *vs* 24.2%; adj. PR=1.6, p<0.001), uptake of the seasonal flu vaccination (30.4% *vs* 8.4%; adj. PR=2.6, p<0.001). Data highlight also that health professionals advise people affected by CVD on healthy lifestyles more than non-CVD people, with concern to all the six items investigated (quitting smoking, losing weight if overweight/obese or in presence of high cholesterol, engaging in physical activity, reducing higher risk alcohol consumption, reducing salt use if blood pressure is high). The major health professions' advice to CVD group is just slightly higher for the suggestion on reducing salt consumption to people with elevated blood pressure.

DISCUSSION

CVD prevalence and comparison with other sources

In Italy, the PASSI surveillance system is a unique epidemiological source that, basing on a continuous data collection on randomised specific groups of resident population, allows global health data analysis. Furthermore, experiences of comparison with health data of hospital admissions are very few and limited because of selection bias; thus, any accurate rate of diagnosis is confirmed so far. It is noteworthy that administrative data and local registries present widely different encoding data collecting. Other Italian sources reveal a comparable prevalence of CVD: the National Institute of Statistics calculates a 3.9% prevalence of heart diseases (heart attacks and other) by its cross-sectional health interview survey in 2015. Others appreciated a valuable CVD burden in Italy where, over ten years (2008-2012), the prevalence of myocardial infarction remained stable (1.6% in men; about 0.5% in women) and that of stroke decreased in men (from 1.2% to 0.7%) [15]. In 2020, the GBD 2017 Italy Cardiovascular Diseases Collaborators found an increase in all-age prevalence of CVD from 5.75 to 7.49 million Italian residents [3].

Socio-demographic factors

PASSI data show higher CVD prevalence in men, older persons and socioeconomically disadvantaged groups. These results by age and gender are comparable with data from other Italian and European statistic studies. According to Eurostat, in the EU in

Table 2
Prevalence (95% CI) of health status/quality of life, cardiovascular risk factors, modifiable risk/aggravating factors in people with and without cardiovascular diseases (CVDs) by Crude/Adjusted Prevalent Ratios (Poisson Regression Model). PASSI 2015-2018 (n = 132,598)

Variables		People w/CVDs (n=6,545)	People w/o CVDs (n=126,053)	People w/CVDs vs People w/o CVDs			
		% (95% CI)	% (95% CI)	Crude PR[a]	p-value	Adj. PR[b]	p-value
Health status/ quality of life	Bad health status perceived	68.5 (67.1-69.9)	27.5 (27.2-27.8)	5.195	<0.001	3.309	<0.001
	+14 unhealthy days (physical health)	19.1 (17.9-20.4)	5.3 (5.2-5.5)	4.747	<0.001	3.319	<0.001
	+14 unhealthy days (psychological health)	16.4 (15.3-17.6)	6.3 (6.1-6.5)	3.147	<0.001	2.634	<0.001
	+14 unhealthy days (daily activity limitations)	12.2 (11.1-13.3)	2.6 (2.5-2.7)	5.084	<0.001	3.381	<0.001
	Depressive symptoms (PHQ-2)	14.1 (13.0-15.3)	5.5 (5.4-5.7)	2.589	<0.001	2.029	<0.001
	At least one chronic disease*	40.1 (38.6-41.6)	13.8 (13.6-14.1)	3.757	<0.001	2.360	<0.001
Cardiovascular risk factors	Diabetes^	18.6 (17.4-19.9)	4.0 (3.9-4.2)	4.581	<0.001	2.380	<0.001
	High blood pressure§	55.9 (54.4-57.5)	17.8 (17.5-18.1)	5.122	<0.001	2.992	<0.001
	High cholesterol°	44.2 (42.6-45.8)	21.3 (21.0-21.6)	2.706	<0.001	1.875	<0.001
	Overweight/ obesity	61.1 (59.6-62.6)	41.5 (41.1-41.8)	2.134	<0.001	1.347	<0.001
Modifiable risk/ aggravating factors	Tobacco smoking						
	Current smokers	22.3 (21.0-23.6)	25.9 (25.6-26.2)	0.830	<0.001	0.867	<0.001
	Former smokers	34.6 (33.2-36.1)	16.7 (16.4-16.9)	2.488	<0.001	1.761	<0.001
	Alcohol consumption						
	Higher risk#	12.1 (11.2-13.1)	17.4 (17.1-17.6)	0.671	<0.001	0.876	0.002
	Usual	4.0 (3.5-4.6)	3.0 (2.9-3.1)	1.325	<0.001	0.920	0.233
	Binge drinking	7.2 (6.5-8.0)	9.4 (9.2-9.6)	0.758	<0.001	0.892	0.042
	Between meals	3.6 (3.2-4.1)	8.5 (8.3-8.7)	0.417	<0.001	0.938	0.368
	Physical inactivity	43.3 (41.7-44.8)	34.0 (33.7-34.3)	1.450	<0.001	1.218	<0.001
	Low fruit and vegetable consumption (≤2 portions/day)	52.5 (51.0-54.0)	48.9 (48.6-49.3)	1.146	<0.001	1.045	0.149

[a]Crude prevalence ratio.
[b]Adjusted prevalence ratio for: gender, age, educational level, perceived economic difficulties, nationality and geographic area of residence.
*Among cancers, respiratory diseases, diabetes, renal failure, liver diseases.
^People told by a doctor that they have diabetes.
§People told by a doctor that they have high blood pressure.
°People told by a doctor that they have high cholesterol.
#This category includes people who, in the previous 30 days, had one or more of the following alcohol consumption modalities: usually high (consuming on average >2 for men and >1 for women alcohol units per day), binge drinking (consuming ≥5 for men and ≥4 for women alcohol units in a unique occasion), exclusively or mostly between meals.

2016 over 609,000 deaths (one in eight overall) were due to coronary diseases, with a rate of deaths from coronary heart diseases standing at 1,190 deaths per million inhabitants. In every EU Member State, the age-standardised rate of men dying from coronary heart diseases was higher than for women, with 1,620 deaths per million men compared to 870 deaths per million women; for Italy, the rates were 148 deaths per 100,000 in men and 96 deaths per 100,000 in women. CVD is often considered a disease of older age, and in-

Table 3
Prevalence (95% CI) of protective behaviours and advice on healthy lifestyles by health professionals in people with and without cardiovascular diseases (CVDs) by Crude/Adjusted Prevalent Ratios (Poisson Regression Model). PASSI 2015-2018 (n = 132,598)

Variables		People w/CVDs (n=6,545)	People w/o CVDs (n=126,053)	People w/CVDs vs People w/o CVDs			
		% (95% CI)	% (95% CI)	Crude PR[a]	p-value	Adj. PR[b]	p-value
Protective behaviours	Current smokers attempting to quit smoking	45.0 (41.6-48.4)	32.9 (32.2-33.6)	1.628	p<0.001	1.754	p<0.001
	Overweight/obese people on diet	34.7 (32.9-36.6)	24.2 (23.7-24.7)	1.598	p<0.001	1.631	p<0.001
	Engaging in leisure-time physical activity	53.2 (51.6-54.7)	61.2 (60.8-61.5)	0.733	p<0.001	0.893	p<0.001
	Reaching out five a day	11.9 (11.0-12.8)	9.9 (9.7-10.1)	1.210	p<0.001	1.085	p=0.063
	Seasonal flu vaccine uptake (last campaign)*	30.4 (28.3-32.5)	8.4 (8.1-8.7)	4.154	p<0.001	2.566	p<0.001
Advice on healthy lifestyles by health professionals	Current smokers advised to quit smoking	77.7 (74.8-80.3)	50.1 (49.3-50.8)	3.284	p<0.001	2.551	p<0.001
	Overweight/obese people advised to lose weight	65.5 (63.5-67.4)	45.9 (45.3-46.5)	2.099	p<0.001	1.994	p<0.001
	Inactive people advised to engage in regular physical activity	41.4 (38.9-43.9)	26.1 (25.5-26.7)	1.892	p<0.001	1.711	p<0.001
	Higher risk alcohol consumers# advised to drink less	14.4 (11.5-17.9)	6.1 (5.6-6.5)	2.461	p<0.001	1.685	p<0.001
	People with high blood pressure§ advised to reduce using salt	88.4 (87.0-89.7)	85.4 (84.8-86.0)	1.256	p<0.001	1.173	p=0.011
	People with high cholesterol° advised to lose weight	57.6 (55.2-59.9)	43.2 (42.3-44.1)	1.666	p<0.001	1.539	p<0.001

[a]Crude prevalence ratio.
[b]Adjusted prevalence ratio for: gender, age, educational level, perceived economic difficulties, nationality and geographic area of residence.
*PASSI data refer to the time interval 2015-2018; interviewees report compliance with seasonal flu vaccination in the previous yearly campaign.
#This category includes people who, in the previous 30 days, had one or more of the following alcohol consumption modalities: usually high (consuming on average >2 for men and >1 for women alcohol units per day), binge drinking (consuming ≥5 for men and ≥4 for women alcohol units in a unique occasion), exclusively or mostly between meals.
§People told by a doctor that they have high blood pressure.
°People told by a doctor that they have high cholesterol.

deed its prevalence does rise with age. However, CVD is responsible for many premature deaths in men and women - around 192,000 people die before the age of 65 (22% of all deaths under 65 years) in the EU [2]. It is widely acknowledged that the risk of developing CVD is inversely related to SES in high income countries, and low SES is associated with worse health outcomes, even if access to medications is equitable. In deprived people, we found a higher CVD prevalence than in advantaged people, which is a consistent result [5]. Even if a non-Italian nationality appears to work as a protection factor, we verified a better cardiovascular health to foreign citizens, but we cannot exclude social vulnerability as barriers in accessing early diagnosis and effective treatments. Conversely, several studies actually show that migrant status could be a marker of social vulnerability only for some ethnic groups with high CVD incidence [16]. The absence of geographic gradient should be framed within the study of other aspects, such as the effect of mortality rate, effectiveness and accessibility to treatments; therefore, continued collection of epidemiological data stratified by socio-demographic characteristics is necessary.

Modifiable factors

The majority of individuals has at least one NCD before death and, given that CVD represents a major disease group [3], lifestyle-based preventive cardiology has a growing research footprint. PASSI findings on people who outlived a CVD event show quite alarming levels as per the four modifiable lifestyle risk factors associated to NCDs. Tobacco smoking is the leading cause of CVD morbidity and mortality, and the relation of this habit to the risk for developing up to 36 different subtypes of CVD, across fatal and non-fatal outcomes, is an actual research subject [17]. From the analysis drawn by PASSI, although the prevalence of current smokers among CVD-patients is lower than the one detected in CVD-free people and, conversely, the former is much keener to quit smoking, however this unhealthy behaviour is adopted by more than a fifth of CVD-diagnosed individuals. If the lower figure of at-risk alcohol consumption among CVD individuals is in line with the strong evidence of cardiovascular health benefiting from decreasing or moderate alcohol consumption [18], scarce consumption of fruit and vegetable (i.e., ≤2 servings per day) hardly occurs regardless of suffering from CVD.

On the contrary, it is worrisome the increased percentage of physically inactive people with CVD because, during the last decade, it has been confirmed how much sedentary behaviour, especially time spent sitting, represents a major CVD risk factor by 15%. Wijndaele *et al*. proved that one additional hour per day spent watching TV is associated with an augmented 6% CVD risk, rising to 8% for the solely coronary disease [19], and on a mid-age female sample, being seated at least 10 hours per day increases the CVD risk by 18% compared to a sedentariness ≤5 hours per day [20].

As expected, in the CVD group raised blood pressure, overweight and/or obesity, high blood cholesterol and diabetes exceed the values characterising CVD-free population. Increased risk of developing CVRF can potentially increase the CVD risk, and exposure to CVRFs during early adulthood is associated with adverse cardiovascular outcomes in later life [21]. Being affected by a CVD represents a health outcome, but also a risk itself: this is evident in the burden of disease reported by CVD patients who suffer from at least one NCD thrice more than CVD-free people as well as from a poor-quality state of living overall and depressive symptoms. The INTERHEART study identified the five major behavioural factors which, together, account for >80% of the incidence of myocardial infarction, and the risk cumulative effects directly relate to the increased number of premature deaths [22]. In addition to that, whereas lifestyle modification is a proven cost-effective mean of reducing premature deaths through both population-based and individual preventive interventions, people with established CVD do not achieve behavioural targets – particularly in smoking and obesity – even though interventions such as a family-based multidisciplinary programme that offers risk reduction interventions to high-risk patients [23].

Although the current Italian NPP 2020-2025 further recognises and acknowledges modifiable lifestyles as health priority issues [9], PASSI shows that preventive cardiology can be further improved in individuals who may be at risk and in those with established disease [6]. Medical advice on healthy lifestyles that is a clearly effective action is nevertheless practiced too little and mainly applied to reduce a certain risk rather than develop specific preventive interventions. A population-based study on individuals without CVD (primary prevention sample) *vs* CVD patients found that a physician-led lifestyle advice is less frequent in the primary prevention sample [24]. The combined presence of hypertension and hypercholesterolemia increases considerably the risk for cardiovascular complications: consequently, non-pharmacological treatment includes weight reduction, appropriate dietary measures such as alcohol and salt restriction, cessation of smoking and increasing physical activity [25]. PASSI indicated low values of health professionals' advice overall, but some issues such as alcohol drinking seem even more neglected if compared to others, as salt use, typically envisaged as relating to cardiovascular health.

Lastly, CVD represents not only a disease condition but also a further aggravating risk in case of infectious diseases: some evidence is available on that about seasonal influenza and already consistently in case of COVID-19 infection, as well. CVDs are in fact associated with significantly worse outcomes in COVID-19 patients [26]. Moreover, the burden of disasters seems to have indirect long-term effects on cardiometabolic health [27] and even COVID-19 pandemic could have such long-term repercussions of cardiometabolic parameters that, in turn, expose to greater risk of CVD. Against this new backdrop, primary prevention is essential to reduce the incidence of CVD overall as well as, in patients with CVD, the control of clinical parameters, through appropriate therapy on the one hand and by monitoring and contrasting unhealthy lifestyle on the other.

Strengths and limitations

The main strength of the study is about the representative sample of the general population in age 18-69 years living in Italy. It means also that data analysis including specific groups of randomised resident population are selection bias free. The PASSI information is currently used both at local such as regional level to evaluate specific preventive interventions goals established by the NPP (e.g., reducing sedentary habits, numbers of smokers and salt consumption). Furthermore, due to its large sample size and proven reliability and validity, through analysis on specific subpopulations (such as the present study on CVD prevalence and socio-demographic characteristics) PASSI identifies groups which might be most at risk and need for interventions, providing insight for high-priority issues and relevant gaps in public health. Despite these assets, it has limitations as follow.

Self-reporting. As per any interview-based health survey, PASSI data (except for the main demographic characteristics: gender, age, residence) are self-reported; the information released can be somehow biased, generating underestimated or overestimated percentages. Socially undesirable behaviours are prone to underestimation, anyway self-reported data on heart diseases show adequate consistency and sensitivity, and are extremely important in public health [28]. Being ever diagnosed or confirmed any CVD refers to a relevant and rare behaviour and is not affected by misclassification or recall bias [29, 30]. Nevertheless, no information is available on age at diagnosis.

Unit nonresponse. Because nonrespondents often differ from interviewees for characteristics under consideration, high nonresponse rates can lead to inaccurate measures of the indicators. There is no general consensus about which value is acceptable, because the alteration of the estimates depends on many factors, such as survey design, study population, reasons for nonresponse, explored variables [31]. However, the PASSI sample is extracted from the LHU lists of residents and this procedure translates to a much wider coverage than similar surveys (e.g., the American BRFSS) so that, as indicated in the "Methods", the final response rate is >80% and, then, goodly assessed [10].

CONCLUSIONS

This study highlights indeed the potential gain in cardiovascular health profiling individuals as for pres-

ence or absence of CVD as well as for modifiable risk factors.

Our study opens up to further in-depth analyses to explore the direct and indirect impact of the SARS-CoV-2-related crisis on people's health with a particular focus on major cardiovascular risk factors.

Strengthening cardiovascular prevention programs and communication campaigns clearly result to be needed in order to achieve a valuable improvement of the advice delivered by health professionals that, even before the pandemic crisis, was at very low levels. Evidence shows worldwide to what extent governments and individuals are in the position for reducing the health and socioeconomic burden caused by CVD risk. Monitoring health-related behaviours is definitely crucial to plan, implement and evaluate effective preventive policies and interventions.

Authors' contributions

All Authors contributed to the conception or design of the work and to the acquisition, analysis, or interpretation of data for the work. In detail, VS conceptualized and designed the study, and carried out the first analysis. VM further refined the analysis. VS drafted the first version of the manuscript. BC, VP, RG and MM critically revised the manuscript. After sharing intermediate versions of the manuscript, all the Authors gave their final approval and agree to be accountable for all aspects of work ensuring its integrity and accuracy.

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Conflict of interest statement

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ORIGINAL ARTICLES AND REVIEWS

Adapting the World Health Organization rapid Assistive Technology Assessment (rATA) to the Italian context: implementation of a TRAPD-based approach

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Abstract

Background. Measuring access to assistive technology (AT) has become a global priority. Recently, the World Health Organization (WHO) has developed the rapid assistive technology assessment (rATA), a population-based household survey that measures the use, need, unmet need, and barriers to accessing AT.

Objective. The aim of this paper is to report on the translation and adaptation process undertaken to implement the rATA survey in the Italian context.

Method. The Translate, Review, Adjudicate, Pretest, and Document (TRAPD) approach was used to translate and adapt the rATA from English to Italian. Eleven independent reviewers and 23 AT users were involved to validate the Italian translation of the rATA and pilot the survey, respectively.

Results. The feedback provided by the first users of the rATA indicate that the data collected are reliable and well reflect the state of AT provision in Italy.

Conclusion. This study confirmed the applicability of the rATA survey to the Italian context. The Italian version of the rATA can be used to support the government, the health system as well as the civil society to monitor the current state of AT access (and abandonment) in the country.

Key words

- access to assistive technology
- population-based survey
- human rights
- rATA

INTRODUCTION

Assistive technology (AT), from spectacles to social robots, enables people to live healthy, productive, independent, and dignified lives by facilitating their participation in education, the labor market and civic life [1]. Given the benefits brought about by AT for the individual and society, access to AT has been recognized as a fundamental human right by the Convention on the Rights of Persons with Disabilities (CRPD). Yet only 10% of the people in need of an AT have access to it [2].

To address the large and growing unmet need for AT and achieve universal coverage, in 2014 the World Health Organization (WHO) has established the Global Cooperation on Assistive Technology (GATE [3, 4]). The primary aim of the GATE initiative is to improve global access to appropriate and affordable AT for people with varying disabilities, diseases, and age-related conditions, through a series of actions involving five interlinked intervention areas: People, Policy, Products, Personnel, and Provision (for further details see [5-9]).

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With regard to the activities related to the Policy area, GATE aims at understanding the need and unmet need for AT through a systematic measurement of AT access in various populations [4]. To date, no data have been systematically collected on a global scale about access to AT [10]. The reason for such lack of data may include the high variability of AT provision practices across systems and countries [11], which in turn may have prevented the development of tools that could be used to collect comparable information about AT access in different contexts.

To overcome this challenge and allow direct comparisons between AT systems across countries and populations, GATE has developed the rapid Assistive Technology Assessment (rATA) questionnaire [12]. According to the developers [13], the rATA is a stand-alone tool for efficiently and rapidly assessing the need, use, supply and impact of AT in a population through which AT stakeholders can: a) obtain data and evidence on access to AT; b) advocate and raise awareness of governments as well as of civil society about the importance of AT; c) advance research and development in AT; and d) support in the design, planning or prioritizing AT programmes, or interventions that should be made at global and country levels [13].

The rATA has been originally developed in English and later translated in Spanish, French, Chinese, Portuguese, Russian, and Arabic [14]. For this tool to be implemented globally, however, further translations are needed, considering cultural (e.g., language) as well as AT system specificities of the countries in which the rATA could be implemented.

The aim of the present paper is to report on the translation and adaptation process undertaken to implement the survey in the Italian context. According to a recent scoping review, little is known on the needs, access, and coverage of AT in the member states of the European region [15]. Italy has a population of about 60 million inhabitants, and it is the third-largest national economy in the European Union. The steady increase in the number and proportion of older persons in Italy combined with direct and indirect effects of the current pandemic situation on the health and social care systems, are expected to widen the challenges faced by people in need of an AT [16]. Strengthening access to AT for people with disabilities and those who are frail can be thus considered a national priority to prevent social inequalities and improve the quality of life of the Italian population.

To this end, a consortium of Italian governmental and non-governmental institutions has recently partnered with WHO to conduct a nation-wide survey using the rATA. This study can be considered relevant as it provides governmental authorities (e.g., Ministry of Health) as well as non-governmental organizations (e.g., AT users associations) with a specific tool to collect baseline data and continuously monitor AT access at national as well as regional level. It also provides researchers and AT professionals in Europe and other countries with a detailed account of the methodology followed to adapt the rATA in a specific context. With reference to this latter point, a further matter of interest for the reader of the journal *Annali dell'Istituto Superiore di Sanità* is the implementation in the current study of a rigorous approach to translation and adaptation of the rATA questionnaire. This approach, named Translate, Review, Adjudicate, Pretest, and Document (TRAPD) is increasingly considered a viable strategy when the focus of translation is on cultural equivalence rather than on literal equivalence [17]. The TRAPD approach has several advantages over other existing methods (e.g., forward translation, back-translation), such as ease of adaptation to the needs and resources available to researchers [18]. In addition, this approach can be replicated in future studies to further refine the current version of the Italian rATA based on feedback from stakeholders, including specific populations of respondents (e.g., people with chronic health conditions or disabilities, frail adults, AT users and their caregivers), professionals and other stakeholders related to the AT provision process (e.g., AT experts, health professionals, policymakers), and the research community at large.

METHOD

The present study took place between February and March 2021. It is part of a larger project conducted by a consortium of partners coordinated by AIAS, a not-for-profit association with more than 50 years of experience in promoting full inclusion of people with disabilities in every life domain through AT. Other partners included: a) the Italian Institute of Health (Istituto Superiore di Sanità; ISS), the main center for research, control and technical-scientific advice on public health in Italy; b) CENSIS (Centro Studi Investimenti Sociali), a foundation with more than 50 years of experience in research, assistance and consultancy activities performed in the main areas of social, socio-economic and socio-political relevance, from education and employment to welfare, healthcare, economic and local development; and c) the Italian network of independent AT centres (GLIC, Gruppo di Lavoro Interregionale Centri ausili informatici e elettronici), a network of 25 specialized AT services in Italy without any commercial interest.

Instrument

The rATA is an interviewer-administered, population-based survey tool, divided into seven sections designed to gather information on: 1) self-reported use of need and unmet need for assistive products; 2) sources of, payers for and barriers to accessing assistive products and related services; 3) satisfaction with assistive products and related services; 4) self-reported functional difficulties; and 5) basic demographic information, such as age and gender [12]. It takes into account 50 prioritized assistive products [19] plus any other relevant products used or needed by respondents. Details on the structure of the rATA are provided in the manual [13].

Overview of the translation and adaptation approach

The aim and description of each stage of the TRAPD process followed in this study is briefly summarized

Table 1
Overview of the translation and adaptation process

Step	Definition	Activities undertaken
1. Translate	Develop a first survey translation using an expert approach	Two expert translators proficient in English and experts in AT collaborated to produce a preliminary translated version
2. Review	Expert review of the translation to identify problems and additional translation options	A committee of 11 AT experts independently checked the translated version against the original version. Their opinions were collected using an online survey
3. Adjudication	Make decision on the final version	Feedback from the AT experts were integrated into a second version of the translated rATA. A consensus approach has been used to identify the best possible solution to any issue encountered with the translation of the scale. The integration of the feedback was performed by the two original translators (see step 1)
4. Pilot	Conduct a field test of the survey translation and use observational methods to identify potential problems with the translated version	A small sample of AT users (n=25) has been interviewed by 8 AT experts to identify difficulties in understanding and answering the questions, and to identify translation issues that impede comprehensibility. Feedback from users and interviewers has been collected to refine the interview
5. Documentation	Reporting of all the outcomes produced in each of the preceding step	A detailed account of the outcomes of phases 1-4 have been sent to WHO contact person

in *Table 1*, along with a summary of the activities undertaken. Following this approach, TRAPD provided opportunities at each step for evaluating and revising translated materials [20]. The revisions that derive from a given step are used as inputs for the following step, with a goal of continuous improvement until a final version of the tool is produced.

Step 1: Translate

In this step, the English version of the rATA questionnaire was first translated independently by two experts who have between 10-20 years of experience in AT provision and proficiency in both languages. The two versions produced were matched and differences discussed until agreement was achieved to create a single preliminary version of the Italian rATA. In case of doubts when translating the English version, the two translators occasionally consulted also: a) the WHO contact person coordinating the global rATA survey implementation; and b) the Spanish and the French versions of the rATA questionnaires to achieve a more reliable translation.

Step 2: Review

In this step, 11 independent reviewers compared the original (English) version of the rATA scale with the preliminary Italian version. The group included nine AT experts from the Italian Institute of Health, three professionals serving as AT service providers, and three AT users. After familiarizing with the original and the translated versions of the questionnaire, each reviewer was asked to provide feedback on the Italian translation by answering two questions: 1) [Fidelity] "How would you rate the fidelity of the translation with the original version?"; 2) [Wording] "To what extent do you think the wording of the Italian translation is adequate to the Italian context?". Both questions used a 10-point Likert scale (1 = not at all; 10 = totally). After answering the two questions, the reviewers were given the opportunity to provide written suggestions for further refining the translation. Feedback was provided online through the Qualtrics platform.

Step 3. Adjudication

The feedback collected in the previous step were collected and summarized by the two original translators. Suggested changes were discussed between the first and second authors and implemented in a second version of the Italian rATA. The newer rATA version has been later presented to representatives of the wider consortium and all revisions proposed were discussed. A final version of the Italian rATA has been finally produced once consensus among all the members was achieved.

Step 4. Pilot

The pilot focused on the assessment of the interviewer's experience with the questionnaire to ensure its applicability to the Italian context. To this end, eight interviewers were involved in this step who were blind to the outcomes of the preceding translation steps (i.e., Step 1-3). The eight interviewers were all AT professionals working in two specialized AT centres located in the central-northern part of Italy with an experience in AT provision ranging from 5 to 20 years. Each interviewer was introduced to the rATA in a 30-minute training session (via either in-person meeting or video-call) and asked to familiarize with the scale before administering it to AT users selected randomly among a group of volunteers. Comparisons between interviewers (i.e., inter-rater agreement) were not planned due to time and resource constraints. All the feedback from interviewee about the rATA were collected by the interviewer. To this end, each interviewer was requested to rate the rATA against four indicators (i.e., applicability, clarity, ease of use, and reliability). Three further open questions were also asked: a) "What are the main critical aspects of the rATA?"; b) "Did the respondents show any negative or positive reaction when answering the rATA?"; c) "Do you have any suggestions to facilitate the administration of the rATA?".

Step 5. Documentation

The results achieved in each step were annotated and a summary report have been sent to the WHO contact point before implementing the rATA survey.

RESULTS

The outcomes of the TRAPD process are briefly reported in the two following sections. *Translation and adaptation* summarizes outcomes from Steps 1-3, while *Pilot* provides a summary of outcomes from the pilot test (Step 4).

Translation and adaptation

Table 2 (available online as Supplementary Material) provides an overview of the main language-related changes in the Italian version compared to the original rATA. The 11 reviewers provided very high ratings for both Fidelity (M = 9.22; SD =.92) and Wording (M = 9; SD = 1.25). Overall, suggested changes to wording can be considered of minor entity and were mainly aimed at clarifying the meaning of some general terms used in the original version. For instance, in place of the original term *assistive product*, in the Italian translation it has been decided to adopt the most commonly used Italian term *ausilio* instead of its literal translation (i.e., *prodotto assistivo*).

Notably, however, the rATA has been adapted to the Italian context by adding a section named "Abandonment". It includes one filter question namely "Have you been given an assistive product (*ausilio*) in the past three years that you have never used? (possible answers: Yes; No)". If the answer is "yes", then the respondent is asked to specify the type of assistive product and the reason for its abandonment or non-use.

Pilot

In total, the interviewers involved 23 AT users. The majority presented with motor disability (n=12), followed by age-related difficulties (n=5), multiple disabilities (n=3), cognitive impairment (n=2), and sensor impairment (n=1). As shown in *Table 3* (available online as Supplementary Material), the rATA was considered overall applicable, clear, and reliable in collecting information related to AT needs, use and provision. In contrast, its use was not considered straightforward as highlighted by the relatively low score in the Ease-of-use indicator.

With reference to answers to the open questions, few comments were left by interviewers (see *Table 3* online). Importantly, no negative reactions from respondents were reported. Critical aspects include the fact that the survey may be not fully capable of capturing all the complexities associated to AT delivery in Italy (i.e., multiple funding sources for the same assistive product may be omitted by the respondent) and that the respondents may have difficulties naming the solution in use or estimating the distance covered to buy/obtain it (see *Table 3* online). Suggestions to facilitate rATA administration concerned exclusively in providing specific training to interviewers to cope with its complexity and length.

DISCUSSION

The present study was aimed at reporting on the Italian translation and adaptation process of the rATA, a questionnaire that is currently being used by WHO to assess global access to AT. Our results indicate that the data collected through the rATA are reliable and well reflect the general state of AT provision in Italy.

With reference to the applicability of the questionnaire to the Italian context, two considerations may be put forward. First, our preliminary results indicate that the Italian version of the rATA is well comprehensible to a wide range of AT users. In contrast, however, it may not be perceived easy to administer by interviewers due to its complexity and length. This aspect should be considered when implementing the survey to a wider population of respondents as it can increase between and within-interviewer variance due to heightened workload, with negative consequences for the quality and accuracy of the data collected [21]. To minimize errors in data collection, we recommend adopting systematic quality assurance procedures such as standardized training and practicing sessions for interviewers (enumerators) before survey implementation as well as continuous monitoring of interviews and data collection when the survey is taking place.

Second, although the rATA has been primarily designed to measure access to AT [13], we argue that it may also represent a unique opportunity to collect comparable data across countries on rates of AT abandonment. Abandonment of AT products, or their "non-use" (see [22] for further insights on this term) can be indeed considered a global issue [11]. Evidence reports abandonment rates up to 78%, depending on the AT considered [23], with most studies converging on AT abandonment rate of about 30% one year after delivery [24]. Although determinants of AT abandonment may vary according to a variety of factors, including age, severity of disability and type and number of AT needed (e.g., [25, 26]), its negative consequences for the individual (and society) are well-known. Accordingly, in the translated rATA we added a new section to investigate the abandonment of AT provided in Italy. In our view, estimating both access to AT and its abandonment may be instrumental in improving the quality of any AT system by facilitating a) the understanding of the factors associated to AT non-use, and b) the development of evidence-based strategies to mitigate discontinuation of AT products after delivery.

Based on current results, two suggestions for improving rATA questionnaire can be further made. First, to collect information on individual functioning, the rATA uses an adapted version of the Washington Group Short Set of Questions on disability (WG-SS) [27]. The WG-SS is an internationally recognized disability question set comprising six questions on respondents' difficulties in conducting everyday activities, including seeing, hearing, mobility, communication, remembering, and self-care [27]. The strength of the WG-SS is that it has been conceived in light of the biopsychosocial model of disability, focusing on the presence and extent of functional difficulties rather than on body structure or health conditions. As such, it is extremely useful for cross-national comparisons on disability data and is becoming the gold standard for censuses aimed at gathering population-level estimate of the number and proportion of persons

with functional difficulties that may need an AT. More recently, the set of six questions has been expanded to provide a more accurate assessment of children between 2 and 17 years of age [28]. To obtain a clearer picture of the state of AT access in a specific country, it may be desirable that future versions of the rATA could be designed to account for differences in functional limitations of different age groups of AT users by employing age-appropriate WG-SS sets of questions.

Second, user involvement is an essential precondition in any aspect of AT research [29]. The original version of the rATA has been developed over a series of consultations with stakeholders to ensure it reflects the views of the users as well as all the actors along the AT provision process [13]. As such, it can be argued that, in its original form, this tool already adopts a user-centred perspective. The Italian translation of the rATA followed as much as possible this approach, by involving stakeholders in almost any step of the TRAPD process. In this view, the relatively small sample of AT users involved in the pilot described in this study should be considered a complementary effort to further center the tool around the perspectives of the local (Italian) users. Moreover, it can be anticipated that the Italian rATA-based census will shed light on the appropriateness of the Italian translation of the rATA in capturing the key aspects of the Italian AT delivery system.

This study further documents the experience of using an adapted version of the TRAPD approach to survey translation. In keeping with available literature [17, 18, 20], current results suggest that the TRAPD approach can be effective in ensuring: a) the quality of the translation when few resources are available (e.g., time); and b) the transparency of the whole translation process [18]. Further research is however needed to compare the efficacy of the TRAPD approach over other translation methods.

CONCLUSIONS

This study confirmed the applicability of the rATA survey to the Italian context. The Italian version of the rATA can be used to support the government, the health system as well as the civil society to monitor for the first time the current state of AT access (and abandonment) in the country. The results of the survey may further inform policies at regional and national levels to improve access to AT and, in turn, the life conditions of people with disability/frailty, people with chronic health conditions, and older adults.

Conflict of interest statement

The Authors declare that there are no conflicts of interest.

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Exploring global needs of migrants with disability within a community-based inclusive development perspective

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Abstract

Introduction. Limited evidence exists on migrants with disability. A comprehensive assessment is mandatory required to organize specific services within the community and reception centers. The present study explores needs of refugees and asylum seeker within a community-based inclusive development framework.

Methods. To interview migrants, in this study we used the Community-Based Rehabilitation Indicators (CBR-Is) developed by the World Health Organization.

Results. The sample consisted of 41 people with disability and 59 without disability. Sample was homogeneous for gender and age. Our findings reveal how migrants with disability experienced poor outcomes in each domain of CBR-Is, namely health, education, livelihood, social end empowerment.

Conclusion. Differences between migrants with and without disabilities have some distinctive features. However, both groups are influenced by the social determinants of health: in addition to health issues, challenges in social life, livelihood and empowerment also clearly emerge. Different stakeholders are invited to promote inclusive communities, facilitating access to social and health services.

Key words

- migrants
- refugees
- disability
- community-based rehabilitation
- community-based inclusive development
- rehabilitation

INTRODUCTION

Disability is part of the human condition. The UN Convention on the Rights of Persons with Disabilities (UNCRPD) recognizes disability as "an evolving concept" [1]. It is therefore not an attribute of the person, but rather the result of the interaction between biological, psychosocial and environmental contingencies.

The World Health Organization (WHO) estimates that over one billion people – about 15% of the world's population – live with some form of disability [2]. Recent studies have shown that people with disabilities experience worse health outcomes than people without disabilities. Moreover, people with disabilities experience greater difficulty in accessing higher levels of education as well as the labor market. In addition, as far as the health component is concerned, people with disabilities quite often do not receive the health services they need and about half of people with disabilities cannot afford health care [3]. Among the barriers that most affect access to services are prohibitive costs, limited availability of services – especially in rural and suburban areas – and architectural and environmental barriers. Lastly, several international bodies note a lack of disability mainstreaming policies, as well as a lack of funding and specific data [2].

To date, the problems encountered are more evident when compared to migration. Being a migrant with a disability – due to economic, political, or environmental reasons – determines an even greater level of vulnerability both in structural and adaptive terms. Moreover, already in 2016, the EU Agency for Fundamental Rights stated a general lack of formal procedures to identify migrants with disabilities, with a negative impact on the possibility of support and assistance. This lack of strategies for territorial care imposes a collective reflection on how to succeed in intercepting the needs and vulnerabilities of migrants with disabilities [4].

Globally, there are 271.6 million migrants [5]. As mentioned above, considering that 15% of the world's population lives with a condition of disability, it is possible to consider with some approximation that, out of 271 million migrants, 40.65 million are people with

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disabilities. Of the 30 million people who migrate each year, 4.5 million have that condition and that, out of 22 million refugees, 3.3 million are refugees with disabilities [6]. In addition to purely numerical data, the dynamics that produce migration are fundamental, as are the migratory experiences of individuals, as well as the heterogeneity of the individual's adaptive capacities within the country of arrival. At the European level, the latest available data, updated as of May 2020, report that 2.4 million people from other non-EU countries entered the borders of the European Union (EU). 21.8 million people (4.9%) of the 446.8 million EU citizens as of January 2019 were non-EU citizens [7]. This percentage inevitably includes not only people who have just entered EU borders, but also those who have been residing in an EU country for some time. Consequently, when considering the disability of migrants, we should also focus on a percentage of foreigners who now live within the European communities. In this macro-category, for example, consideration should be given to persons who acquire a disability as a result of accidents at work, or all those persons who, as they age, experience the same health issues as all the elderly, encountering lack of self-sufficiency or the development of co-morbidities [8].

In Italy, the latest available data report the presence of 6.3 million migrants [5]. In spite of recent political debates, the percentage of migrants entering our country has undergone a sharp decline in recent years. The reasons behind this decrease vary, however this fact is likely attributable to the agreements between Europe, Turkey and Libya. Although in different ways, these agreements aim to discourage the departure towards the EU borders. Nevertheless, the documentation supporting the inadequacy of these policies is starting to be preponderant, as well as reports on the inhuman conditions in which migrants are forced in detention camps. In addition, some scholars argue that the reception process in Italy and Greece, as well as the lengthy detention of asylum seekers in other host states, does not alleviate health problems, but rather contributes to the exacerbation of illness and trauma [9].

Limited evidence exists regarding the prevalence of disability among refugees and asylum seekers, with an estimated rate of disability between 3% and 10% [10]. Moreover, it is estimated that 1 in 6 migrants experience some form of physical health problems [11], while the proportion increases for mental health to 2/3 of the population [12]. As seen above, in most immigration centers, there is the challenge of successfully "recognizing" all those forms of disability that are less evident and, consequently, proposing specific services on the community or targeted activities within the centers for asylum seeker and refugees. It is also worth reflecting on the condition of "institutionalized" migrants with disability. In some circumstances, these migrants see the exacerbation of certain problems that have remained silent until then. This is the case of victims of torture, of people with mental disorders or cognitive disabilities, who experience the onset of psychotic disorders [13].

If the well-being of these people is affected by this dualism – a migrant and person with disabilities within "protected structures" – their quality of life is challenged once they leave the international protection system. Consequently, there are many cases in which these people are unable to request housing assistance or they experience barriers to reaching a satisfactory level of livelihood in society. The result is an increase in social marginality, discrimination, and significant deterioration of their health [14]. A comprehensive assessment of individual needs and living priorities should be undertaken in the field [15]. Therefore, the objective of the present investigation is to evaluate the needs of migrants with disability within a community-based inclusive perspective, with a particular focus on asylum seekers and refugees.

RESEARCH PROCESS

Study overview

The research group was formed by professionals affiliated with Sapienza University of Rome and Rehabilitation & Outcome Measures Assessment Association, a non-profit organization with a great deal of experience in outcome measures and disability studies. In the last few years, the research group was involved in the validation of different projects, also with particular interest focused on disability and global health education [16-19]. The research was carried out from November 2018 to March 2019, involving different stakeholders in Italy. However, due to the COVID-19 pandemic, data collection was interrupted in March 2019.

Study setting

In Italy, the reception system for asylum seekers and refugees has changed many times. Particularly in the years 2018-2020, several reforms have been made that have had an important impact on procedures and requirements for access to the international protection system. In order to better understand the Italian landscape, a brief overview of the Italian legislative context is reported below [20].

In 2001 the ANCI - Associazione Italiana Comuni Italiani (the National Association of Italian Municipalities), UNHCR (the UN Refugee Agency) and the Italian Ministry of the Interior signed a memorandum of understanding to set up the National Asylum Programme (PNA). The PNA was the first public system for the reception of asylum seekers and refugees, throughout the Italian territory and instituted the sharing of responsibilities between the Ministry of the Interior and local authorities.

Then, in 2002, the Law no. 189 of 30 July institutionalized the PNA by setting up the SPRAR – Sistema Protezione Richiedenti Asilo e Rifugiati (Protection System for Asylum Seekers and Refugees). Subsequently, the Ministry of the Interior established a central co-ordination office (called Servizio Centrale), and appointed ANCI to manage it.

In 2018, SPRAR was renamed SIPROIMI – Sistema di protezione per titolari di protezione internazionale e per minori stranieri non accompagnati (Protection System for Beneficiaries of International Protection and for Unaccompanied Foreign Minors) (Decree-Law no. 113 of 4 October 2018, enacted as Law no. 132 of 1

December 2018). The new legislation sets out that access to SIPROIMI's integrated reception services can also be provided to holders of a residence permit for special reasons: as victims of violence, trafficking, domestic violence, labor exploitation or calamities, or for poor health, or for acts of particular civic value.

In 2020, SIPROIMI was renamed SAI – Sistema di Accoglienza e Integrazione (Reception and Integration System) (Decree-Law no.130 of 21 October 2020, enacted as Law no.173 of 18 December 2020). The new legislation sets out that access to SAI's integrated reception services can be provided to refugees, asylum seekers, unaccompanied foreign minors, foreigners entrusted to the social services on reaching majority age. Moreover, SAI can also accommodate victims of disasters, migrants whose special civil value is recognized, holders of a residence permit for medical treatment, holders of a special- protection residence permit (recipients of social protection, victims of domestic violence, victims of labor exploitation). The primary objective of SAI is to provide support for each individual in the reception system, through an individual program designed to enable that person to regain a sense of independence, and thus enjoy effective involvement in life in Italy, in terms of employment, housing and access to local services and social interaction as well as scholastic integration for minors.

Data collection measure

In order to obtain data on a Community-Based Inclusive Development perspective, the research group decided to use the Community-Based Rehabilitation Indicators (CBR-Is) developed by the WHO [21]. The CBR-IS are available in different languages, such as English, French, Spanish, Arabic. An Italian version is also available, thanks to a previous translation and cross-cultural adaptation process of the same research group [22]. The survey consists of an introductory part containing personal details and socio-demographic information. There are 13 base CBR indicators: health (2); education (6); livelihood (3); social (1); and empowerment (1). Base CBR indicators are broad enough to capture the difference CBR makes in the lives of people with disability. For comparability among settings, countries, and over time, WHO recommends these 13 base CBR indicators be consistently included in all monitoring and evaluation procedures. There are 27 supplementary CBR indicators that provide more specific coverage of the elements of the CBR components. From these users may select those that match the specific goals and strategies. Considering the objective of the study, the working group included all the questions related to the five components of the CBR matrix: health, social, education, livelihood and empowerment, excluding those questions related to developmental age. For more information on CBR Indicators, please see information on WHO CBR-Is Manual [23].

Sampling, procedures and data analysis

The sample population was selected in order to respect the following criteria: women and men, healthy or disabled people, age 18 or more, status as a refugee or asylum seeker in Italy. The only exclusion criterion was the refusal to participate in the study. To be considered person with disability, the research group asked if the person considered him/her self as person who live with a condition of disability or if the person had a disability certificate. To recruit participants, the research team engaged different stakeholders working on the topic of migration. First an email was sent out explaining the project, its objectives and expected results, then the staff involved and data protection system. Subsequently, the willingness to participate was requested, asking for the availability of working group members within the SIPROIMI centers. Considering that these centers are directly appointed by the Servizio Centrale (please see above the Italian legislation within the Study Setting sub-section), an official communication was sent to request permission to proceed with the interviews. Once the response was received from the Servizio Centrale, and permission was obtained from the organizations managing the SIPROIMI centers, the working group began interviewing asylum seekers and refugees in the centers.

However, before starting, the research group participated in an internal training course in order to level out confidence with the CBR-Is, and to ensure consistency on administration and scoring. The first investigator (MT) led the training: learning modules, organized into theoretical and practical activities, were based on the information available on the WHO website and within the CBR-Is manual. To measure how the training was effective, at the end of the training session, the research group participated in a practical test and discussed the case study together.

In order to obtain preliminary evidence on how the IT-CBR-Is can properly capture the differences between migrants with and without disability, an independent sample t-test was applied for those questions in which it was possible to transform nominal variables into numerical, as provided in the original manual produced by WHO. Therefore, some questions of a descriptive nature were excluded (e.g., H06 and H09 "Which reason(s) explain(s) why you did not get that health/rehabilitation service?") or other questions related to the use of assistive technologies. Significance was set for a $p<0.05$ with 95% confidence intervals. All data were collected on android tablets using a mobile application and transferred daily to a secure cloud-based server. All analyses were then performed by using Statistical Package for the Social Science (SPSS) version 20.0.

Risks of bias

As already mentioned, CBR-Is are available in several languages. However, in order to minimize comprehension problems – even where respondents did not have a very good command of the available languages – the research team made use of language mediators when necessary. These, prior to the interview, attended a one-day training and were able to view the CBR indicators manual.

Due to the COVID-19 pandemic, and in order to have comparable and reliable data, the research group decided to stop collecting data during the national lock-

down. Continuing the interviews during this period could have affected the validity of the results because the possibilities to socialize, work, etc. were rather limited, paired with the fact that access to specific social and health services could be reduced.

RESULTS

The research project was carried out in cooperation with a few reception centers in the Lazio and Apulia regions. 103 people met the inclusion criteria and were eligible to participate in the study. However, 3 people decided not to participate. Consequently, the CBR-Is were administered to 100 individuals: 41 people with disability (mean age 35.75, SD 11.72) and 59 without disability (mean age 29.08, SD 7.07). No significant differences between groups were found for age and gender. The majority of women (73.68%) lived with a condition of disability, while among men only 20.96% defined themselves as persons with disabilities. The majority of people with disability (65.85%) came from the Near and Middle East (Libya, Syria, Iraq, Afghanistan), while among people without disability the majority (69.50%) were from North and West Africa (Tunisia, Morocco, Nigeria, Ghana, Gambia). *Table 1* summarized sample characteristics.

Significant differences between migrants with and without disability were found: one for education, two for social and two for empowerment component. However, both groups showed poor outcomes in each component of the CBR matrix. *Table* 2 reports mean scores, differences between two groups and reference values considered as good, for each question.

DISCUSSION

This investigation reports one of the first attempts to analyze global health needs for migrants with disability in Italy. A person forced to migrate, and who is also living with a disability, represents a double vulnerability and requires a multifaced approach in order to propose adequate support in different aspects and domains of life [24]. The sample consisted of both people with and without disabilities and it allowed to analyze differences between the two groups. The subsample of persons with disabilities was predominantly female; this can be explained for two main reasons: firstly, because refugee women have a higher risk of experiencing violence [25], and secondly because some of the centers offered services specifically for women victims of violence.

According to the Community-Based Inclusive Development framework, for migrants with and without disability, our findings reveal poor outcomes in each domain of CBR-Is, namely Health, Education, Livelihood, Social end Empowerment. Among these, migrants with disability have a lower educational level than migrants without disability ($p=0.03$), and they cannot make decisions regarding personal assistance ($p<0.01$) and their relationships ($p<0.05$). Regarding Empowerment component as well, migrants with disability feel they cannot make big decision in their life (for example who to live with, where to live or how to spend money) ($p<0.01$) and they are discouraged on the effectiveness of policies for the rights of persons with disability ($p<0.05$). Asylum seekers and refugees experience prejudice on an institutional level as a result of the asylum system and interpersonally from host communities. Moreover, they often report stigma and discrimination [26]. Results showing how they experience barriers to personal assistance and relationships are in line with the World Report on Disability [2].

Interesting topics emerged from a qualitative analysis of outcome scoring. Migrants – regardless of disability condition – are met with challenges in all domains of the Community-Based Inclusive Development framework. For example, regarding the "Health component" migrants are not satisfied with the level of respect with which they are treated. Moreover, during their last visit to healthcare providers, they did not feel to be involved in making decisions for their treatment. A recent study [27] reveals how healthcare providers face important challenges in providing care for refugees and migrants and risk not being able to ensure equal access to quality care for these vulnerable groups. Lack of funds, as well as a shortage of trained and stable human resources, paired with organizational malfunctioning and poor coordination among the different players, are all mentioned as factors hindering the provision of healthcare for migrants and refugees [28]. Migrants may also face obstacles arising from lack of cultural awareness by those providing care or due to language barriers, even though there is now considerable experience on how to overcome these challenges [29].

Table 1
Socio-demographic characteristics of refugees and asylum seekers (sample n 100)

	People without disability	People with disability	T-Student
Age mean (SD)	**29.08 (7.07)**	**35.75 (11.72)**	**0.341**
Gender			
Female	10	28	
Male	49	13	
Total	59	41	0.778
Country of origin	N (%)	N (%)	
Horn Africa	9 (15.26)	0 (0.00)	
Nord Africa	26 (44.07)	11 (26.83)	
West Africa	15 (25.43)	3 (7.32)	
Near East	8 (13.55)	14 (34.14)	
Middle East	1 (1.69)	13 (31.71)	

Table 2
Differences in CBR-Is score between migrant people with and without disability

Questions	Without disability N Mean (SD)	With disability N Mean (SD)	P	Positive outcomes
H01. In general, how would you rate your health today?	2.02 (1.14)	2.30 (0.51)	0.320	<2
H02. On your last visit to a health-care provider, to what extent were you satisfied with the level of respect you were treated with?	3.71 (1.11)°°	3.60 (1.26)°°	0.787	>4
E01. What is the highest level of education you have achieved, or are working to achieve?	3.85 (1.95)	2.40 (1.57)°°	0.035*	>4*
L02. Do you have enough money to meet your needs?	1.75 (0.81)°°	1.80 (0.78)°°	0.861	>4
S01. Do you feel that other people respect you? For example, do you feel that others value you as a person and listen to what you have to say?	3.30 (1.10)	3.80 (1.03)	0.209	>4
M01. Do you get to make the big decisions in your life? For example, deciding who to live with, where to live, or how to spend your money?	3.64 (1.32)	2.20 (1.54)°°	0.005**	>4
H03. Has your (doctor, CBR worker, or any other health professional) ever discussed with you the benefits of eating a healthy diet, engaging in regular physical exercise, or not smoking?	1.47 (0.50)	1.40 (0.52)	0.678	1
H04. When was the last time you had a regular health check-up?	1.47 (1.06)	1.00 (0.12)	0.167	1
H05. In the last 12 months, has there been a time when you needed health care but did not get that care?	2.02 (0.53)	2.00 (0.94)	0.911	2 to 3
H07. On your last visit to a health-care provider, to what extent were you involved in making decisions for your treatment?	2.97 (1.62)°°	2.61 (1.57)°°	0.524	>4
H08. In the last 12 months, has there been a time when you needed rehabilitation services, such as physical, occupational, or speech therapy, but did not get those services?	2.68 (0.63)	2.33 (1.03)	0.259	2 to 3
E04. Do you participate in learning opportunities to improve your skills for everyday life or work?	1.28 (0.46)	1.20 (0.42)	0.581	1
E05. To what extent does it fit your needs?	3.07 (1.18)°°	2.75 (0.42)°°	0.461	>4
L03. Do you get to decide how to use your money?	4.30 (1.11)	4.40 (1.27)	0.806	>4
L04. Do you know how to get financial services such as credit, insurance, grants, savings programs?	1.76 (0.40)°°	1.60 (0.51)°°	0.209	1
L05. Do you currently benefit from any social protection programme, such as loss of income through old age, sickness or disability?	1.80 (0.41)°°	1.80 (0.42)°°	0.989	1
L06. Do you know how to get social protection against loss of income resulting from old age, sickness or disability?	2.00 (0.00)	2.00 (0.00)	0.419	1
S02. Do you get to make decisions about the personal assistance that you need (who assists you, what type of assistance, when to get assistance)?	4.03 (1.17)	2.21 (1.54)°°	0.001**	>4
S03. Do you get to make your own decisions about your personal relationships, such as friends and family?	4.26 (1.17)	3.25 (1.07)°°	0.047*	>4
S04. Do you get to participate in artistic, cultural or religious activities?	3.60 (1.26)°°	3.26 (1.23)°°	0.501	>4
S05. Do you get to participate in community recreational, leisure and sports activities?	2.75 (1.31)°°	2.40 (1.42)°°	0.463	>4
S06. To what extent do you know your legal rights?	2.41 (1.35)°°	2.00 (0.94)°°	0.372	>4
S07. Do you know how to access the justice system?	1.64 (0.48)°°	1.80 (0.42)°°	0.372	1
M02. Do you think that the policies in your country provide people with disability equal rights as other people?	1.70 (1.11)°°	1.01 (0.25)°°	0.048*	>4
M03. Are you satisfied with your ability to persuade people of your views and interests?	2.90 (0.96)°°	2.05 (1.03)°°	0.178	>4
M04. Do you get to influence the way your community is run?	3.04 (1.42)°°	2.74 (1.31)°°	0.799	>4

°°Mean score below references values considered as good; * p<0.05; ** p<0.01

Regarding the "Education component", although all migrants participate in learning opportunities to improve their skills for everyday life of work, these training courses do not fit their actual needs. This can lead to feelings of frustration, already strongly challenged by occupational deprivation as well as by occupational imbalance and change [30]. Furthermore, refugees with disability have been invisible in policy and service provisions. In addition, reliable data is quite limited, and there has been little research into their experiences of educational inclusion and exclusion [31]. An international effort in this field is highly recommended.

With regard to the "Social component", migrants experience barriers that limit their participation in cultural or religious activities. These barriers are even greater when considering the opportunities for recreational, leisure and sport activities (good outcome >4, mean score for each group 2.75-2.41). Furthermore, they are not very aware on how get access to the justice system and they do not know much about their legal rights (good outcome >4, mean score for each group 2.41-2.00). Regarding the 'Livelihood component', all migrants of both groups are not aware of legal issues, especially aspects regarding how to obtain financial services or social protection. Research has highlighted the multiple barriers that migrants with health impairments face in accessing formal support [32]. These barriers may be structural, social or cultural, or may relate to the challenges facing refugee and minority ethnic community organizations, which often become the key source of support in the absence of, or restrictions in, statutory provision [33].

With reference to the "Empowerment component", both groups are not very satisfied with their ability to persuade people of their interests and points of view. Moreover, they feel that they are not able to influence the community where they live (good outcome >4, mean score for each group 3.04-2.74). Indeed, increasing refugee and migrant participation in the design and implementation of integration policies is crucial for developing effective policies that are tailored to the needs of the main beneficiaries. Actively involving migrants, asylum seekers and refugees, while also promoting their participation in consultative and decision-making processes that concern them, can contribute to their empowerment and long-term integration into society. This is the direction of the European Commission Action Plan [34] on the integration of third-country nationals from 2016, stressing that the involvement of third-country nationals in the design and implementation of integration policies is essential to improve their participation and their integration outcomes.

Limitations

Despite these encouraging results, the present investigation has some limits. These results may not generalize broadly to other samples, because participant sample was relatively small and restricted. Considering the explorative nature of the study, the research group did not conduct a statistical power analysis, and this does not allow to generalize findings. Secondly, we did not have normative data on the Italian population to compare outcomes of migrants with and without disability, as well as similar data that refer to migrants in other countries. Furthermore, to identify people with disability the research group asked if the subject considered himself as person living with a condition of disability, instead to use specific tool. Lastly, in this investigation children or non-accompanied minors are not included. Further research should investigate global needs of children and young migrants, in order to focus more in depth on the services and inclusion strategy within the community they live in.

CONCLUSIONS

The differences between migrants with and without disabilities have some distinctive features. However, both groups are influenced by the social determinants of health. In addition to health issues, challenges in social life, livelihood and empowerment also clearly emerge. Governments and different stakeholders are urgently called to intervene with multi-sectoral and cross-cutting strategies. Only by acting as a European Community will it be possible to overturn and change a discriminatory system and guarantee the respect of human rights, regardless of one's legal status, disability or sexual orientation, or the country to which one is forced to migrate.

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Conflict of interest statement

No potential conflict of interest was reported by the Authors.

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Adverse events related to herbal dietary supplements and over-the-counter medications containing laxatives: a 10-year update from the Italian Phytovigilance and Pharmacovigilance systems

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Abstract

Introduction. Products containing anthraquinones (AQ) are associated with an increased risk of serious adverse events (AEs). We performed an update of the available evidence retrieved by the spontaneous reports of AE associated with herbal dietary supplement (DS) and over-the-counter medications (OTC-M) used as laxatives.

Methods. Analysis and evaluation of AE reports retrieved from the Italian Phytovigilance and Pharmacovigilance systems was performed from February 2011 to December 2020.

Results. Totally 110 AE reports, 24 related to herbal DS and 86 to OTC-M, were analyzed. Most subjects were females. Herbal products analyzed mostly contained AQ derivatives. Most AEs were gastrointestinal (41.6%), central nervous system (18.2%), and dermatological disorders (12.6%).

Conclusions. The number of AE reports recorded in the last 10 years is still relatively low. However, given the seriousness of some AEs, that does not represent a guarantee of safety. This study may contribute to enhance public awareness on the risks associated with misuse or abuse of laxatives.

Key words

- dietary supplement
- herbal medicinal product
- adverse event
- phytovigilance
- pharmacovigilance

INTRODUCTION

Chronic constipation is a common functional bowel disorder among adults, it is characterized by persistently difficult, infrequent, or incomplete intestinal evacuation, and can originate from several causes [1]. Self-reported constipation and the consequent use of laxatives increase with age [2] and are more common among women [3]. Lifestyle and dietary modifications are considered the first steps in the treatment of chronic constipation. Laxatives, which work by influencing bowel movements and facilitating intestinal evacuation through different mechanisms and often of plant origin,

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are reserved for patients who do not respond to non-pharmacological approaches [1].

Herbal products derived from medicinal plants commonly promoted to treat constipation include aloe (*Aloe* spp.) juice, leaves and fruits of senna (*Cassia angustifolia*, *C. acutifolia*), cortex of *Cascara sagrada*, hypogeal parts of rhubarb (*Rheum* spp.), psyllium husk (*Plantago psyllium*), and radix of liquorice (*Glycirrhiza glabra*) [4]. In Italy, these herbal products are usually marketed as dietary supplements (DS), notified to the Ministry of Health and/or as medications (M), mainly over-the-counter (OTC), registered by the Italian Medicines Agency (AIFA, Rome, Italy).

Herbal DS and OTC-M are generally bought as self-prescription, therefore often without advice from healthcare professionals (i.e., general practitioner, community pharmacist) [5]. In general, DS are marketed with claims of nutritional and physiological effects, whereas OTC-M are authorized for treating or preventing disease, or for restoring, correcting or modifying physiological functions [5].

In Italy, suspected adverse events (AEs) associated with DS are reported to the Italian National Institute of Health (ISS, Rome, Italy) [6], while those associated with OTC-M are notified to the AIFA. The number of AE reports associated with DS has increased in the recent years [7], raising concern among healthcare professionals [8]. Products containing anthraquinones (AQ) derivatives are known to be used primarily worldwide as oral laxatives and have various biological effects, also associated with an increased risk of serious AEs [9, 10].

In 2021, the European Commission has confirmed the adoption of the regulation prohibiting the use of all preparations based on *Aloe* spp., as well as those containing emodin and aloe-emodin, through specific amendment relating to botanical species containing AQ derivatives [11]. Furthermore, as there is the possibility of harmful effects on health associated with the use of *Rheum* spp., *Cassia* spp. and *Rhamnus* and their preparations in DS, such substances were placed under Union safety evaluation [12].

In this context, we performed an update of the available evidence retrieved by the spontaneous reports of AE associated with herbal DS or OTC-M used as laxatives through an analysis of the Italian Phytovigilance and Pharmacovigilance systems.

METHODS

Following our previous publication [4] and considering the new Union legislation [12], this updated analysis of spontaneous AE reports retrieved from the Italian Phytovigilance [6, 7, 13, 14] and Pharmacovigilance [15-20] systems was performed by evaluating all suspected AEs associated with herbal DS or OTC-M used as laxatives recorded from February 2011 to December 2020.

The Italian Phytovigilance system, under the coordination of the ISS, collects spontaneous reports of suspected AEs related to DS, while the Italian Pharmacovigilance system, coordinated by AIFA, collects spontaneous reports of suspected AEs related to OTC-M, allowing also online reporting through two dedicated web sites (www.vigierbe.it and www.vigifarmaco.it).

The following demographic, clinical and pharmacological characteristics were collected and analyzed: (1) patient data (age, sex, and clinical history); (2) suspected DS or OTC-M information (product type, dosages, and duration of treatment); (3) AEs description (criteria of seriousness, dechallenge, rechallenge and outcome); (4) and concomitant treatments if present.

The seriousness of each AE was evaluated according to the World Health Organization (WHO) criteria. The classification by Edward and Aronson was also considered [21]. A comparison between serious and non-serious AEs was performed both for reports submitted to the ISS and AIFA. Moreover, AEs were codified through the Medical Dictionary for Regulatory Activities (MedDRA), described and organized in terms of System Organ Class (SOC) and Preferred Term (PT) [22]. In the phytovigilance and pharmacovigilance fields, "dechallenge" refers to the stopping of the suspected product, usually after an AE [19]. A positive dechallenge refers to the AE disappearing after the stopping of the suspected product. On the contrary, a negative dechallenge refers to the persistence of the AE after the withdrawal of the suspected product. Moreover, "rechallenge" refers to the restarting of the same suspected product. A positive rechallenge refers to the AE recurring after restarting the suspected product. Conversely, if the AE does not recur after the restarting of the suspected product the rechallenge is defined as negative.

A multidisciplinary group, composed of clinical pharmacologists, toxicologists, pharmacists, epidemiologists, and experts in phytotherapy and phytovigilance, evaluated each AE report calculating the causality assessment according to the WHO criteria [23]. When more than one active compound was present in the suspected product (both in the case of DS or OTC-M), the attribution of causality concerned the whole commercial product. The composition of products was reported, excluding excipients, as on the label of the package.

Continuous data were expressed as mean ± standard deviation (SD) and categorical variables were expressed as count or percentages.

RESULTS

Italian National Institute of Health

Up to December 2020, the ISS received a total of 2,365 reports of AE, of which 42 (1.8%) concerned AEs related to herbal DS used to treat constipation. From February 2011 to December 2020, 24 new AE reports were recorded in the Italian Phytovigilance system *(Table 1)*. The mean age of patients was 52±17.3 years, and 62.5% were females. Overall, 66.7% of AE reports were defined as "serious" and required hospitalization, but in one report seriousness was unknown. Healthcare professionals reporting the suspected AEs were mainly physicians (66.7%) and pharmacists (25.0%). Most subjects (54.2%) reported to use herbal DS for constipation. The information on the dosage taken by the patients was compatible with what was reported on the label of the suspected products in 6 AE reports (25.0%), while the dosage was higher in 9 cases

Table 1
Characteristics of patients reporting suspected adverse events to dietary supplements and medicinal products used as laxatives

Characteristics	Italian Phytovigilance System (ISS)			Italian Pharmacovigilance System (AIFA)		
	Overall	Serious[a]	Non-serious[a]	Overall	Serious[b]	Non-serious[b]
	n=24 (%)[c]	n=16 (%)[c]	n=7 (%)[c]	n=86 (%)[c]	n=31 (%)[c]	n=53 (%)[c]
Age (mean ± SD)[d]	52±17.3	51.3±15.9	57.1±19.7	64.9±21.5	60.5±25.4	68.1±18.2
Sex						
Male	9 (37.5)	7 (43.7)	2 (28.6)	36 (41.9)	10 (32.3)	25 (47.2)
Female	15 (62.5)	9 (56.3)	5 (71.4)	50 (58.1)	21 (67.7)	28 (52.8)
Comorbidities						
≥1 comorbidities	11 (45.8)	8 (50.0)	3 (42.9)	35 (40.7)	18 (58.1)	16 (30.2)
No comorbidities	-	-	-	-	-	-
Not reported	13 (54.2)	8 (50.0)	4 (57.1)	51 (59.3)	13 (41.9)	37 (69.8)
Comedications						
≥5 drugs	1 (4.2)	-	1 (14.3)	12 (14.0)	2 (6.5)	10 (18.9)
1-4 drugs	15 (62.4)	9 (56.3)	5 (71.4)	16 (18.6)	9 (29.0)	6 (11.3)
No drugs	1 (4.2)	1 (6.2)	-	-	-	-
Not reported	7 (29.2)	6 (37.5)	1 (14.3)	58 (67.4)	20 (64.5)	37 (69.8)
Reason of use						
Constipation	13 (54.2)	8 (50.0)	5 (71.4)	51 (59.3)	13 (41.9)	38 (71.7)
Abuse	-	-	-	7 (8.0)	7 (22.6)	-
Weight loss	3 (12.5)	3 (18.8)	-	1 (1.2)	-	1 (1.9)
Meteorism	2 (8.3)	2 (12.5)	-	-	-	-
Others	3 (12.5)	2 (12.5)	1 (14.3)	7 (8.0)	4 (12.9)	3 (5.7)
Not reported	3 (12.5)	1 (6.2)	1 (14.3)	20 (23.3)	7 (22.6)	11 (20.7)
Causality assessment						
Definite	-	-	-	-	-	-
Probable	9 (37.5)	7 (43.7)	2 (28.6)	11 (12.8)	10 (32.3)	1 (1.9)
Possible	15 (62.5)	9 (56.3)	5 (71.4)	18 (20.9)	11 (35.4)	6 (11.3)
Unlikely	-	-	-	-	-	-
Not reported	-	-	-	57 (66.3)	10 (32.3)	46 (86.8)
Reporter qualification						
Physician	16 (66.7)	13 (81.3)	3 (42.7)	49 (57.0)	22 (71.0)	27 (51.0)
Pharmacist	6 (25.0)	2 (12.5)	3 (42.7)	22 (25.6)	6 (19.3)	16 (30.2)
Other professional	1 (4.2)	1 (6.2)	-	5 (5.8)	2 (6.5)	2 (3.7)
Patient	1 (4.1)	-	1 (14.2)	8 (9.3)	1 (3.2)	6 (11.3)
Drug company	-	-	-	2 (2.3)	-	2 (3.8)
Outcomes						
Recovered	12 (50.0)	6 (37.5)	6 (85.7)	38 (44.2)	12 (38.7)	26 (49.0)
Improvement	3 (12.5)	1 (6.3)	1 (14.3)	27 (31.4)	12 (38.7)	15 (28.3)
Sequelae	2 (8.3)	2 (12.5)	-	1 (1.1)	1 (3.2)	-
Persistent	1 (4.2)	1 (6.2)	-	3 (3.5)	-	3 (5.7)
Not reported	6 (25.0)	6 (37.5)	-	17 (19.8)	6 (19.4)	9 (17.0)
Latency*						
≤7 days	8 (33.3)	7 (43.7)	-	56 (65.1)	21 (67.7)	34 (64.3)
8-30 days	4 (16.7)	2 (12.5)	2 (28.6)	7 (8.1)	2 (6.5)	5 (9.4)
>30 days	4 (16.7)	1 (6.3)	3 (42.8)	3 (3.5)	1 (3.2)	2 (3.7)

Continues

Table 1
Continued

Characteristics	Italian Phytovigilance System (ISS)			Italian Pharmacovigilance System (AIFA)		
	Overall	Serious[a]	Non-serious[a]	Overall	Serious[b]	Non-serious[b]
	n=24 (%)[c]	n=16 (%)[c]	n=7 (%)[c]	n=86 (%)[c]	n=31 (%)[c]	n=53 (%)[c]
Not reported	8 (33.3)	6 (37.5)	2 (28.6)	20 (23.3)	7 (22.6)	12 (22.6)
Duration of treatment						
≤7 days	9 (37.5)	7 (43.7)	-	57 (66.3)	23 (74.2)	33 (62.3)
8-30 days	4 (16.7)	2 (12.5)	2 (28.6)	4 (4.6)	1 (3.2)	3 (5.6)
>30 days	3 (12.5)	1 (6.3)	3 (42.8)	3 (3.5)	1 (3.2)	2 (3.8)
Not reported	8 (33.3)	6 (37.5)	2 (28.6)	22 (25.6)	6 (19.4)	15 (28.3)
Dechallenge						
Positive	14 (58.3)	8 (50.0)	6 (85.7)	42 (48.8)	18 (58.0)	24 (45.3)
Negative	-	-	-	1 (1.2)	-	1 (1.9)
Not reported	10 (41.7)	8 (50.0)	1 (14.3)	43 (50.0)	13 (42.0)	28 (52.8)
Rechallenge						
Positive	2 (8.3)	-	2 (28.6)	2 (2.3)	-	2 (3.8)
Negative	22 (91.7)	16 (100)	5 (71.4)	-	-	-
Not reported	-	-	-	84 (97.7)	31 (100)	51 (96.2)
Laboratory test						
Yes	13 (54.2)	9 (56.3)	3 (42.8)	30 (35.0)	13 (42.0)	17 (32.1)
No	-	-	-	-	-	-
Not reported	11 (45.8)	7 (43.7)	4 (57.2)	56 (65.0)	18 (58.0)	36 (67.9)
Specific treatment						
Yes	16 (66.7)	14 (87.4)	1 (14.3)	34 (39.5)	17 (54.8)	17 (32.1)
No	3 (12.5)	1 (6.3)	2 (28.6)	27 (31.4)	7 (22.6)	20 (37.7)
Not reported	5 (20.8)	1 (6.3)	4 (57.2)	25 (29.1)	7 (22.6)	16 (30.2)

AE: adverse event; AIFA: Agenzia Italiana del Farmaco, Italian Medicines Agency; ISS: Istituto Superiore di Sanità, Italian National Institute of Health; SD: standard deviation.
*Days between starting of treatment and AEs onset.
[a]In one case seriousness was *Not reported*.
[b]In two cases seriousness was *Not reported*.
[c]% refers to the total of each column.
[d]In the Italian Pharmacovigilance System, in 6 cases "age" was not reported.

(37.5%). In all other cases, the dosage was not reported. The treatment duration varied from 1 day to 10 years. In more than half of the AE reports (66.6%), users were also taking other pharmacological and/or non-pharmacological treatments. The presence of concomitant conditions was described in 45.8% of the suspected AE reports. Information on dechallenge was reported in 14 (58.3%) cases and it was always "positive". Information on rechallenge was reported in 24 (100%) cases and it was "positive" in two. According to the WHO criteria, 9 (37.5%) AE reports were judged as "probably" and 15 (62.5%) "possibly" related to the suspected herbal DS. Following the MedDRA classification system, the majority of AEs were related to the SOC "Gastrointestinal disorders" (n=17, 32.1% out of 53), followed by "skin and subcutaneous tissue disorders" (n=14, 26.4% out of 53), and "central nervous system disorders" (n=5, 9.4% out of 53) *(Table 2)*. Considering both the total number of AEs belonging to different SOCs and the total number of subjects reporting at least one AE, there are no differences in the order of the most reported SOCs. In particular, "gastrointestinal disorders" were reported by 80.91% of subjects, "central nervous system disorders" by 35.45%, and "skin and subcutaneous tissue disorders" by 24.55%. Herbal DS associated with suspected AEs mostly involved AQ derivatives (79.2%), and only one case of *melanosis coli* was found. Details of each AE report retrieved from ISS are described in the *Supplementary Table available online*.

Italian Medicines Agency

Up to December 2020, the AIFA collected about 581,219 reports of suspected AE, of which 94 (0.02%) were associated with the use of OTC-M to treat constipation. From February 2011 to December 2020, 86 new AEs were recorded in the Italian Pharmacovigilance system *(Table 1)*. The mean age of patients was 64.9±21.5 years, and 58.1% were females. Overall, 36.1% of AE reports were defined as "serious" and required hospitalization, while in two cases seriousness was not reported. Healthcare professionals reporting the suspected AEs were mainly physicians (57%), fol-

Table 2
Adverse events (AE) grouped by System Organ Class (SOC)

SOC	N. AEs (ISS)	N. AEs (AIFA)	Total (%)	% on total number of AEs (a)	% on total number of subjects (b)
Gastrointestinal	17	72	89 (41.59)	41.59	80.91
Central nervous system	5	34	39 (18.22)	18.22	35.45
Skin	14	13	27 (12.62)	12.62	24.55
Investigations	2	13	15 (7.01)	7.01	13.64
Other	1	8	9 (4.21)	4.21	8.18
Electrolyte imbalances	1	7	8 (3.74)	3.74	7.27
Cardiovascular system	3	3	6 (2.80)	2.80	5.45
Metabolism	1	4	5 (2.34)	2.34	4.55
Immune system	4	1	5 (2.34)	2.34	4.55
Renal system	1	2	3 (1.40)	1.40	2.73
Musculoskeletal	1	2	3 (1.40)	1.40	2.73
Hepatic system	2	1	3 (1.40)	1.40	2.73
Respiratory system	1	1	2 (0.93)	0.93	1.82

(a) Total number of AEs belonging to the different SOCs: 53 from ISS + 161 from AIFA = 214.
(b) Total number of subjects reporting at least one AE: 24 from ISS + 86 from AIFA = 110.
AIFA: Agenzia Italiana del Farmaco, Italian Medicines Agency.

lowed by pharmacists (25.6%). The information on the dosage taken by the patients was compatible with the therapeutic indications reported in the summary of product characteristics of the suspected OTC-M in 46 AE reports (53.4%), while the dosage was higher in 18 cases (20.9%). In all other cases, the dosage was not reported, or it was described as overdose, abuse or out of therapeutic indications (off-label). The treatment duration varied from 1 day to 7 years. In 32.6% of the AE reports, users were also taking other pharmacological and/or non-pharmacological treatments. The presence of concomitant conditions was described in 40.7% of cases. Information on dechallenge was reported in 43 cases (50%) and was "positive" in 42 of them. Information on rechallenge was reported in 2 cases (2.3%) and was always "positive". According to the WHO criteria 11 (12.8%) AE reports were judged as "probably" and 18 (20.9%) "possibly" related to OTC-M. Fifty-seven reactions were unclassified because of insufficient information. Most AEs were "gastrointestinal disorders" (n=72, 44.7% out of 161), followed by "nervous system disorders" (n=34, 21.1% out of 161) and "skin and subcutaneous tissue disorders" (n=13, 8.1% out of 161) *(Table 2)*. As mentioned above, "gastrointestinal disorders" were reported by 80.91% of subjects, "central nervous system disorders" by 35.45%, and "skin and subcutaneous tissue disorders" by 24.55%. OTC-M associated with the suspected AEs mostly involved AQ derivatives (91.9%). Details of each AE report retrieved from AIFA are described in the *Supplementary Table available online*.

DISCUSSION

The evaluation of the Italian Phytovigilance and Pharmacovigilance spontaneous reporting systems allowed us to characterize a total of 110 new AE reports. Of these, 24 were associated with herbal DS and 86 were related to OTC-M. Among the latter, only one report was related to a synthetic drug containing bisacodyl. It is worth highlighting the high increase in the number of AE reports between the analysis period discussed in the previous publication (N=26, period 2002-2011) [4] and the second period analyzed in this paper (N=110, period 2011-2020), especially in the Pharmacovigilance system. Nevertheless, the underreporting effect has to be taken in account. Of notice, given the seriousness of some AEs, the relatively low number of reports collected in the last decade does not represent a guarantee of safety.

Concerning demographic characteristics, most AE reports involved females, and the mean age was lower for subjects experiencing AEs associated with herbal DS containing laxatives. In general, in most countries laxative use in females is higher than males [24]. However, evidence published in the literature describing the use of laxatives in the community is controversial. In fact, some studies reported a higher laxative use in women, in particular in the United States, United Kingdom, Germany, France, Italy, Brazil and South Korea [25]. Laxative use generally increases with age, although with relevant differences between countries [24]. Moreover, it is well known that women experience several constipation symptoms and abnormal bowel habits more frequently than men [26], thus explaining a relatively higher prevalence of laxative use and the potentially associated AEs in this subgroup. Considering our evidence, it is difficult to draw any conclusions in terms of patients' characteristics due to the relatively small sample size, composed by subjects who experienced a laxative-related AE, and the lack of information on the total number of laxative users. However, to improve constipation management in community and primary healthcare settings, knowledge of the true prevalence and utilization of laxative use and consumers' characteristics is still required [24].

Products associated with suspected AEs in our analysis mostly involved AQ derivatives. Considering the reports collected by the phytovigilance system, we evaluated the characteristics of herbal DS available on the market in terms of their composition and formulation. This relevant aspect should always be taken into consideration by both healthcare professionals and consumers. In fact, most of the reports concerned products containing more than one active compound and, sometimes, more than one AQ-containing plant. In particular, the majority of serious AEs were related to products with two or more plants containing AQs. This is an extremely important safety issue because there is no scientific evidence that demonstrates a favorable benefit risk profile in the case of combination of multiple active substances [27].

Considering data for both herbal DS and OTC-M, in our sample gastrointestinal disorders were the most frequently reported AEs, both by analyzing the total number of AEs belonging to different SOCs and the total number of subjects reporting at least one AE. In particular, abdominal pain and cramps, which are associated with the well-known pharmacological properties of AQ derivatives [9]. Laxatives containing AQ derivatives should be used following their specific indications (acute constipation and/or as purgatives prior to diagnostic endoscopy) and only for a short-term period (not to be used for more than 1 week) [28]. AQ derivatives increase the release of prostaglandin and other inflammatory mediators, and the concentrations of fluids and electrolytes in the colon, resulting in a stimulation of peristalsis that could be responsible for gastrointestinal symptoms [29]. Regarding the case of *melanosis coli*, the use of AQ-containing laxatives has been already associated to its occurrence [30]. In particular, *melanosis coli* is a dark-brown discoloration of colon mucosa, and it is induced by AQ derivatives in 9-12 months, disappearing over weeks to months after the end of treatment [31]. However, even though AQ laxatives can be associated with *melanosis coli*, it is noteworthy that, in the case observed in our analysis, the causality assessment was judged as "probable" due to the concomitant assumption of other pharmacological treatments. This does not exclude the possibility that there are several cases of *melanosis coli* or other similar disorders caused by prolonged use of AQs, difficult to detect due to their long-term onset. The occurrence of gastrointestinal AEs observed following the use of this kind of laxatives could also be associated with their duration of treatment. We cannot exclude the inappropriate use of these products in our sample, considering that a relatively high number of subjects reported intake of these laxatives for more than 1 week.

In general, the cause of constipation should always be ascertained and, if a laxative is needed, soft laxatives (*i.e.*, osmotic laxatives, poo-softener laxatives, etc.) should be the treatment of choice because they are generally safe and well-tolerated [32], particularly in specific subgroups of patients (*i.e.*, pregnancy, lactation, elderly, etc.) [33-36]. In this context, it is mandatory to clarify the possible association between an inappropriate AQ laxative use and the onset of serious diseases. Recently, our research units conducted a systematic review and meta-analysis reporting a higher risk of colorectal cancer (CRC) in subjects using AQ laxatives compared to "other" or "no laxative" use [10]. Although not at a statistically significant level, and considering all limitations affecting these analyses, our study provides the best risk estimate available for subjects undergoing AQ laxatives use. Of notice, no eligible studies included in the meta-analysis reported information on dosage and length of treatment with AQ laxatives, highlighting the need of further high-quality population-based safety studies.

The second most frequently reported AEs were included in the "skin and subcutaneous tissue disorders" SOC, mainly related to suspected products containing senna (*Cassia angustifolia*) compounds and experienced by subjects within 6 days of use. In the literature little evidence, regarding dermatological reactions to sennosides, is present. A review by Vilanova-Sanchez and colleagues [37], evaluating the safety of senna-based laxatives as long-term treatment for constipation in children, reported that senna-induced dermatitis is a rare event, but may occur when patients need a higher dosage. No evidence on the safety of AQ laxatives use in adults regarding dermatological reactions was found. In many cases, dandelion (*Taraxacum officinale*) and senna were involved together in the same products, often in association with fennel (*Foeniculum vulgare*) or cascara (*Rhamnus purshianus*). Despite dermatological reactions associated with AQ derivatives being generally infrequent, considering the high prevalence of use of these products in the community [24], healthcare professionals should consider this clinical occurrence. Moreover, these medicinal plants should be used with caution by patients with known hypersensitivity.

Another clinically relevant condition associated with inappropriate use of laxatives, in particular those containing AQ derivatives, is electrolyte imbalance [38]. Long-term and high dose treatment with laxatives can lead to dehydration and electrolyte imbalances like hyponatremia, hypokalemia, hyperuricemia, and hyperaldosteronism. If electrolyte imbalance is not properly corrected, it can lead to alterations of heart function (such as arrhythmias), muscle weakness, and other clinically relevant medical occurrences [4]. For instance, dehydration and hypokalemia together can cause renal insufficiency [39].

As previously mentioned, due to the lack of standardization in the production process of herbal DS, the number of active compounds can vary, further complicating the assessment of potential drug-DS interactions [27]. In this context, we observed a relatively high number of subjects who experienced an AE associated with laxative use during an oral anticoagulant therapy. AQ compounds (i.e., sennosides), increasing bowel motility, potentially decrease vitamin K absorption causing elevated INR (international normalized ratio) values [40]. Therefore, in subjects treated with warfarin, such as those observed in our analysis, AQ laxatives may play a role in the exaggerated anticoagulation and subsequent bleeding complications. Healthcare professionals and consumers should consider that AQ-containing plants and soluble fibers can decrease drug absorption by decreasing gastrointestinal transit time [41].

Our study has several strengths. First, the phytovigilance and pharmacovigilance spontaneous reporting system play a key role in exploring the safety profile of DS and OTC-M both from a local and international perspective, thus increasing generalizability of our findings. In addition, the causality assessment was performed for all AE reports, thus providing valuable insights concerning the clinical relevance of serious AEs associated with herbal DS and OTC-M used as laxatives. Furthermore, considering that data concerning the use of these products is not always available, neither in term of packages sold nor in terms of population exposed, and that population-based studies for risk estimation are difficult to conduct, national spontaneous reporting systems are

the first valuable approaches to monitor safety signals from DS and OTC-M for regulatory actions.

This update analysis conducted on AE reports retrieved by national spontaneous reporting systems has also several limitations. The first one is represented by the underreporting, which is likely to affect herbal DS and OTC-M to a higher extent as compared to prescription drugs, due to their perceived better safety profile by both consumers and healthcare professionals, who may not always take into consideration these products as suspected causative agents in the onset of an AE. Additionally, post-marketing surveillance is not mandatory for DS, thus spontaneous/voluntary reporting may further underestimate the real prevalence of DS-related AEs. Finally, spontaneous AE reports may lack or report incomplete clinical data (i.e., concomitant products, concomitant medications, comorbidities, etc.), thus making the application of the causality assessment challenging.

CONCLUSIONS

Despite the wide use of herbal DS and OTC-M containing laxatives, the total number of AE reports recorded in the last 10 years is still relatively low. However, the extent of underreporting may be significant since they are bought by consumers mainly as self-prescription products. In particular, based on the "natural origin" of herbal DS, they are usually perceived by the community as being safe and free of side effects. Furthermore, given the seriousness of some AEs, especially related to DS, the low number of reports does not represent a guarantee of safety.

This study may contribute to increase public awareness and alert healthcare professionals on the health risks associated with the use of DS and OTC-M containing laxatives, especially those containing AQ derivatives. Finally, this study may enhance consumers' attention regarding the risks associated with the misuse or abuse of laxatives containing AQ derivatives.

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Mortality of people with AIDS in Italy: comparison of AIDS surveillance and multiple cause-of-death registries

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Abstract

Aims. To assess whether the use of multiple cause-of-death data could improve reporting of AIDS mortality in Italy.

Method. Population-based, record-linkage study, on 3,975,431 deaths recorded in the National Registry of Causes of Death (RCoD) and 4,530 deaths recorded in the National AIDS Registry (RAIDS), during 2006-2012.

Results. The record-linkage identified 3,646 AIDS-related deaths present in both registries, 884 deaths in the RAIDS without mention of HIV/AIDS in the RCoD, and 3,796 deaths in the RCoD with mention of HIV/AIDS that were not present in the RAIDS. In the latter, in-depth analysis of multiple cause-of-death allowed the identification of 1,484 deaths that were AIDS-related. On these results, we estimated 6,014 deceased people with AIDS. Of them, 14.7% (884) were not present in the RCoD and 24.7% (1,484) derived from the RCoD only.

Conclusions. The integration of different nationwide registries allowed a more comprehensive estimate of the impact of AIDS-associated mortality in Italy.

Key words

- AIDS
- HIV infection
- death certificates
- multiple cause-of-death
- Italy

INTRODUCTION

Estimates of AIDS related mortality vary considerably according to data source. In Europe, figures provided by HIV and/or AIDS surveillance systems have shown great across-country variability due to different approaches [1]. Moreover, mortality figures provided by surveillance systems are systematically lower than those reported by cause-of-death registries derived from death certificates [2].

Mortality patterns of people with HIV/AIDS have radically changed following the introduction of highly active antiretroviral therapy (HAART), resulting in an increased frequency of deaths due to non AIDS-related conditions [3]. New issues have therefore emerged, and various efforts have been put in place to assess causes of death among people with HIV/AIDS [4-6].

Despite well-known limits, death certificates remain of primary importance and one of the most useful tools for international comparisons of mortality. For people with HIV/AIDS, the cause of death classification system – e.g., the International Classification of Diseases, tenth revision (ICD-10) – lacks of specificity in the coding of AIDS defining conditions, and criteria adopted for the identification of people deceased for HIV/AIDS might differ from clinical definitions adopted by surveillance systems for the identification of HIV/AIDS cases. In particular, it is worth stressing that mortality statistics focus on the cause of death, i.e. on people deceased because of AIDS, whereas AIDS surveillance systems collect data on all people with AIDS (PWA), even if death is caused by other conditions.

The majority of the studies conducted to evaluate discrepancies among causes of death and clinical conditions in people with HIV/AIDS are based on the linkage between data from cause-of-death registries and surveillance systems [7-13]. In Italy, the only nationwide study [14] was conducted in 1997 and never updated. It was based on i) the National Registry of Causes of Death (RCoD) – where mortality data were coded according to the Ninth Revision of the International Classification of Diseases (ICD-9); and ii), the National AIDS

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Registry (RAIDS) fitting the 1987-CDC AIDS case definition.

In this investigation, by using a multiple cause of death (MCoD) approach, we carried out a record linkage between the RCoD and the RAIDS to assess whether the use of death certificates could contribute in identifying AIDS cases missed by the national surveillance system, and to identify possible sources of miscoding of AIDS deaths in RCoD.

METHODS

This study is part of a larger, nationwide, investigation on the survival and mortality patterns of Italian PWA included in the Italian National Statistical Plan, authorized by the Italian Data Protection Authority [15].

Source of data

Data were obtained from two Italian nationwide registries: the RAIDS, managed by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS), and the RCoD, managed by the Italian National Institute of Statistics (Istituto Nazionale di Statistica, ISTAT). The RAIDS collects data on people newly diagnosed with AIDS according to the 1993 revised European definition [16], which requires the diagnosis of specific clinical conditions (AIDS-defining conditions) in people with a HIV-positive laboratory test *(Supplementary Table available online)*. The RCoD collects death certificates where the causes of death (i.e., sequence of conditions directly leading to death and other contributing causes) are registered.

In the 2006-2012 period, the ICD-10 was used [17] (incorporating WHO recommended updates until 2009), with an automated coding system that coded about 80% of all certificates without manual intervention. According to the MCoD coding process, all causes reported in the death certificates were analyzed, not only the underlying cause (the disease or external cause that initiated the train of events directly leading to death). For the MCoD analysis, AIDS-related deaths were defined by ICD-10 codes B20-B24 ("HIV disease") and/or R75 ("laboratory evidence of HIV").

Record-linkage procedure

For the 2006-2012-period, the records of the RAIDS and of the RCoD were linked using a validated, semi-automated software application that guarantees anonymity and high sensitivity [18] with the aim to identify deaths of PWA.

In this article we define as PWA a person included in the RAIDS and a PWA death a record from RAIDS successfully linked to RCoD.

Because the linkage procedure uses name, surname, and date of birth as matching criteria, in order to improve linkage effectiveness, we excluded: (a) the records from the provinces of Trento and Bolzano, because names/surnames and multiple causes of death are not available in the RCoD database; (b) the records of foreigners, because of the high frequency of spelling errors in names/surnames and the increased probability of losses to follow-up due to migration. For the aims of this analysis, only individuals deceased at an age greater than 15 years were considered. Details of the linkage procedure have been provided elsewhere [19]. The record-linkage procedure to identify deceased PWA was carried out through the following three steps.

All records from RAIDS linked to RCoD records are considered PWA deaths, irregardless from the cause of death reported in the RCoD.

Step 1

The record-linkage between the RAIDS and the RCoD databases allowed identifying three groups of deceased PWA *(Table 1)* taking into account also the cause of death reported in the death certificate:

- Group A: AIDS-related deaths identified by the RCoD and pertaining to people notified to the RAIDS (i.e., agreement between the two data sources); these deaths are considered PWA deaths;
- Group B: i.e. AIDS-related deaths for RCoD of people not notified to RAIDS; this group has been examined in further steps since potentially hides some PWA deaths;
- Group C: Deaths pertaining to people notified to the RAIDS but who were not considered as AIDS-related deaths by the RCoD (i.e they did not include mention of ICD-10 codes B20-B24 – HIV disease – or R75 – laboratory evidence of HIV); deaths in this group are considered PWA deaths although the cause of death is not AIDS-related.

Step 2

To evaluate the nature and the extent of the disagreement between the RAIDS and the RCoD, deaths in

Table 1

Distribution of deaths certificates in the RCoD, by mention of HIV/AIDS (ICD-10 codes: B20-B24, R75) and results of the record-linkage to the RAIDS. Italy, 2006-2012

Deaths in RCoD		Linked to RAIDS		
		Yes	No	Total
Mention of HIV/AIDS in death certificate	Yes	3,646 (Group A)[1]	3,796 (Group B)[2]	7,442
	No	884 (Group C)[3]	3,967,105	3,967,989
Total		4,530	3,970,901	3,975,431

RAIDS: National AIDS Registry; RCoD: National Registry of Causes of Death.
[1]Group A: AIDS-related deaths identified by the RCoD and pertaining to people notified to the RAIDS;
[2]Group B: AIDS-related deaths for RCoD of people not notified to RAIDS;
[3]Group C: Deaths pertaining to people notified to the RAIDS but who were not considered as AIDS-related deaths by the RCoD.

Group B (i.e. AIDS-related deaths for RCoD of people not notified to RAIDS) were individually assessed for AIDS by means of an in-depth analysis of ICD-10 codes derived from death certificates. Every ICD-10 code was flagged either as "certain", if the description matched an AIDS-defining disease, or "uncertain", if the code description was not specific enough to identify an AIDS-defining disease. Based on these criteria, and using the MCoD analysis, deaths in Group B were classified as follows: (a) "deaths fitting RAIDS criteria", when death certificates included an explicit mention of AIDS, or HIV disease, or HIV-positive status (ICD-10 codes: B20-B24, R75) together with at least one AIDS-defining condition (flagged as "certain" in *Supplementary Table available online*); (b) "deaths not fitting RAIDS criteria", when death certificates did not include the above mentioned patterns, therefore excluding a PWA death; (c) "AIDS uncertain": death certificates reporting ICD-10 codes for AIDS-defining conditions but not for HIV-positive status, therefore not certainly indicating a PWA-death (flagged as "uncertain" in *Supplementary Table available online)*.

Step 3

Deaths classified as "AIDS uncertain" in step 2 underwent an individual text analysis of the original death certificate: every certificate was manually reviewed to analyze in detail all causes of death and to assess whether they fitted with an AIDS diagnosis. Certificates containing medical entries indicating an AIDS-defining condition were considered "deaths fitting RAIDS criteria", whereas the others were considered "deaths not fitting RAIDS criteria". At the end of the evaluation process, we estimated the number of total PWA deaths in the 2006-2012 period by summing up the following:

1. the number of deaths of people notified to the RAIDS with also an AIDS-related cause of death reported in the RCoD (i.e., all Group A deaths, irregardless from the cause of death);
2. the number of deaths of people with an AIDS-related cause of death reported in the RCoD (i.e., "deaths fitting RAIDS criteria", derived from Group B), but not notified to the RAIDS; and
3. the number of deaths pertaining to people notified to the RAIDS, although without an AIDS-related cause of death reported in the RCoD (i.e., Group C).

RESULTS

In Italy, between 2006 and 2012, 3,975,431 death certificates were reported to the RCoD. HIV disease or HIV-positive status was mentioned in 7,442 cases *(Table 1)*. According to the linkage procedure, 3,646 (49.0%) of these 7,442 deceased people were identified in both RAIDS and RCoD (Group A), whereas 3,796 deaths (51.0%) were not found in the RAIDS (Group B). In addition, there were 884 deceased people recorded in the RAIDS without mention of HIV disease or HIV positive status in the RCoD (Group C) *(Table 1)*.

Table 2 shows the distribution of the most frequent MCoD mentioned in the death certificates for each of the three groups. The most frequently reported conditions in Group A and in Group B included unspecified HIV disease (mentioned in 93.9% of certificates in Group A and in 87.6% in Group B), liver diseases (41.2% in Group A and 58.7% in Group B), viral hepatitis (28.4% and 37.8%, respectively), influenza and pneumonia (17.7% and 15.0%, respectively), and renal failure (11.3% and 12.5, respectively). Other worth mentioning conditions included malignant neoplasms of lymphoid and hematopoietic tissue (13.7% in Group A and 7.9% in Group B), other bacterial diseases (17.7% in Group A and 15.1% in Group B), and other forms of heart diseases (14.2% in Group A and 14.5% in Group B) *(Table 2)*.

The most frequent causes of death listed in Group C (i.e., PWA whose death certificate did not mention HIV infection) included liver diseases (23.5%), other forms of heart diseases (20.8%), disorders involving the immune system (17.0%), and viral hepatitis (9.8%). External causes of death (ICD-10 codes: V01-Y98) were frequently reported (e.g., poisoning 4.5%, self-harm 4.6%), in contrast to the distribution observed in Group A and Group B.

According to the results of step 2, i.e. the MCoD analysis of 3,796 cases included in Group B by step 1 *(Table 3)*, 842 deaths (22.2%) were classified as "deaths fitting RAIDS criteria", and 216 cases as "deaths not fitting RAIDS criteria" (i.e., people with a laboratory evidence of HIV with no AIDS-defining disease). For the 2,738 (72.1%) remaining cases in Group B, the MCoD analysis evidenced ICD-10 codes not clearly identifying AIDS; therefore they were classified as "AIDS uncertain".

In step 3, the 2,738 cases classified as "AIDS uncertain" by step 2 underwent a text analysis of the medical description reported in every death certificate. Among them, we classified 642 certificates as "deaths fitting the RAIDS criteria", that summed to the 842 sorted in step 2 made up 1,484 "deaths fitting RAIDS criteria" derived from Group B (39.1% of the initial 3,796 cases identified as PWA deaths by RCoD but not by RAIDS) *(Table 3)*.

Thus, we estimated a total of 6,014 PWA deaths in the 2006-2012 period as the sum of deaths notified to the RAIDS (i.e., Group A + Group C, N=4,530, 75.3%) and deaths retrieved from the RCoD and confirmed as PWA deaths after the in-depth analysis of ICD-10 codes (N=1,484, 24.7%, from Group B after steps 2 and 3).

DISCUSSION

The present study based on MCoD analysis found that during the 2006-2012 period, in addition to the 4,530 people notified to the RAIDS and deceased, there were 1,484 (24.7%) additional people whose death certificate included AIDS-defining causes of death, but who were never notified to the RAIDS as PWA. The disagreement between the two registries may have been due to differences in the definition of AIDS death, inaccuracy in causes of death reporting in the RCoD, or underreporting of deceased PWA in the RAIDS.

Table 2
Distribution of death certificates in the RCoD, by mention of selected causes according to the three groups of deaths identified through the record-linkage between RCoD and RAIDS. Italy, 2006-2012

ICD-10 codes	Cause of death	Group A[1]		Group B[2]		Group C[3]		Total	
		N	%	N	%	N	%	N	%
Total		**3,646**	**100**	**3,796**	**100**	**884**	**100**	**8,326**	**100**
A30-A49	Other bacterial diseases	645	17.7	572	15.1	63	7.1	1,280	15.4
B15-B19	Viral hepatitis	1,034	28.4	1,436	37.8	87	9.8	2,557	30.7
B20-B23	Human immunodeficiency virus (HIV) disease (resulting in specified diseases)	53	1.5	23	0.6	0	0.0	76	0.9
B24	Unspecified human immunodeficiency virus (HIV) disease	3,424	93.9	3,326	87.6	0	0.0	6,750	81.1
B25-B34	Other viral diseases	231	6.3	73	1.9	33	3.7	337	4.0
B35-B49	Mycoses	259	7.1	107	2.8	13	1.5	379	4.6
B50-B64	Protozoal diseases	322	8.8	115	3.0	23	2.6	460	5.5
C00-C14	Malignant neoplasms of lip, oral cavity and pharynx	25	0.7	31	0.8	9	1.0	65	0.8
C15-C26	Malignant neoplasms of digestive organs	243	6.7	467	12.3	66	7.5	776	9.3
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs	170	4.7	228	6.0	49	5.5	447	5.4
C43-C44	Melanoma and other malignant neoplasms of skin	7	0.2	27	0.7	6	0.7	40	0.5
C50	Malignant neoplasm of breast	6	0.2	30	0.8	3	0.3	39	0.5
C51-C58	Malignant neoplasms of female genital organs	52	1.4	34	0.9	16	1.8	102	1.2
C64-C68	Malignant neoplasms of urinary tract	14	0.4	35	0.9	11	1.2	60	0.7
C81-C96	Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	500	13.7	301	7.9	58	6.6	859	10.3
D80-D89	Certain disorders involving the immune mechanism	93	2.6	78	2.1	150	17.0	321	3.9
E10-E14	Diabetes mellitus	176	4.8	231	6.1	30	3.4	437	5.3
F10-F19	Mental and behavioural disorders due to psychoactive substance use	149	4.1	225	5.9	31	3.5	405	4.9
I10-I15	Hypertensive diseases	94	2.6	148	3.9	18	2.0	260	3.1
I20-I25	Ischaemic heart diseases	165	4.5	273	7.2	114	12.9	552	6.6
I30-I52	Other forms of heart disease	519	14.2	551	14.5	184	20.8	1,254	15.1
I60-I69	Cerebrovascular diseases	171	4.7	238	6.3	50	5.7	459	5.5
J10-J18	Influenza and pneumonia	644	17.7	568	15.0	73	8.3	1,285	15.4
J40-J47	Chronic lower respiratory diseases	130	3.6	134	3.5	30	3.4	294	3.5
K70-K77	Diseases of liver	1,503	41.2	2,228	58.7	208	23.5	3,939	47.3
N17-N19	Renal failure	410	11.3	473	12.5	66	7.5	949	11.4
R75	Laboratory evidence of human immunodeficiency virus (HIV)	249	6.8	495	13.0	0	0.0	744	8.9
X40-X49	Accidental poisoning by and exposure to noxious substances	3	0.1	15	0.4	40	4.5	58	0.7
V01-W19, X58-X59	Other accidents	34	0.9	37	1.0	52	5.9	123	1.5
X60-X84	Intentional self-harm	5	0.1	8	0.2	41	4.6	54	0.6

RAIDS: National AIDS Registry; RCoD: National Registry of Causes of Death.
[1]AIDS-related deaths identified by the RCoD and pertaining to people notified to the RAIDS;
[2]AIDS-related deaths for RCoD of people not notified to RAIDS;
[3]Deaths pertaining to people notified to the RAIDS but who were not considered as AIDS-related deaths by the RCoD.

The definition of AIDS death used by the RAIDS is "the death of a person diagnosed with AIDS" whereas the one used by RCoD is "a death for which AIDS was among the causes reported on the death certificate". As a consequence, it is reasonable that PWA who die for causes other than AIDS (such as external causes, non AIDS-related neoplasms, drug addiction, heart disease, chronic liver disease) are not found in the RCoD as AIDS deaths. The profile by cause of death for the 884 cases in Group C (i.e., notified to RAIDS but with no mention of AIDS in RCoD) suggests that most of them could indeed be included in this latter case, since they show higher frequencies of non AIDS-related causes compared to other groups *(Table 3)*.

Also, an inaccurate classification of causes of death may occur in this group of deaths. Some cases notified to RAIDS but not found in RCoD include sometimes causes of death such as AIDS-related neoplasms, infections generally occurring in PWA, or ill-defined diseases referring to virosis or immunodeficiencies. For instance, in this group, lymphomas and other lymphoid tumours were observed in 6.6% of cases, protozoal diseases, especially toxoplasmosis, in 2.2%, non-specific retroviruses in 3.7%, and unspecified immunodeficiency in 17%. In addition, the lack of mention of HIV or AIDS in the RCoD can be intentional to prevent relatives and acquaintances from knowing about the deceased's infection and avoid the stigma associated with HIV [20, 21].

Finally, underreporting of deceased AIDS cases to the RAIDS may explain the remaining disagreement between the two registers. The present study estimates about 25% underreporting of deceased AIDS cases to the RAIDS based on 1,484 people who had HIV/AIDS mentioned in the death certificate but that were not reported in RAIDS. This estimate is consistent with the findings from other previous studies carried out in Italy: Barchielli *et al.* [7] estimated in one region 23% of underreporting of deaths to RAIDS in the period 1987-91; in the same period a nationwide study conducted by Conti, *et al.* [14] in 1992 estimated 21.7% underreporting of AIDS deaths for RAIDS.

Some factors may be associated with underreporting of deceased PWA to the RAIDS. Firstly, delayed reporting of new AIDS diagnoses to RAIDS may hinder the linkage with death certificates because a number of AIDS case reports may have not yet been recorded in RAIDS [21]. Secondly, a concurrent first diagnosis of both HIV and AIDS may lead to only one report sent to either the RAIDS or the HIV registry (in Italy these two registries are separated), thus resulting in underreporting to the other registry. Thirdly, a missed notification of AIDS may occur when the AIDS diagnosis is performed at/or close to death; in this case, the physician could certify the death without reporting the case to RAIDS.

The present study highlights some limits of the ICD-10 in the classification of AIDS deaths, especially in distinguishing full-blown AIDS from HIV-positive status (the expression "HIV" is often used to indicate HIV-positive status, nevertheless AIDS and "HIV" are both classified in the same ICD-10 code B24). This factor can contribute in overestimating AIDS cases in RCoD when considering multiple causes. In this paper, in order to overcome these limits, a methodology for the evaluation of cases mentioning HIV/AIDS (ICD-10 codes B20-B24 or the R75) to identify full-blown AIDS and HIV-positive status only was developed.

It is worth noting that more comprehensible and precise rules for AIDS classification, in particular for the selection of underlying cause in PWA and in identifying AIDS-defining causes, have been introduced in the 2016 ICD-10 version [22].

Table 3
Classification of deaths into PWA or non-PWA deaths after the analysis of the multiple causes of death (MCoD), according to the three groups of deaths identified through the record-linkage between RCoD and RAIDS. Italy 2006-2012

	Group A[1]		Group B[2]		Group C[3]		Total
MCoD Group	N	%	N	%	N	%	N
Total	3,646	100.0	3,796	100.0	884	100.0	8,326
(a) Deaths fitting RAIDS criteria	3,646	100.0	842	22.2	-	-	4,488
(b) Deaths not fitting RAIDS criteria	-	-	216	5.7	-	-	216
(c) AIDS uncertain, manual revision:	-	-	2,738	72.1	-	-	2,738
(c.1) Deaths fitting RAIDS criteria	-	-	*642*	*16.9*	-	-	*642*
(c.2) Deaths not fitting RAIDS criteria	-	-	*2,096*	*55.2*	-	-	*2,096*
(d) Deaths in RAIDS					884	100.0	884
PWA deaths (a + c.1 + d)	3,646	100.0	1,484	39.1	884	100.0	6,014
(Row %)	(60.6)		(24.7)		(14.7)		(100.0)
Non-PWA deaths (b + c.2)	0	0.0	2,312	60.9	0	0.0	2,312
(Row %)	(0.0)		(100.0)		(0.0)		(100.0)

PWA: people with AIDS; RAIDS: National AIDS Registry; RCoD: National Registry of Causes of Death.
[1]AIDS-related deaths identified by the RCoD and pertaining to people notified to the RAIDS;
[2]AIDS-related deaths for RCoD of people not notified to RAIDS;
[3]Deaths pertaining to people notified to the RAIDS but who were not considered as AIDS-related deaths by the RCoD.

The strengths of the study are the following: 1) the national coverage of the two population-based registries (RAIDS and RCoD), which allowed not to miss any notified case of AIDS or any death occurred in Italy; 2) the high sensitivity of the record-linkage procedure [18], which allowed to link also people reported with spelling errors in names/surnames or errors in the dates of birth; and 3) the use of multiple causes of death, which allowed the study of all the conditions mentioned in the death certificates, rather than a single cause identified as responsible for the death. The proposed methodology that links the ICD-10 MCoD with the diagnoses from RAIDS provides a generalized basis for further studies of the same type.

In summary, by integrating the two nationwide registries, a total of 6,014 PWA deaths were estimated for the 2006-2012 period, of which 14.7% were not present in the RCoD, whereas 24.7% were of individuals not included in the RAIDS. Thus, the integration of different national data sources allowed a more comprehensive estimate of the impact of AIDS on mortality. The study findings stress the urgent need, in Italy, for a combined HIV/AIDS surveillance and a more accurate ICD coding for HIV and AIDS-defining conditions.

Authors' contribution

BS, LF and DS designed the study; FG, EG, and BS drafted the manuscript; FG, EG, and MP analyzed data; VR, and LP managed the National AIDS Registry data used in this study; EG, FG, and MP managed data of the National Register of Causes of Death used in this study; AZ and MT performed the record-linkage and managed the final database used in this study. All Authors contributed to data interpretation and revised the manuscript for intellectual content.

Conflict of interest statement

All Authors declare that they have no conflicts of interest.

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Book Reviews, Notes and Comments

Edited by
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COVID-19: scienza e immaginazione per il mondo che verrà
Filippo Belardelli
2022; Kindle edition.
98 p.
[*COVID-19: Science and imagination for the world to come*]

Is it possible to report with simplicity and clarity the biological features and the disastrous consequences of a pandemic whose spread has created the tragic and surreal scenario in which we have been living in the last two years? After reading this little book of less than a hundred pages, the answer comes with a definitive yes.

The author, Filippo Belardelli, is a trustworthy scientist who likes to exploit an unassuming writing style to tackle the complex and tragic problems of this pandemic. First, the book accounts the fundamental discoveries in microbiology, with the explanation of what viruses and bacteria are and the meaning of the terms whereby the infectious disease spread is classified. Within this framework, putting COVID-19 into perspective with the great pandemics of the past, the current one loses its uniqueness as well as most of its anxiogenic potential.

Having transformed the pandemic into a natural event, the book reports how slow the World has been in perceiving its dramatic potential: the hesitation of the Chinese authorities first, then the contradictory behavior of the WHO in the first months, and last the unpreparedness of local authorities in facing such an unexpected event. Somehow our society was erroneously persuaded that human progress had made pandemics a thing of the past.

Then, with its clear and calm gaze, the book describes synthetically the features of the SARS-CoV-2, the clinical signs of the human disease, and the struggle between different mechanisms of the immune system and the invading virus. Here the Author cannot forget that he is one of the most authoritative researchers among those who have studied the mechanisms of innate immunity and the biology of the interferon system. Interferons are the key molecules that play a fundamental role in controlling the SARS-CoV-2 infection. After contagion, innate immunity mechanisms and a prompt interferons release are almost always able to control the viral invasion and block the spread of the infection. It is therefore obvious that the invading SARS-CoV-2 seeks and, in some cases, manages to sabotage this fundamental protection mechanism. The breadth of the infection is directly dependent on how effective is the virus's ability to interfere with the production of interferons. Furthermore, even marginal deficiencies in the ability to produce interferons of the infected person can give rise to serious COVID-19. The need for large clinical trials to validate the new treatments and the mechanism by which the newly arrived anti-viral drugs are working is then progressively illustrated. Then, a brief description of the origin of vaccination and the importance of vaccines introduces an accurate presentation of the different technological platforms on which COVID-19 vaccines have been developed. Lastly, thanks to the speed of "online" publications, the book already provides an accurate assessment of the current pandemic situation where the vaccines are confronted with the highly infectious and antigenically mutated omicron variant.

At this point, the narrative of the book changes register, passing from the description and explanation of the events connected to COVID-19 to their ethical evaluation. When confronted with the pandemic, the socioeconomic differences between rich and poor countries of the World take on cruder aspects that are ethically more difficult to accept. The much-proclaimed goal of a "Universal Health Coverage", that is, that all individuals on Earth have the right to access essential prevention and treatment services, is almost countered by the even more serious issue of hunger - the most evident consequence of the above-mentioned inequalities. Only in the next few years, it will be possible to assess how much COVID-19 has impacted the health, hunger, and food insecurity of millions of people in Asia, Africa, Latin America, and the Caribbean.

However, as highlighted already by the book subtitle (*Science and imagination for the world to come*), imagination is a fundamental aspect of scientific research. Thanks to imagination it is possible to make innovative hypotheses. Thus, in the last chapters of the book, the "realistic dreams" of the Author lead us to imagine how new methodological approaches, including personalized medicine and the exploitation of the off-target efficacy of vaccines, could lead to completely new therapeutic scenarios. Keeping with this vision, the book ends with a discussion of nine critical issues: nine lessons for change that the pandemic has taught the author as a scientist. Suggestions that spur towards society no longer based only on the logic of profit and competition between governments, international organizations, and pharmaceutical companies. The dream is about a society aimed at structurally solving the problems of poverty, inequality, and the environment. A society in which

scientific research should be increasingly oriented towards the health of the citizen and the development of knowledge and education. To build this new social scenario a major boost of imagination and perseverance is required. Thus, the last dream is that the required great "wing stroke" could be achieved by the younger generation. After having better focused some of the many issues related to the pandemic guided by the calm and clear narration of this book, the reader cannot but hope that the author may really be right.

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Publications from International Organizations on Public Health

Edited by
Annarita Barbaro

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS (FAO)

Assessment of agricultural plastics and their sustainability: A call for action. Rome: Food and Agriculture Organization of the United Nations 2021; 160 p. ISBN 978-92-5-135402-5. Over the last 70 years, the use of plastics in agri-food systems and food value chains has become pervasive. Low-cost and adaptable plastic products have crept into every part of the food systems – from fishing gear and tree guards to greenhouses. While they can increase productivity and efficiency in all agricultural sectors and help minimize food loss and waste, plastics are a major source of contamination. This report presents the results of a study on agricultural plastic products used globally in a range of different value chains. The investigation covered all sectors under FAO's mandate: crop production, livestock, aquaculture, fisheries and forestry, including subsequent processing and distribution and assessed the types and quantities of plastic products, their benefits and trade-offs. Sustainable alternative products or practices were identified for products assessed as having high potential to cause harm to human and ecosystem health or having poor end-of-life management. This report is based on data derived from peer-reviewed scientific papers, governmental and non-governmental organization's research reports, as well as from industry experts, including relevant trade bodies. Its recommendations were verified during extensive consultation and review with FAO and external experts. This report serves as a loud call for coordinated and decisive action to facilitate good management practices and curb the disastrous use of plastics across the agricultural sectors.

Climate change, biodiversity and nutrition nexus. Evidence and emerging policy and programming opportunities. Rome: Food and Agriculture Organization of the United Nations and World Health Organization 2021; 74 p. ISBN: 978-92-5-134920-5. Humankind is facing a perfect storm of climate change, biodiversity loss, and multiple forms of malnutrition (stunting, wasting, micronutrient deficiencies, and obesity) coexisting in the same country, community, household, and even individual. Challenges from each of these areas are well known and recognized, but what seems to be missing in many development and policy circles is a recognition that food is at the centre of all three of these issues. This working paper highlights the linkages between climate change, biodiversity loss and malnutrition, using an approach that puts food at the centre as the single strongest lever to optimize human health and environmental sustainability. This paper identifies entry points within agri-food systems to improve biodiversity and diets, two levers that can be used to enhance nutrition and optimize environmental sustainability while ensuring social equity, especially of the most vulnerable people. Based on these findings, the study makes a number of recommendations for concrete actions by key stakeholders – governments, academia, civil society, private sector, and development partners –to build resilient, inclusive, and sustainable agri-food systems.

Microbiological hazards in spices and dried aromatic herbs. Meeting report. Microbiological Risk Assessment Series No. 27. Rome: Food and Agriculture Organization of the United Nations and World Health Organization 2022; 63 p. FAO ISBN: 978-92-5-135792-7, WHO ISBN 978-92-4-004518-7 (electronic version), WHO ISBN 978-92-4-004519-4 (print version). Spices and dried aromatic herbs impart flavour when added to food, and they may include many parts of the plant, including berries, flowers, leaves, roots and seeds. A number of different pathogens have been found in spices on the market, especially Salmonella spp., B. cereus and C. perfringens. There have also been several disease outbreaks associated with spices and dried aromatic herbs. This Report is the result of the FAO/WHO Joint Expert Meeting on Microbiological Risk Assessment (JEMRA) which considered the global evidence on the burden of illness, prevalence and concentration of selected microbial hazards with respect to various spices and dried aromatic herbs, and interventions aimed at controlling them in these commodities.

INTERNATIONAL SCIENCE COUNCIL (ISC)

Global Risks Perception Report 2021. Paris: Future Earth, Sustainability in the Digital Age, and International Science Council 2021; 27 p. There is increasing recognition across multiple sectors of society that the global risks we face are increasingly complex, uncertain, and systemic. The Global Risks Perceptions Initiative strives to capture and analyse the perceptions on global risk of different scientific communities with the aim of sparking and informing a pluralistic dialogue around risks that draws on a diversity of experience and knowledge. This report shares the findings of the second iteration of the Global Risks Scientists' Perceptions survey. In repeating the exercise first conducted in 2019, the project team recognizes the importance of revisiting risk perceptions over time. In particular, given the manifestations of global risks which have taken

place since 2019, the time is ripe to reassess scientists' perceptions of global risks as a critical contribution to dialogues about potential solutions.

Drury, L. 2022. **The normalization of preprints.** Paris: International Science Council 2022; 14 p. The last few years have seen an explosive growth in the use of preprints and the associated preprint servers by large sections of the scientific community. This ISC Occasional paper addresses the history of the preprint, its advantages and potential disadvantages, and concludes with some recommendations for how the growing acceptance of preprint posting should be handled within academia and the changes in cultural norms (in other words its normalization) that this entails. This article is part of a series of publications from the International Science Council as part of the Future of Scientific Publishing project, exploring the role of publishing in the scientific enterprise, and asking how the scholarly publishing system can maximize benefit to global science and to wider audiences for scientific research.

UNITED NATIONS ENVIRONMENTAL PROGRAMME (UNEP)

Reducing Consumer Food Waste Using Green and Digital Technologies. Copenhagen and Nairobi: United Nations Environmental Programme 2021; 96 p. ISBN 978-87-93458-06-2. The world is facing a food-waste crisis. It is estimated that 931 million tonnes of food were wasted by households, retailers, restaurants and other food services in 2019. Around 61% of this waste occurs within households. Reducing food waste offers multiple benefits for people and the planet, contributing to improving food security, cutting pollution, saving money, reducing the pressures on nature and climate, and creating opportunities for economy and society. This report provides an overview of the causes of consumer food waste and the opportunities for reducing it through different means: behavioural change, technological solutions, and public and private initiatives to mitigate the problem. This study aims to improve understanding of how green and digital technologies could be used to reduce consumer food waste and what could be done to further unlock this potential. By combining global research cutting across multiple disciplines with city case studies, it aims to provide a comprehensive and integrated approach to support countries and cities in combating food waste and in "Building Back Better" a more sustainable economy.

Guidance on Policy and Legislation for Integrated Waste Management during a Pandemic. Nairobi: United Nations Environmental Programme 2022; 93 p. ISBN 978-92-807-3925-1. The Guidance on Policy and Legislation for Integrated Waste Management during a Pandemic provides support to countries in their efforts to develop or revise their legislation and policies to be better prepared for and respond to health and environment risks associated with waste management in case of a future pandemic. The Guidance presents the elements of framework measures that could be adopted by countries (or used as a basis for revision of existing structures) to enhance preparedness to deal with waste management challenges in future pandemic scenarios. Rather than recommending a one-size-fits all approach, the guidance offers also a checklist with a menu of options for countries to consider for inclusion in pandemic waste legislation and policy guidelines, recognizing the varying context for application in different countries.

EUROPEAN FOOD SAFETY AUTHORITY (EFSA)

European Food Safety Authority (EFSA), Luis Carrasco Cabrera and Paula Medina Pastor. **The 2020 European Union report on pesticide residues in food.** EFSA Journal 2022; 20(3): 7215, 57 p. Under European Union legislation (Article 32, Regulation (EC) No 396/2005), the EFSA provides an annual report which examines pesticide residue levels in foods on the European market. This report is based on data from the official national control activities carried out by EU Member States, Iceland and Norway and includes a subset of data from the EU-coordinated control programme, which uses a randomised sampling strategy. For 2020, 94.9% of the overall 88,141 samples analysed fell below the maximum residue level (MRL), 5.1% exceeded this level, of which 3.6% were non-compliant, i.e. samples exceeding the MRL after taking the measurement uncertainty into account. For the subset of 12,077 samples analysed as part of the EU-coordinated multiannual control programme, 1.7% exceeded the MRL and 0.9% were non-compliant. To assess acute and chronic risk to consumer health, dietary exposure to pesticide residues was estimated and compared with health-based guidance values. Dietary exposure to pesticides for which health-based guidance values were available is unlikely to pose a risk to EU consumer health. In the rare cases where dietary exposure for a specific pesticide/product combination was calculated to exceed the health-based guidance value, and for those pesticides for which no health-based guidance value could be established, the competent authorities took appropriate and proportionate corrective measures to address potential risks to consumers. Recommendations are proposed to increase the effectiveness of European control systems, thereby continuing to ensure a high level of consumer protection throughout the EU.

EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control). **The European Union Summary Report on Antimicrobial Resistance in zoonotic and indicator bacteria from humans, animals and food in 2019-2020.** EFSA Journal 2022; 20(3):7209, 197 p. Data on antimicrobial resistance (AMR) in zoonotic and indicator bacteria from humans, animals and food are collected annually by the EU Member States (MSs), jointly analysed by the EFSA and the ECDC

and reported in a yearly EU Summary Report. The annual monitoring of AMR in animals and food within the EU is targeted at selected animal species corresponding to the reporting year. The 2020 monitoring specifically focussed on poultry and their derived carcases/meat, while the monitoring performed in 2019 specifically focused on fattening pigs and calves under 1 year of age, as well as their derived carcases/meat. This report provides an overview of the main findings of the 2019-2020 harmonised AMR monitoring in the main food-producing animal populations monitored, in carcase/meat samples and in humans. Where available, monitoring data obtained from pigs, calves, broilers, laying hens and turkeys, as well as from carcase/meat samples and humans were combined and compared at the EU level, with particular emphasis on multidrug resistance, complete susceptibility and combined resistance patterns to critically important antimicrobials, as well as Salmonella and E. coli isolates possessing ESBL-/AmpC-/carbapenemase phenotypes. The key outcome indicators for AMR in food-producing animals, such as complete susceptibility to the harmonised panel of antimicrobials in E. coli and the prevalence of ESBL-/AmpC-producing E. coli have been specifically analysed over the period 2014–2020.

WORLD HEALTH ORGANIZATION (WHO)

Report of the technical consultation on measuring healthy diets: concepts, methods and metrics. Geneva: World Health Organization 2021; 73 p. ISBN 978-92-4-004027-4 (electronic version) ISBN 978-92-4-004028-1 (print version). Food systems and diets are changing everywhere and monitoring the healthfulness of diets at global and national levels is becoming increasingly important. Better measurement and monitoring are needed to support governments in establishing policies and programmes to promote healthy diets and assess the effectiveness of these actions. There are critical gaps in global, regional, and national monitoring of characteristics and trends in diets. Currently, there are no harmonized metrics for tracking how diets around the world are evolving and the impact of these changes on human health and the environment. In order to promote increased communication, coordination, and collaboration to accelerate progress toward identifying or developing a parsimonious set of metrics for global monitoring of healthy diets, a technical consultation was organized by the WHO-UNICEF Technical Expert Advisory Group on Nutrition Monitoring (TEAM) and the Food and Agriculture Organization of the United Nations (FAO), with technical and logistical support from USAID Advancing Nutrition. Eighty-five expert participants representing a wide range of institutions, geographic areas, and roles in the data value chain, engaged in the consultation from 18–20 May 2021. This report provides a summary of the consultation presentations, working group contributions, discussions and recommendations. The report highlights three overarching topics addressed during the consultation: overview of global diet monitoring and prioritization of metric criteria and characteristics; methods, tools and metrics to measure diets; and definition and prioritization of next steps for identifying a global metric for monitoring of healthy diets.

WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition: use of mRNA tests for human papillomavirus (HPV). Geneva: World Health Organization 2021; 63 p. ISBN 978-92-4-004043-4 (electronic version) ISBN 978-92-4-004044-1 (print version). This WHO guideline is designed to help countries make faster progress, more equitably, on the screening and treatment of cervical cancer. This document includes guidance on an important additional option for cervical screening, the use of mRNA (messenger RNA) HPV testing. This gives countries additional options when considering which type of HPV nucleic acid amplification tests (NAAT) to use in their screening programs.

Health effects of the use of non-sugar sweeteners: a systematic review and meta-analysis. Geneva: World Health Organization 2022; 210 p. ISBN 978-92-4-004642-9 (electronic version) ISBN 978-92-4-004643-6 (print version). Non-sugar sweeteners have been developed as an alternative to sugars and are widely used both as an ingredient in pre-packaged foods and beverages and added to food and beverages directly by the consumer. Individual non-sugar sweeteners undergo toxicological assessment by the by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and other authoritative bodies to establish safe levels of intake (i.e. acceptable daily intake or ADI). While results of randomized controlled trials have generally suggested non-sugar sweeteners may have little impact on glucose metabolism and result in lower body weight when coupled with energy restriction in the short-term, there is no clear consensus on whether non-sugar sweeteners are effective for long-term weight loss or maintenance, or if they are linked to other long-term health effects at intakes within the ADI. This systematic review brings together the most current scientific evidence on health effects of non-sugar sweetener use.

Guidelines for drinking-water quality: Fourth edition incorporating the first and second addenda. Geneva: World Health Organization 2022; 614 p. ISBN 978-92-4-004506-4 (electronic version) ISBN 978-92-4-004507-1 (print version). The fourth edition of the World Health Organization's Guidelines for drinking-water quality (GDWQ) builds on over 60 years of guidance by WHO on drinking-water quality, which has formed an authoritative basis for the setting of national regulations and standards for water safety in support of public health. It is the product of significant revisions to clarify and elaborate on ways of implementing its recommendations of contextual hazard identification and risk management, through the establishment of health-based targets, catchment-to-consumer water safety plans and independent surveillance.

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Articles in journal

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Books and chapters in a book

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

Van Weely S, Leufkens HGM. Background paper: orphan diseases. In: Kaplan W, Laing R (Eds). Priority medicines for Europe and the world – a public health approach to innovation. Geneva: World Health Organization; 2004.

Proceedings

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

Technical reports

Della Seta M, Di Benedetto C, Leone L, Pizzarelli S, Siegmund U. ETHICSWEB technical guides. Manual for the creation of standards and guidelines for sharing information about knowledge organization systems on ethics and science. Roma: Istituto Superiore di Sanità; 2011. (Rapporti ISTISAN, 11/32).

Legislation

Italia. Decreto legislativo 29 ottobre, n. 419. Riordinamento del sistema degli enti pubblici nazionali, a norma degli articoli 11 e 14 della legge 15 marzo 1997, n. 59. Gazzetta Ufficiale – Serie Generale n. 268, 15 ottobre 1999.

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

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