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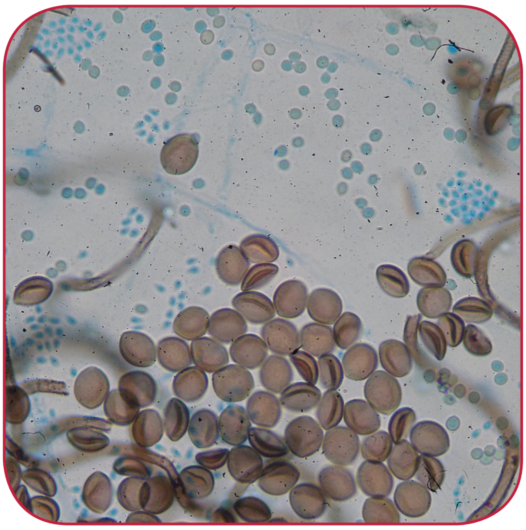

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EDITORIAL

From the *impatient* doctor to the *patient*-doctor

Oreste Tolone

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Over the last century, we have witnessed the transformation of the *paternalistic* doctor-patient relational model – which had characterized the existence of medicine in its first two millennia of activity – into a *shared* model. A model, that is centred on the patient (*patient centred medicine*), and no longer on the disease (*disease centred medicine*) [1-4] – as Ludolf Krehl and Viktor von Weizsäcker had already argued at the beginning of the 20th century [5, 6]; a model based on the recognition, to the actors, of equal powers and responsibilities. The shared model, which inaugurates a form of new therapeutic alliance between doctor and patient, risks, however, to assume, within a health apparatus that moves in the triangulation economy/technology/politics [7], the appearance of a pact, of a contract, which hides a model of defensive medicine (*information* model). The practices of informed consent [8, 9], if on the one hand have represented a way to make the patient aware and responsible for therapeutic choices, on the other hand they channel the doctor-patient relationship through the tracks of the formal, legal and contractual relationship. An all-out information hides, in fact, an *autonomist* model [10], in which it is fundamental to inform, not to communicate. This transfer of communication procedures that are valid among strangers, to the intimate and trustworthy dimension [11], determines a passage not so much to good medicine, but to safe medicine. Distrust, however, reigns in it.

The increase in disputes, *malpractices* and attacks against doctors (according to the Federation of Associations of Doctors, 1420 only in 2017 in Italy) [12] is a sign of an epoch-making crisis: the end of a hierarchical, paternalistic relationship and the need for a new *hierarchy to be negotiated*. This reconsideration of roles and functions puts both the doctor and the patient in crisis, both of whom are now forced to reconsider their own and other people's roles. The loss of an exclusive top position on the part of the doctor, and the need for a continuous (sometimes exhausting) coming to terms with the patient, can induce the doctor to retreat in the name of scientific knowledge and of objective knowledge. This attempt to recover the summit, bypassing the relational need of the therapeutic alliance, feeds the figure of an "impatient doctor", not very inclined to negotiate. On the other hand, the sick person appears to be increasingly freed from a privileged relationship; in particular, the growing specialization and technologization of medicine, the affirmation of a business model of care, a nomadism which makes the patient itinerant, in search of the best services where they are offered, the interference of the *mass media* (which heavily affects the communication between doctor and patient) [13], interrupt the bond of trust. The "patient-doctor", who knows, who undermines the authority of the doctor and of medicine, who proposes the various therapeutic options, in fact overturns the traditional paternalistic model into an extreme autonomous model.

However, this overturning seems to duplicate rather than undo the error of perspective of paternalism; it is rebutted to subject with subject, to preeminence with preeminence, to hegemony with hegemony. With the difference that, in an age of "moral foreigners" [14] the primacy seems to belong to the freedom (of the patient), rather than to the truth.

This difficulty in re-establishing a new balance between the protagonists has its philosophical roots in modernity and in the subject/object separation it entails. Both these options (impatient doctor and patient-doctor), in fact, are based on a hard, drastic reading of modern subjectivity. The Evidence-Based Medicine revolution has as its premise the Cartesian dualism between *res extensa* and *res cogitans*, the experimental method, specialization, a certain form of reductionism, the distance from one's own research object, which in medicine becomes "therapeutic distance". This brings with it, in addition to immeasurable benefits, the risk of a "removal of the patient" [15, 16].

This is even more evident with the advent of technology, that is, with the affirmation of the indissoluble union between science and technology. As Hans Jonas clearly pointed out in his *Technique, Medicine and Ethics*, the exponential development of technology over the last century has brought about a qualitative leap: once something becomes technically possible, feasible, it is inevitable that it will be done [17]. Action, in other words, is no longer dictated by the object in front of us, but by action itself as "feasible". However, to the doctor «the purpose is given by the internal purpose of its object, the "raw material" is already the last and the whole, that is the patient, and the doctor must identify himself with the purpose proper to the latter» [18]. This submission of the object (the patient) to the technician (the doctor) has considerable repercussions on the medicine: the patient and the anthropological dimension of the relationship and of the care are lost, or completely overshadowed. This, however, means forgetting the deeply dialogical dimension of medicine [19]. In fact, it is born keeping together the need for healing with the need for care, the need for a therapeutic distance with that of a humanitarian *ethos* [20, 21]. The *seduction of the technique*, instead, has traced a deep furrow, whose effects are tangible in the changed relationship between doctor and patient. On the one hand, there is the need to recover a relationship of trust with the patient, of esteem, which, however, is mainly established by virtue of taking care, of taking charge of the sick man, even and in particular in chronic diseases, in unfortunate events; on the other hand, the union between science and technology feeds the opposite tendency, to remove from the priority tasks of the doctor precisely these functions [22]. Usually delegated to third parties.

This short circuit risks stiffening the doctor/patient relationship in a relationship between self-sufficient subjects, who claim their rights (to know and to decide). On the contrary, medical anthropology, medical humanities, narrative medicine, each from its own specific perspective, move precisely in the attempt to recover the *dialogical* dimension of medicine. This does not mean limiting the rights of the doctor by claiming those of the patient (which is closer to the war of position, to the “role play”), but promoting a *circular hierarchy*, in which the recovery of a «logic of care» by the doctor plays an essential part. A medicine that cures, that does not renounce to being medical art [23], does not put aside the clothes of science, but guarantees, even in an age of hyper-subjects, an open confrontation between doctor and patient.

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Commentary

West Nile virus infection in Europe: need for an integration of occupational health practice and public health activities

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Abstract
In these days, the West Nile virus (WNV), which is the most widespread arthropod-borne virus infection in the world, is an emerging issue in Europe, wherein 2018, partial figures (until 25 October) showed a number of WNV infection cases more than doubled in comparison with previous five years. This mosquito-transmitted disease is surely a challenge for policymakers, but it is an occupational hazard for outdoor workers, as well. Occupational medicine is a public health discipline based on the principles of epidemiology. Therefore, we argue that addressing the WNV hazard may be an opportunity for integrating the occupational health practice with public health activities to boost their respective preventive strategies.

Key words
- communicable diseases control
- epidemiology
- occupational medicine
- public health
- risk assessment
- West Nile virus

The West Nile Virus (WNV) is the most widespread arthropod-borne virus infection in the world [1]. This mosquito-transmitted microrganism is amplified in birds; mammals (human and horses) are just only dead-end hosts [2]. In recent decades, this disease, which prevails in tropical regions of world, is becoming an emerging issue with outbreaks in a certain number of European countries including Italy, Hungary, Romania and Greece [2]. Data from European Centre for Disease Prevention and Control (ECDC) reported 220 human cases of WNV in 2014, 315 in 2015, 225 in 2016 and 204 in 2017 [3].

However, it should be noted that 2018 has been an unusual WNV transmission season in Europe in general and in Italy specifically. Indeed, as of 25 October 2018, EU Member States have reported 1460 human cases, with Italy (n = 550) to the top of the figures, followed by Greece (n = 307), Romania (n = 276), Hungary (n = 212), Croatia (n = 53), France (n = 24), Austria (n = 19), Bulgaria (n = 14), Slovenia (n = 3) and the Czech Republic (n = 2) [4]. Cases are both imported and indigenous and this is depicted as an emerging public health threat. To date, 170 deaths due to WNV infection have been reported in Italy (n = 44), Greece (n = 42), Romania (n = 42), Serbia (n = 35), Kosovo (n = 3), Bulgaria (n = 2), the Czech Republic (n = 1) and Hungary (n = 1).

Transmission of WNV to humans is mainly through the bite of an affected mosquito, which in Europe is the common house *Culex pipiens* mosquito [1] and the reoccurrence of WNV infection in the same places over the years could be a sign of the endemic nature of the disease [5]. In addition, transmission is also possible through infected blood and blood components, tissues and cells, and organ transplants. Cases of vertical transplacental mother-to-child transmission and breastfeeding have been also reported [6].

In occupational settings, the transmission of this infection has been documented in entomologists collecting mosquitoes for surveillance [7]; in a veterinary student after performing an autopsy on a Welsh pony and in laboratory-workers after accidental percutaneous inoculation [8, 9].

Paradoxically, a possible matter of concern is due to the fact that infected humans are generally asymptomatic or are reporting, in 15-20% of the cases, flu-like

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symptoms. Consequently, the disease is often unrecognized. According to the US CDC, only less than 1% of those infected develop a serious, sometimes fatal, neurologic illness [9], and mortality is generally associated with older age groups, pregnancy, immunodeficiency or co-morbidities [6]. The occurrence of epidemics is therefore often reconstructed from these sentinel cases. However, due to the low prevalence of cases that are being diagnosed and the outdoor widespread dissemination of the common mosquito, it is also likely that the true prevalence rate of WNV infection may be underestimated in both general and occupational population.

Outdoor workers may be exposed to many types of biological hazards including vector-borne diseases, venomous wildlife and insects, and poisonous plants [9]. Exposure to vector-borne diseases depends on type of work, geographic region, season, and duration of time workers are outside [10]. Employers must be aware of the risk and must assess this type of biological hazard that may be dangerous to many categories of workers such as farmers, foresters, landscapers, groundskeepers, gardeners, painters, roofers, pavers, construction workers, and so on.

Mosquito-transmitted diseases like WNV and others, therefore, should not be only considered as a hazard for general population and an issue of public health, but they should be viewed as a specific occupational risk to be addressed in the framework of occupational and health safety legislation, as well. Employers should specifically evaluate this biological hazard, especially in those regions of European countries where epidemiological data provided by public health surveillance systems have been showing an increasing trend of WNV infection cases.

The risk assessment should focus on the type of workplace, season, time of the day and geographical zone where employee do their job. Data obtained by the surveillance systems of public health should be used as well. Employers must provide outdoor employees with specific preventive measures such as protective clothing, mosquito repellents and permethrin-containing products to apply on clothing, as well as specific training for workers and interventions at worksites, the so-called primary measures, to eliminate standing water and carry out disinfestations when needed [10]. Workers' education focused on prevention of bites of mosquitoes and insects could be a workplace measure of prevention. These measures should be firstly individuated, planned and managed within the framework of the occupational risk assessment process.

Finally, medical health surveillance should be conducted, with pre-assignment and periodical medical examinations, for the early detection of effects on health of workers exposed to this biological hazard. Occupational health surveillance is a secondary prevention measure required by national law whenever workers are liable to be exposed to occupational risks that primary measures cannot eliminate [11]. In this case, it should focus on potential individual restrictions in case of older, pregnant, or immunodeficient workers, especially when they are affected by comorbidities. However, the aim of occupational health surveillance is not only to check the worker's fitness to work, but also to evaluate and to provide the entire evaluation process with epidemiological information, which may be useful for risk prevention [11].

In 2013, the ECDC has released a technical report containing the "WNV risk assessment tool" that uses information gathered through the surveillance mechanisms set up by public health stakeholders to ascertain the level of risk for human transmission of WNV within an area. This instrument categorizes risk areas, defines risk levels, and provides options for enhanced surveillance and highlight additional public health actions to be considered. This paper defines criteria for diagnosing the human case of disease and provides public health actions and interventions that feed into WNV risk assessment [5]. This risk assessment tool, therefore, could be very useful for employers to be used for the risk assessment process, within the framework of occupational health and safety (OHS), for outdoor workers in endemic areas.

The epidemiology of WNV in Europe is complex because clusters of cases and small outbreaks occurred in different Regions and different strains of both WNV lineage 1 and lineage 2 were identified, even co-circulating in the same area [12, 13].

WNV lineage 1 has been responsible for repeated disease outbreaks in the countries of the Mediterranean basin over the past 50 years. WNV lineage 2, the first WNV lineage to be isolated, was believed to be restricted to sub-Saharan Africa causing a relatively mild fever in humans. However, in 2004, it was associated with a case of encephalitis in Hungary, and in subsequent years, the virus appeared to spread into Austria, Greece (2010), Italy (2011) [14] and Romania (2015) [15]. The new scenario is the spread of lineage 2 in European countries where lineage 1 strain is still circulating creating favourable conditions for genetic reassortment and emergence of new strains [16].

In addition, climatic and environmental conditions may influence the seasonality of disease transmission due to increased number of mosquito replication cycles (consequently also a higher rate of overwintering virus-carrying mosquitoes) and increased virus transmission rates [16]. This may explain why in Italy, results from the integrated (veterinary and human) surveillance system, during the period 2008-2015, revealed that 91% (157/173) of the WNV cases detected occurred in three regions (Emilia-Romagna, Lombardy and Veneto) in the Po river plain area, with the Emilia-Romagna and Veneto regions reporting the highest incidence (1.60 and 1.46/1000 000 respectively) [17]. Indeed, some climatic factors such as temperature, precipitation, relative humidity and winds are drivers in WNV epidemiology. Climate change is favouring the spreading of WNV infection in certain geographical zones [18] and its role in the European area remain to be elucidated.

Currently, a recent (2018) national plan for the detection and control of West Nile and Usutu viruses, that integrate human and veterinary (animals and vectors) surveillance, is issued and revised annually by the Italian National Institute of Health, under the supervision of the Ministry of Health, according to the observed epidemiological changes [17, 19].

This surveillance system that has been set up by epidemiologists, should be taken into account by occupational health stakeholders. Occupational physicians could usefully contribute to this national system, actively seeking out symptoms in exposed workers and promptly reporting suspected cases.

Addressing timely the mosquito-transmitted diseases is surely a priority for the general population and, therefore, has to be considered as a challenge for policy makers but, at same time, it constitutes an opportunity for occupational health stakeholders, as protecting workers' health may strengthen strategies carried out by public health stakeholders. Addressing the WNV hazard may be an opportunity for integrating the occupational health practice with public health activities to boost their respective preventive strategies. Reconnecting public health and occupational health and safety may truly improve the health of both general public and working populations [20, 21].

Conflict of interest statement

The authors have no potential conflict of interests and received no financial support.

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Commentary

Organ donor families should be free to meet their recipients under controlled conditions if both sides wish, Italian National Committee for Bioethics says

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Abstract

On 27 September 2018 the Italian Committee for Bioethics (ICB) adopted an opinion regarding the possibility of an exception to the anonymity obligation when both parties agree and have signed an appropriate informed consent form. According to the IBC any contact between the donor's family and recipient must be managed by a third-party body pertaining to the National Health Service, established to guarantee strict control over the expression of consent in order to avoid any risk of inappropriate behaviour. The paper traces how Reg and Maggie Green, on holiday from California, donated the organs of their seven-year old son, Nicholas, to seven Italians after he had been shot in a carjacking on the Salerno-Reggio Calabria highway in 1994. Reluctant as a foreigner to propose a change in Italian law that effectively prevents the two sides from contacting each other, Reg Green held back for 22 years until, at age 87, he began a public campaign to voice his concern that the law was hurting transplant families rather than helping them.

Key words
- ethics
- healthcare legislation
- organ donation
- organ transplantation

INTRODUCTION

Article 18 of Italian Law no. 91 of 1 April 1999 [1], establishes the "Duties for personnel working on retrieval and transplant activities". Subsection 2 of this article states that "Sanitary and administrative personnel working on retrieval and transplant activities should guarantee the anonymity of the data of the donor and of the recipient". Current regulations in Italy therefore require absolute anonymity between the family of the deceased organ donor and the recipient/s.

The National Transplant Centre (Centro Nazionale Trapianti) of the Italian National Institute of Health (Istituto Superiore di Sanità) asked the Italian Committee for Bioethics (ICB, Comitato Nazionale per la Bioetica) for its opinion regarding the possibility of an exception to the anonymity obligation "when both parties agree and have signed an appropriate informed consent form".

On 27 September 2018, the ICB adopted the opinion "Anonymity of organ donors and receivers (requested by the Italian National Transplant Centre)" [2].

The ICB analyses the various arguments in favour of anonymity and identifiability, making a distinction between before and after the transplant. The ICB concludes that identification could be possible if both parties express an intention to come into contact with one another.

According to the ICB, anonymity is essential during the initial stage of organ donation in order to guarantee equality, in order to observe stringent clinical criteria and priority on the list and to avoid possible organ trafficking. However, the ICB believes that, after a suitable period, it is admissible from an ethical point of view and following an explicit declaration of consent, to allow each party to be informed of the other's identity, in order to allow them to make contact with one another and meet.

This calls for a new law that caters for this possibility, whilst guaranteeing the observance of the guiding principles of organ transplantation (privacy, gratuity, justice, solidarity and benefits). According to the ICB, any contact between the donor's family and recipient must be managed by a third-party body pertaining to the National Health Service, established to guarantee

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strict control over the expression of consent in order to avoid any risk of inappropriate behaviour. The ICB suggests that the Italian National Institute for Health draw up a template consent form valid for the entire country. The information that the two parties must be given most importantly includes the fact that being informed of the donor's identity is not a right, but a possibility that is ethically justified at certain conditions that must be stringently established and confirmed.

In the following paragraphs Mr. Reg Green, the father of Nicholas, describes his experience and his engagement. The history that sprang from Nicholas' tragedy is enlightening on the possible impact of the new approach suggested by the ICB.

A LONE CAMPAIGN BEARS FRUIT

I am the father of Nicholas Green, a seven-year old American boy who was shot during an attempted carjacking on the Salerno-Reggio Calabria highway in 1994 and whose organs and corneas were donated to seven very sick people, four of them teenagers, two of them on the point of death.

Nicholas was a magical little creature who looked for the best in everyone and nothing has been quite the same since he died. But my wife, Maggie, and I have never had a moment's doubt about our decision and, if we had had any doubts, they would have been banished by the first sight of his recipients four months after the transplants at a ceremony arranged by the Bonino-Pulejo Foundation in Messina. It was one of the most fulfilling experiences of our lives.

When the recipients came in the hall as a group, with just their immediate families, it was like a small army – some smiling, some tearful, some ebullient, some shy. Did one little body do all this? I asked myself. For the first time I fully understood the power of transplantation.

Only a short time before, the healthy bodies we now saw had been gaunt, frightened shadows, shuffling like old men and women, in pain, in and out of hospitals, and never knowing when they went to bed at night whether they would wake up in the morning.

To pick just one of them, Maria Pia Pedalà, 19 years old, who was in her final coma from liver disease on the day Nicholas died. Her doctor told us, "We had given up on her." But instead of dying, she woke up with a new liver, quickly bounced back to good health, married her childhood sweetheart and four years after the transplant had a baby – a boy whom she named Nicholas. After all this time her devotion to our Nicholas still brings tears to my eyes. Maria Pia is now a sturdy woman in her forties and a strong advocate for organ donation and her Nicholas, in a family with a history of debilitating liver disease, is fit enough to be in training as a non-commissioned officer in the navy.

Nowadays none of these relationships would be possible because in 1999 a law was passed that by forbidding health care personnel from divulging any information about families involved in a transplant effectively stops donor families from knowing anything other than the most basic facts about the other side – age, sex, if the transplant operation was successful. As time passes the donor family does not even know if the recipients are still alive.

For many families, that is not a problem: they want to put the transplant behind them and get on with their lives. But for many others it is a nagging feeling of incompleteness, some important piece missing in their lives, and for some it is a chronic state of anguish, as some well-publicized cases show of families going public in their desperate search for their recipients. Many – I'd guess most – recipients too feel there is something missing. They are profoundly grateful to the people who saved their lives and yearn to thank them.

In the United States where I live communication between the two sides is not only allowed but is strongly encouraged because in the overwhelming majority of cases in thousands and thousands of contacts over more than twenty-five years the results have been therapeutic for both sides.

I knew all this but felt that it would be out of place for me to propose changes in the law in a foreign country. I raised the question in private conversations with doctors and health care administrators but no one thought repeal was feasible, most thought it was also undesirable and those who agreed preferred not to get involved in so controversial an issue.

By 2016, however, I realized that at 87 years of age I might not have many more opportunities to bring the topic into the open and so, after more than twenty years of maintaining silence, I took a deep breath and began to contact the media to try to have a national discussion. I was surprised and gratified by the response. I am a journalist myself and was proud of my profession when I found that the media understood instinctively the deep feelings of people involved in these transplant situations.

I had just one partner, Andrea Scarabelli, from Rome who when a university student of 21 was one of many hundreds of Italians who wrote to us when Nicholas died. Andrea became a friend and, now in his forties, has been an invaluable guide in steering me through the complexities of a country I love but am still a foreigner in.

A turning point came when the open-minded *Journal of Italian Nephrology* accepted a paper from me [3-5]. From then on the arguments for relaxing the law were seen not to be the wild ideas of an amateur who did not understand Italian customs but a problem deserving serious consideration. Leading newspapers, magazines and television channels began featuring stories asking what precisely was the justification for keeping the two sides apart.

The campaign began gathering support from the public, the most notable coming from Marco Galbiati, a determined, intelligent and imaginative man from Lecco who in January 2017 was caught in one of those crushingly unforeseeable developments that mark brain death. Skiing with his 15-year old son, Riccardo, Marco reached the end of the slope but Riccardo did not arrive. He was found unconscious on the slope and was rushed to hospital in Bergamo but died two days later.

Devastated, his parents donated his organs and only a few weeks later, Marco on a night when, as he told me, his desire "to know who the recipients were was particularly strong" decided to start a petition to change the law (I can picture that restless night, can't you?). So far, almost alone and without financial help from anyone, he has collected 46 000 signatures! So much for the argument that this is an issue no one cares about. Now Marco continues as committed as ever, working with anyone who will cooperate with him, to ensure that any new law is fair and efficient. Three eminent Italian transplant surgeons working in top transplant centers in the United States – Professors Ignazio Marino, Cataldo Doria and Cristiano Quintini – spoke up strongly in favor of allowing contacts.

But in Italy the medical establishment remained unconvinced, however, and I felt like a voice crying in the wilderness. Or, rather, like Don Quixote with Sancho Panza. What if the two sides met and didn't like each other? We were asked. What if one party wanted a much more intense relationship than the other? What if a donor family told the recipients they needed money and expected someone whose life they had saved to help them out? Suppose the recipient died soon after the transplant.

All those nightmare scenarios are possible, of course. But the actuality is in the statistics: in the tens of thousands of cases where the two sides have communicated in the United States only a small minority have gone wrong. And even then the problem has normally been dealt with reasonably soon.

Partly that is because transplant families have had to deal with far more difficult problems. The thought that they are helpless to deal tactfully with potentially embarrassing situations is to seriously under-estimate them. But in addition a formidable set of rules have been worked out based on decades of experience.

First, no communication is allowed unless both parties express a desire for it. If they do the normal procedure is for one of the families to write an anonymous letter to the other with information about itself. That letter is examined by the hospital to make sure nothing abnormal is in it. It then is passed to the other family. If they do not want to start a relationship, the process ends there.

If that second family does want to reply, however, it does so, also anonymously and also through the hospital. The two sides can continue anonymous correspondence for as long as they wish or they can reveal their identity. Sometimes there is frequent exchange of letters, sometimes just on rare occasions – on the anniversary of the transplant, for example.

Anonymous letters may sound a little dry but imagine the thrill of receiving one from a boy who tells you that before the transplant he could walk to the door of his apartment only by stopping for breath and was receiving blood transfusions twice a week but now has a job and can even play soccer. That's not an imaginary recovery. I know someone who did just that.

In time the parties may decide they want to meet, their hearts beating wildly as the day approaches. Sometimes, as the critics say, the differences between the two sides are too great for them to want to continue but more often, much more often, the two sides seem to melt into each other's arms.

Why not? One side is meeting recipients who have inside them part of the body of someone they themselves loved, the other is meeting people who despite all the temptations to turn inwards in grief or bitterness had the warmth of human understanding to help a perfect stranger, when no one else could. In most cases it is a natural fit.

The people who choose to meet face to face are only a small proportion of those who write to each other – it is after all a step into the dark – but some become best friends, visit each other for Sunday lunch, give each other strength when their spirits droop.

But the clinching evidence comes from the abundant statistics, collected by the organ procurement organizations (OPOs) that are responsible to the US Department of Health for looking after transplant families in their area and work hand in glove with hospitals there that range from small rural institutions to some of the world's best-known transplant centers. There are 58 of them and every one promotes communication between the two sides.

Here are what the CEOs of some of the largest Organ Procurement Organizations from every region in the United States say:

- "In New England, with a total population of 14 million, about 52% of donor families will connect with a recipient within the first two years of their loved one's organ donation". Alexandra Glazier, President and CEO, New England Donor Services.
- "Having the ability to exchange letters between donor families and recipients is profoundly healing and therapeutic for both parties". Kevin O'Connor, chief executive officer of Life Center Northwest.
- Our experience with donor family and recipient communication has been "overwhelmingly positive for all involved". Kathleen Lilly, Executive Vice President of LifeLink Foundation in Florida.
- "Donor families have only one request and that is that we save as many lives as we can with their gift. Those who meet the recipients get a chance to see that promise fulfilled". Kevin Cmunt, CEO of Gift of Hope, whose area includes Chicago, home to two hundred thousand people whose families came from Italy.
- "In the last twenty years in an area that includes 20 million people and 200 hospitals in Southern California no families who met each other have regretted it". Tom Mone, CEO, OneLegacy.

The volume of these communications should also finally put to rest any idea that families are not interested in contacting each other: in 2017 a survey of 35 of the 58 OPOs recorded almost 13 000 letters between pairs of families.

Admittedly conditions are different between the United States and Italy and many practices that work well would have to be modified, but I refuse to believe Italian grief is so much different from American grief that principles that work so well in one would be ineffective in the other. I was delighted to learn that the ICB agreed with the main arguments for allowing contacts to take place under controlled conditions. I hope we can look forward to an early change in the law and the consolation it will bring to people who have already suffered more than most of us can imagine.

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Measuring health literacy in Italy: a validation study of the HLS-EU-Q16 and of the HLS-EU-Q6 in Italian language, conducted in Florence and its surroundings

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Abstract
Health literacy (HL) is the capacity of individuals, families, and communities to make sound health decisions in the context of everyday life: at home, at the workplace, and in the community, marketplace, healthcare sector, and political arena. The aim of this study, as a part of a research conducted in Florence (Italy) and its surrounding, is to validate the Italian version of the short form (HLS-EU-Q16) and of the short-short form (HLS-EU-Q6) of the HLS-EU-Q47, as a part of a research conducted to assess the level of HL in a population-based sample in Florence. Two-hundred twenty-three subjects (57% females; age: 53.7 ± 11.8 years) were interviewed. The results provided the first evidence for the reliability and validity of the HLS-EU-Q instruments (HLS-EU-Q16, HLS-EU-Q6, General-HL Index) in Italian general population. The differences in some of the results with respect to other published studies lay for specific cultural characteristics, that affect HL level and the relationships between HL, antecedents, and outcomes.

Key words
- public health literacy
- HLS-EU-Q16
- HLS-EU-Q6
- Italian language
- validation process

INTRODUCTION

Health literacy (HL) is the capacity of individuals, families, and communities to make sound health decisions in the context of everyday life: at home, at the workplace, in the community, marketplace, health care system, and political arena [1]. The concept of HL was originally limited to functional skills (i.e. basic reading, writing, and literacy skills) [2] that are needed to obtain, process, and understand health related information, but has been expanded to cover broader competences that are needed to communicate, navigate, and actively participate within modern health care systems [3]. Public health literacy can be viewed as an additional level, where individuals understand not only how health information affects them, but also the community and society [4], and where the acquisition of health knowledge is an integral part of HL, rather than a separate outcome [5]. Sørensen *et al.*'s integrated definition encompasses the public health perspective: "Health literacy is linked to literacy and entails people's knowledge, motivation, and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention, and health promotion to maintain or improve quality of life during the course of life" [6].

Several instruments have been developed to measure HL and explore how health outcomes relate to HL, but only a few of them have the purpose or have been used to measure HL at the population level [7-11], although the measure of HL in the general population is considered an important step for achieving a more public health-literate society [4]. To measure HL in an adequate way for public health-oriented surveys of general population in Europe, the Health Literacy Survey (HLS-EU) was conducted in 2012 [12] using a new measurement tool developed from the conceptual model of Sørensen *et al.* [6]: the "47-item European Health Literacy Survey Questionnaire" (HLS-EU-Q47) [13]. Since 47 items were excessively time-consuming for some HL research-

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es, two short forms have been validated in seven languages to be used in the European Health Literacy Survey (English, Bulgarian, Dutch, German, Greek, Polish, and Spanish) to be used for efficient studies with some possibility to benchmark with researches that use the long form of the instrument [11, 14].

The aim of this study, as a part of a research conducted in Florence (Italy) and its surrounding, is to validate an Italian version of the short form (HLS-EU-Q16) and of the short-short form (HLS-EU-Q6) of the HLS-EU-Q47.

MATERIALS AND METHODS

Study design and sampling procedures

This study is a part of a research conducted to assess the level of HL in a population-based sample in Florence, and to validate some other HL measures in Italian language. The study protocol was published elsewhere [15]. Briefly, it adopted a cross-sectional design and was conducted in Florence, Italy, and its surroundings. The population-based sample was randomly selected from the registries of eleven general practitioners (GPs) working in primary healthcare centres of the municipality of Florence. The GPs were recruited using convenience criteria: according to the study protocol, the first eight to voluntarily join the study were included and were asked to randomly select 80 subjects among those registered as one of his/her patients [15]. Since oversampling was not enough to reach the sample size of 480, three more GPs were included, with a second random sample for the first eight. Overall, 984 subjects were selected.

Inclusion criteria were the following: 18-69 years of age, and Italian speaking (since the survey is conducted in Italian). Exclusion criteria included cognitive impairment, severe psychiatric diseases and end-stage diseases. Each GP verified the inclusion and exclusion criteria when selecting the sample.

Each subject was randomly allocated to one of the two arms of the research project (A and B), according to the questionnaires used during the interview (type I and type II questionnaires, respectively). To meet the specific aims of the present study, only B arm of the research were considered as only in this arm the HLS-EU-Q16 was administered [15].

Data collection

Data collection started in February 2017 and finished on 31st December 2017. Each selected subject was contacted via postal mail. Subjects received an information sheet signed by the GP and the person in-charge of the study, which included a short description of the study, an invitation to participate, and a consent form. Participants were asked to sign the consent form and return it via mail to the researchers in charge. The mail also contained the nutritional label of the Italian version of the Newest Vital Sign (NVS-IT). After receipt of the signed consent forms, the subjects were contacted for the computer-assisted telephone interview. Nine interviewers, who were part of the research group, made the phone calls. Written instructions on how to conduct the interview were drawn up and shared within the research team to standardize the procedure and limit interviewer bias. Each subject was randomly assigned to one of the nine interviewers and contacted a maximum of six times before being considered unreachable [15].

The questionnaire had a general section that includes questions on sociodemographic, familial data (antecedents), and health-related outcomes (consequences), as described in the previous paper [15].

In addition, the questionnaire included the NVS-IT and the HLS-EU-Q16 tools.

Health literacy measures

The HLS-EU-Q16 and the HLS-EU-Q6 are, respectively, the short form and the short-short form of the HLS-EU-Q47 [11, 14], developed by selecting 16 and 6 items, respectively, and already used both in general and specific populations [16-32]. The HLS-EU-Q47 includes 47 items covering 12 subdomains (including domains such as accessing and obtaining, understanding or appraising information relevant to healthcare, disease prevention, and health promotion), grouped in three sub-indices according to the domains of application of HL (healthcare, disease prevention, and health promotion) [13]. It is a self-reported tool with Likert-type responses ("very easy", "fairly easy", "fairly difficult", "very difficult") and an associated final score that measures interaction, comprehension, information seeking, application/function, decision-making/critical thinking, evaluation, responsibility, confidence, and navigation skills.

Correlations of both the HLS-EU-Q16 and the HLS-EU-Q6 with the index of the long form HLS-EU-Q47 were very high in the HLS-EU [11].

To generate the score of the HLS-EU-Q16, the items are dichotomized into two categories with two scores, "easy" ("fairly" or "very" easy = 1) and "difficult" ("fairly" and "very" difficult = 0). In this study, "don't know/refusal" answer was recoded as missing, as suggested by other Authors [22, 28, 30, 31, 33]. The scale score is calculated as the sum of the scores of each item and varied between 0 and 16. Only respondents who answered at least 14 items were considered, according to other studies [26, 28]. Considering the HLS-EUQ16 score, three levels of HL were defined: inadequate HL (0-8), problematic HL (9-12) and adequate HL (13-16). Moreover, according to Gele [30] and similarly to HLS-EU-Q47 score analysis, a General HL index (G-HL Index) was calculated as follows: G-HL Index = (mean-1) * (50/3) where "mean" is the mean of all participating items for everyone. For index calculation, only subjects who answered at least 14 items were considered as well.

Considering the score of the HL index (range: 0-50), four levels of HL were defined as for HLS-EUQ47: inadequate HL (0-25), problematic HL (25.1-33), sufficient HL (33.1-42), and excellent (42.1-50).

To generate the score of the HLS-EU-Q6, the categories and scores of the HLS-EU-Q47 were considered: "very easy" = 4; "fairly easy" = 3; "fairly difficult" = 2; "very difficult" = 1; "don't know/refusal" = missing. The scale score was the mean value and varied between 1 and 4. Only respondents who answered at least 5 items were considered [28].

The English versions of the HLS-EU-Q16 and the HLS-EU-Q6 have been translated in the Italian language and adapted using standard procedures, including forward and backward translation (performed by Italian and English native speakers). A final Italian version was drafted and then shared and discussed with the members of the research group [34]. A previous paper reports the Italian versions of the tools adopted [15].

For the European Survey, the NVS was included in the study for comparison. It is a commonly used objective measure of functional HL. It was originally developed in the USA for English speakers and Spanish speakers and NVS has seen increased application in other countries including Italy (NVS-IT) [35, 36].

The NVS-IT consists of an ice cream nutrition label, with seven associated questions that measure literacy and numeracy. It produces a final score ranging from 0 to 6, allowing subjects to be classified in three categories-high likelihood of limited HL (score: 0-1), possibility of limited HL (score: 2-3) and adequate HL (score: 4-6). This instrument takes 3-5 min to be administered. Since the information needed to answer the questions had to be derived from the nutritional label, the label was included in the postal mail to be sent to the GP-assisted participants.

Statistical analysis

Data are presented as percentages or as means ± standard deviations. HLS-EU-Q16, HLS-EU-Q6, G-HL Index and NVS-IT scores were tested for normality using the Kolmogorov-Smirnov test.

Correlation analysis (Pearson or Spearman, depending on normality) between the single items, and between the scales scores were performed.

Cronbach's alphas for HLS-EU-Q16 and HLS-EU-Q6 score, as well as for G-HL Index were calculated as measures of reliability (internal consistence).

For comparison, associations between the HL scores (HLS-EU-Q16, HLS-EU-Q6, G-HL Index and NVS-IT), antecedents, and consequences were assessed using $\chi 2$ test or correlation analysis (Pearson or Spearman, depending on normality).

Statistical analysis has been performed using IBM SPSS Statistics for Windows, V.25.0 (IBM). For each analysis, an alpha level of 0.05 has been considered as significant.

RESULTS

A total of 452 subjects were interviewed (compliance equalled to 46.1%) considering both arms of the research project. The refusal rate was 15.6% while 38.2% was the rate for those unreachable. Two-hundred twenty-three subjects (57% females; age: 53.7 ± 11.8 years) were interviewed in the B arm of the study and the majority (96.9%) were Italian with high school (36.3%) or university (44.4%) degree, with a paid job (61%), made ends months quite or very easily with financial resources available (68.6%), and did not have any chronic diseases or long-term illnesses (50.7%) or had only one of them (32.3%).

Items responses

Table 1 reports the responses to the HLS-EU-Q items. The percentages of "don't know/refuse" responses varied from 0% to 14.3%. Item 8 (*…find information on how to manage mental health problems like stress or depression*) presented the highest percentages of "don't know/refuse" responses; for most of the other items the percentages of "don't know/refuse" responses were very low.

Items 12 (*…decide how you can protect yourself from illness based on information in the media*), 8 (*…find information on how to manage mental health problems like stress or depression?*) and 11 (*…judge if the information on health risks in the media is reliable*) reported the highest percentages of "very difficult" responses (19.7%, 19.3%, and 15.2%, respectively), while items 10 (*…understand why you need health screenings*), 9 (*…understand health warnings about behaviour such as smoking, low physical activity and drinking too much*), and 4 (*…understand your doctor's or pharmacist's instruction on how to take a prescribed medicine*) the highest percentages of "very easy" responses (68.6%, 65%, and 50.7%, respectively).

Most of the items was significantly correlated *(Table 2).*

HLS-EUQ16, HLS-EUQ6 and G-HL Index

Cronbach's alphas for HLS-EU-Q16, G-HL Index, and HLS-EU-Q6 were 0.799, 0.769, and 0.672, respectively.

Eleven (5%) and 20 (9%) participants were excluded from generating the score of HLS-EU-Q16 and HLS-EU-Q6, respectively, due to excess of "don't know/refusal" responses.

HLS-EU-Q16, HLS-EU-Q6 and NVS-IT scores, and G-HL Index were not normally distributed. *Table 3* reports the descriptive analysis of the scores. NVS-IT score was J-shaped, with ceiling effect for higher HL, while HLS-EU-Q16 score, HLS-EU-Q6 score and G-HL Index were more like normal distribution *(Figure 1).*

HLS-EU-Q16 and HLS-EU-Q6 were strongly correlated (Spearman rho: 0.861; $p < 0.05$). G-HL Index was strongly correlated with both HLS-EU-Q16 and HLS-EU-Q6 (respectively, Spearman rho: 0.856, $p < 0.05$; 0.881, $p < 0.05$). NVS-IT score was significantly correlated only with G-HL Index, with a low correlation coefficient (Spearman rho: 0.169; $p < 0.05$).

According to HLS-EU-Q16, 11.8% presented inadequate HL, 55.2% problematic HL%, and 33.0% enough HL; according to HLS-EU-Q6, 8.9% presented inadequate HL, 66.5% problematic HL%, and 24.6% enough HL. The concurrent classification between the two tests was 72.6%.

Considering G-HL Index, 13.2% presented inadequate HL, 42.9% problematic HL, 36.3% enough HL, 7.5% excellent HL.

According to NVS-IT, 11.7% presented high likelihood of limited HL, 28.7% possibility of limited HL, high 59.6% likelihood of adequate HL.

Comparison of predictors and outcomes

As far as antecedents are concerned, many differences emerged between the scores *(Table 4)*. The differences emerged between functional objective HL tool (NVS-IT) and self-reported tools (HLS-EU-Q16,

Table 1
Responses to the HLS-EUQ-16/6 items (percentages)

Area	On a scale from very easy to very difficult, how easy would you say it is to	Very easy	Fairly easy	Fairly difficult	Very difficult	Don't know/ refusal
HC	1. find information on treatments of illnesses that concern you?	13.0	61.0	19.7	4.5	1.8
HC	2. find out where to get professional help when you are ill?	23.3	47.1	22.0	6.3	1.3
HC	3. understand what your doctor says to you?	38.1	53.8	6.7	1.3	0.0
HC	4. understand your doctor's or pharmacist's instruction on how to take a prescribed medicine?	50.7	46.6	2.7	0.0	0.0
HC	5. judge when you may need to get a second opinion from another doctor?*	11.2	39.0	35.9	9.0	4.9
HC	6. use information the doctor gives you to make decisions about your illness?*	20.6	60.5	14.8	2.2	1.8
HC	7. follow instructions from your doctor or pharmacist?	36.3	60.1	2.7	0.9	0.0
DP	8. find information on how to manage mental health problems like stress or depression?*	9.4	18.4	38.6	19.3	14.3
DP	9. understand health warnings about behaviour such as smoking, low physical activity and drinking too much?	65.0	30.9	2.2	0.9	0.9
DP	10. understand why you need health screenings?	68.6	28.3	2.2	0.4	0.4
DP	11. judge if the information on health risks in the media is reliable?*	9.9	27.4	45.7	15.2	1.8
DP	12. decide how you can protect yourself from illness based on information in the media?	6.7	21.1	49.3	19.7	3.1
HP	13. find out about activities that are good for your mental well-being?*	18.4	48.0	22.9	4.5	6.3
HP	14. understand advice on health from family members or friends?	26.5	44.4	19.3	5.4	4.5
HP	15. understand information in the media on how to get healthier?*	14.8	38.6	37.2	8.1	1.3
HP	16. judge which everyday behaviour is related to your health?	37.2	43.5	15.7	2.2	1.3

*Items included in the HLS-EU-Q6. HC: Health Care; DP: Disease Prevention; HP: Health Promotion.

Table 2
Spearman correlation analysis of the HLS-EU-Q16/6 items

	Item 1	Item 2	Item 3	Item 4	Item 5°	Item 6°	Item 7	Item 8°	Item 9	Item 10	Item 11°	Item 12	Item 13°	Item 14	Item 15°	Item 16
Item 1	1.000															
Item 2	0.092	1.000														
Item 3	**0.207***	0.029	1.000													
Item 4	**0.159***	**0.200***	0.154*	1.000												
Item 5°	0.031	0.123	0.102	0.113	1.000											
Item 6°	**0.222***	0.123	**0.278***	0.062	**0.280***	1.000										
Item 7	0.054	0.036	**0.208***	**0.415***	0.098	0.215*	1.000									
Item 8°	**0.154***	**0.211***	**0.150***	0.046	0.177*	**0.212***	0.072	1.000								
Item 9	0.132	**0.169***	0.041	-0.030	0.078	-0.022	-0.035	0.002	1.000							
Item 10°	0.030	0.079	-0.050	-0.028	0.112	-0.010	-0.032	0.046	0.129	1.000						
Item 11	0.020	**0.166***	**0.155***	0.073	**0.307***	**0.187***	0.101	**0.230***	0.036	0.073	1.000					
Item 12	0.037	0.114	**0.142***	0.042	**0.156***	0.046	0.013	**0.266***	0.057	-0.019	**0.576***	1.000				
Item 13°	0.027	-0.045	**0.135***	0.067	**0.231***	0.120	0.025	**0.281***	-0.010	0.128	**0.172***	**0.153***	1.000			
Item 14	0.114	0.090	0.048	-0.042	**0.296***	0.060	-0.067	**0.149***	0.060	-0.042	0.069	0.060	0.096	1.000		
Item 15°	0.032	0.080	0.128	0.126	**0.233***	0.040	0.162*	**0.233***	0.043	0.013	**0.477***	**0.415***	**0.211***	**0.255***	1.000	
Item 16	0.073	0.078	0.081	-0.008	0.114	0.125	-0.092	**0.223***	0.112	-0.007	0.142*	0.112	0.194*	0.118	0.015	1.000

°Items included in the HLS-EU-Q6 test. *p < 0.05.

Table 3
Distributions of HLS-EU-Q16, HLS-EU-Q6, G-HL Index and NVS scores

		HLS-EU-Q16* (n = 212)	HLS-EU-Q6° (n = 203)	G-HL Index^ (n = 212)	NVS-IT# (n = 223)
Mean		11.3	2.6	32.3	4.0
Standard deviation		2.6	0.5	6.2	1.9
Skewness		-0.161	0.233	0.261	-0.518
Kurtosis		-0.479	-0.136	-0.044	-0.938
Range		5.0-16.0	1.33-4.00	16.67-48.96	0-6
Centiles	25	9.0	2.3	28.1	2.0
	50	11.0	2.6	32.3	4.0
	75	13.0	2.8	36.5	6.0

*°^#Kolmogorov-Smirnov test for normality: $p < 0.05$.

HLS-EU-Q6, and G-HL Index). Gender was associated with G-HL Index; age with NVS-IT; educational level was associated with all the HL scores except for G-HL Index; chronic diseases with HLS-EU-Q16 and G-HL Index. Income (financial resources and employment status) was associated with NVS-IT; having received training or is/has been employed in the field of healthcare was associated with HLS-EU-Q scores. Nationality and marital status were not associated with any HL scores.

Considering HL consequences, self-perceived health status was associated with each score, while BMI and health services used in the last 12 months were not associated with any HL scores.

DISCUSSION

According to Gazmararian *et al.* [4], an important step for achieving a more public health-literate society is to develop measures of public HL, to obtain baseline data on the magnitude of the problem, and to assess the impact of public health efforts to improve public HL. Considering this, a population-based study was conducted in Florence, to assess the level of HL using an already validated measurement tool (the NVS-IT), and to validate some HL measures in Italian language.

The HLS-EU-Q16 and the HLS-EU-Q6 versions that have been used in the study have shown a low percentage of "don't know/refuse" responses, aspects that give evidence on people's acceptance and understanding of the items.

Differently from the EU survey [37], the items regarding mental health (number 8 and 13) present the higher percentage of "don't know/refuse" responses (14.3% *vs* 5.6% for item 8, 6.3% *vs* 3.9% for item 13). As suggested by other Authors [11], the difficulty of item proposes instrument sensitivity, which should be country (and area) specific. Considering this, the high percentage of "don't know/refuse" responses for mental well-being and health problems highlights critical issues that should be due, on the one hand, to the lack

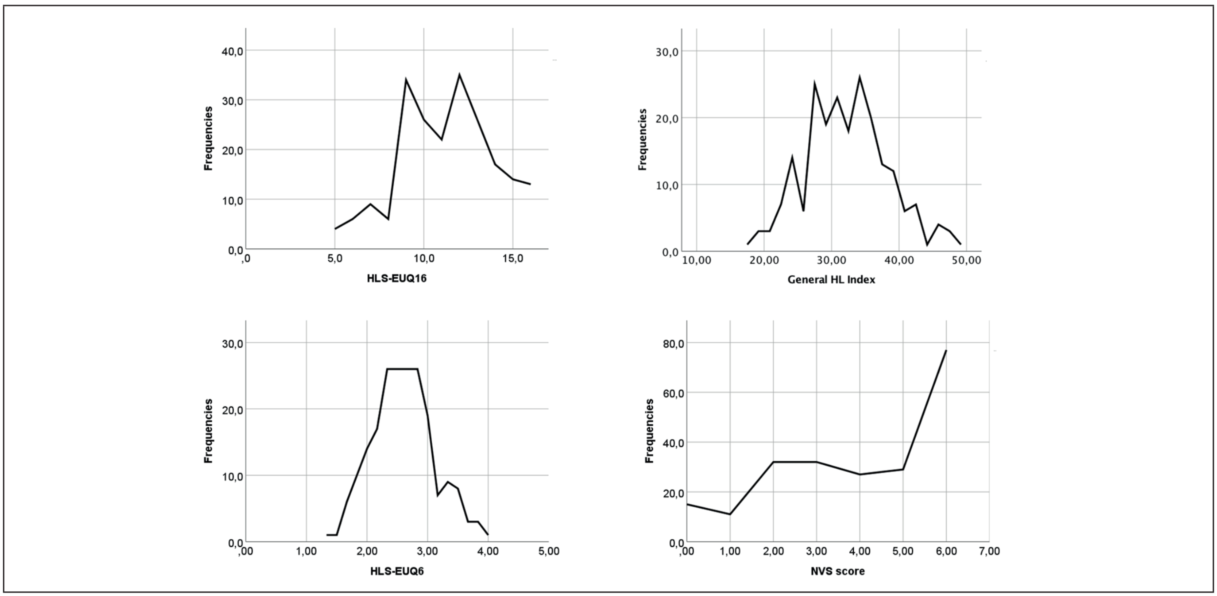

Figure 1
Distributions of HLS-EU-Q16, HLS-EU-Q6 and NVS scores.

Table 4
Antecedents and consequences of HL: association with different HL measures (Chi^2 test)

Variables		**HLS-EU-Q16 (n = 212)**	**HLS-EU-Q6 (n = 203)**	**G-HL Index (n = 212)**	**NVS-IT (n = 223)**
Antecedents	Gender	$p \geq 0.05$	$p \geq 0.05$	**$p < 0.05$**	$p \geq 0.05$
	Age*	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$	**$p < 0.05$**
	Nationality	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$
	Educational level	**$p < 0.05$**	**$p < 0.05$**	$p \geq 0.05$	**$p < 0.05$**
	Financial resources	$p \geq 0.05$	$p = 0.05$	$p \geq 0.05$	**$p < 0.05$**
	Training or employed in the field of healthcare	**$p < 0.05$**	**$p < 0.05$**	**$p < 0.05$**	$p \geq 0.05$
	Employment status	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$	**$p < 0.05$**
	Long-term illnesses (yes/not)	**$p < 0.05$**	$p \geq 0.05$	**$p < 0.05$**	$p \geq 0.05$
	Marital status	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$
Consequences	Self-perceived Health status	**$p < 0.05$**	**$p < 0.05$**	**$p < 0.05$**	**$p < 0.05$**
	BMI class	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$
	Doctor visits	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$
	Emergency department admissions	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$
	Hospitalizations	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$
	Outpatients specialist care access	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$	$p \geq 0.05$

*Spearman correlation analysis.

of experience on mental problems by the interviewed subjects, and, on the other hand, to the prejudice and denial that still surrounds these issues.

The items were partly significantly correlated with each other. This datum, as well as the responses to each single item, present a good diagnostic opportunity to identify topics where citizens have difficulties with specific health-related tasks, to plan specific interventions to improve HL. For example, for the health care area, almost all the items present a percentage of very/fairly easy response greater than 70% (with the exception of item 5 "*…judge when you may need to get a second opinion from another doctor?*"), indicating a good relationship, trust and understanding between the subjects and their doctors or other health personnel. Instead, in our sample it resulted more difficult to understand and process advice and information reported by the media, friends and family (items 11, 12, 14, 15). As far as the media were concerned, data also portrays difficulties in judging the reliability of the information on health risks provided, and that item (number 11) is significantly correlated (r = 0.576) with those related to the understanding of the information in the media on how to get healthier (item number 15). This result raised criticism in the information on health provided by the media, as perceived by people included in the research, that must be investigated with specific studies on Media HL [38].

On the other hand, two items were poorly correlated with the others: the item 9 ("*…understand health warnings about behaviour such as smoking, low physical activity and drinking too much?*) was significantly correlated only with one item, and the number 10 ("*…understand why you need health screenings?*") with none, probably due to ceiling effect linked to the high percentages of "very easy" responses.

Considering the HLS scores, the number of participants that were excluded from the analysis due to excess of "don't know/refusal" responses were very low (11 and 20 for the HLS-EU-Q16 and the HLS-EU-Q6, respectively), confirming people's good acceptance of the test.

The results of the study present many differences with respect to other published researches. First of all, the level of HL measured using the HLS-EU-Q tools was lower than those observed in other population-based researches [11, 14, 20], while considering the NVS-IT there was the opposite situation [37]: it seems that, in our sample, there is a high objective functional HL, and a low subjective HL. Moreover, the distribution of the scores results quite different than those observed in the European Survey [11, 14]: in our study, the HLS-EU-Q16 and HLS-EU-Q6 scores are well shaped (similar to normal distribution) while in the HLS-EU survey the HLS-EU-Q16 score was J-shaped (as for the NVS-IT in this study) and the HLS-EU-Q6 score was well shaped. The difference in the HLS-EU-Q16 score distribution is due to the percentage of subjects classified as with problematic HL (score: 9-12), while in the European survey there is a ceiling effect for better HL. On the other hand, the same ceiling effect for better HL was observed in this study for what concerns NVS-IT differently from the European data. Furthermore, HLS-EU-Q scores do not significantly correlate with NVS-IT, while in the European Survey a significant – but low – positive correlation was observed [37]. Finally, the association between HL, antecedents and outcomes presents different results with respect to published data [12, 20].

The observed differences should be due to dissimilarities in the characteristics of the sample: although a population-based sample was investigated, the high percentage of unreachable subjects could have introduced a selection bias – a limitation of the study. Moreover, to have conducted the study on subjects recruited through the GPs may have added a bias in the responses to the HLS-EU-Q items due to social desirability, embarrassment or reverence. The NVS-IT, as an objective measure, could have been less influenced by those biases.

Part of the differences could also be due to cultural aspects, peculiar of the Italian population – and of the Florentine one. Since HL is a dynamic construct and the cumulative outcome is a combination of cognitive capacities, life experiences, knowledge, opportunities, and the context [38, 39], so the culture, the setting (i.e. healthcare, education welfare, social and market systems, the cultural norms, the role of the family, and the usability of media sources), and the history of a country – and that of a specific area in the country – could also contribute to explain the differences across geographical areas and populations in the distribution of HL as a whole and of its different domains (functional, critical and interactive, in Nutbeam's perspective), as well as in the relationship between HL, its antecedents and consequences. As a matter of fact, the Florentine population has higher life expectancy, as well as educational level, employment rate, and financial resources than those observed in the rest of the Tuscan and Italian population [40], probably as a result of a better general context (i.e. healthcare, education welfare, social and market systems).

For these reasons, local studies must be encouraged, using different measurement tools.

In conclusion, the results provide the first evidence for the reliability and validity of the HLS-EU-Q instruments (HLS-EU-Q16, HLS-EU-Q6, General-HL Index) in Italian general population, which should be confirmed with larger samples. Since HLS-EU-Q6 has been included in 2017 in the Italian lifestyle surveillance systems (PASSI – Progress by local health units towards a healthier Italy), limited to the Tuscan sample as a pilot test, the first confirmation of the reliability and applicability of this instrument will come in the next months by analysing PASSI data. Moreover, the differences in antecedents and consequences of HL with respect to other published studies and the scores itself lay for specific cultural relationships between HL, antecedents and outcome.

Author's contribution statement

Chiara Lorini: conception and design of the study; analysis and interpretation of data; drafting and revision of the manuscript. Vieri Lastrucci: conception and design of the study; generation, collection, assembly and interpretation of data; drafting and revision of the manuscript. Sarah Mantwill: conception and design of the study; drafting and revision of the manuscript.Virginia Vettori: conception and design of the study; generation, collection, assembly of data; drafting and revision of the manuscript. Guglielmo Bonaccorsi: conception and design of the study; interpretation of data; drafting and revision of the manuscript. Other component of the Florence Health Literacy Research Group: conception and design of the study; generation, collection, assembly of data; drafting and revision of the manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

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Hospital discharge diagnoses in patients with positive blood cultures in an Italian academic hospital

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Abstract

Objective. To assess the sensitivity of hospital discharge diagnoses for identifying sepsis in patients with blood culture confirmation.

Methods. A cross-sectional study was conducted at the Italian 1000-bed University Hospital of Udine. The administrative databases of the Hospital were used as the source of information. Laboratory data were linked with hospital discharge data. We estimated the proportion of hospitalizations with at least 2 positive blood culture tests in which at least one discharge diagnosis indicated bloodstream infection.

Results. From 2011 to 2017, 3571 hospitalizations (1.2%) had positive blood culture tests. Of them, only 49.5% had at least one ICD-9-CM discharge diagnosis code of sepsis, with lower proportions in surgical than in medical wards.

Conclusions. The sensitivity of ICD-9-CM discharge codes for sepsis is low as compared with the blood culture gold standard. Using discharge codes for epidemiological estimates of sepsis, health planning and risk management may yield biased results. Audits and ICD coding training are needed.

Key words
- χ^2 test
- hospital discharge records
- discharge diagnosis
- sepsis
- blood culture
- sensitivity

INTRODUCTION

Sepsis is a severe and costly condition, whose incidence has been shown to be increasing by several studies in the USA [1] and in Europe [2].

However, the epidemiology of sepsis has often been studied using discharge diagnosis codes [1, 2], whose accuracy is controversial. In fact, sepsis definitions based on clinical data have been shown to have greater sensitivity for identifying hospitalizations with severe sepsis than methods based on claims data [3]. In addition, the use of "explicit" sepsis coding (i.e., ICD-9-CM codes 995.92 for severe sepsis or 785.52 for septic shock) seems to be more common in cases characterized by greater severity, care intensity and in-hospital mortality [4].

Some studies have validated discharge diagnoses against laboratory findings, estimating the positive predictive value (PPV) of selected discharge diagnosis codes. For example, in Denmark, hospital discharge records reporting ICD-10 codes for Gram-negative septicemia/sepsis and urosepsis were compared with Gram-negative bacteremia according to blood culture results obtained from the laboratory information system: the ICD-10 code A41.5 was quite accurate, whereas the A41.9B was not [5]. In the USA, the PPV of ICD-9 codes against laboratory values from medical records varied between 66 and 100% depending on the discharge diagnosis [6]. Those studies, however, did not estimate the sensitivity of discharge diagnoses to identify patients with a laboratory-confirmed blood infection. Another study estimated both sensitivity and PPV of Methicillin-resistant Staphylococcus aureus (MRSA)-specific hospital discharge codes using laboratory-confirmed infection as the gold standard in an American children's hospital and found low sensitivity and low PPV, concluding that pediatric MRSA bloodstream infections will be underestimated if only those discharge codes are used to identify cases [7]. Another study validated ICD administrative data for sepsis identification in Canada using medical charts and clinical diagnostic criteria as the gold standard; the authors could identify ICD-10-CA codes that optimized the performance of coded information both among intensive care unit (ICU) patients and among non-ICU patients, increasing sensitivity while slightly decreasing specificity and PPV. Nonetheless, sepsis still resulted undercoded [8].

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In Italy, the validity of hospital discharge diagnosis codes for identifying cases of sepsis has never been assessed. In the University Hospital of Udine, North-East of Italy, a health information system including both hospital discharge records and laboratory values is available.

The main objective of this study was to assess the sensitivity of hospital discharge diagnoses to identify sepsis in patients with blood culture confirmation, analyzing the administrative data of the health information system of the University Hospital of Udine. Secondary objectives were to describe characteristics of cases where discharge diagnoses failed to identify blood-culture-confirmed sepsis and to assess the frequency of sepsis-related discharge diagnoses in hospitalizations with no blood culture confirmation.

MATERIALS AND METHODS

This cross-sectional study was conducted at the University Hospital of Udine, a 1000-bed academic hospital located in the North-East of Italy and serving a population of more than 250 000 inhabitants. The administrative databases of the Hospital health information system were used as the source of information. All databases included in the health information system are completely anonymous; however, they can be linked with each other at the individual patient level through an anonymous stochastic key which is univocal for each subject across databases.

In particular, we analyzed data on all the blood culture tests processed by the Hospital Microbiology Laboratory from 2011 (the first year with complete laboratory data on blood culture tests) to 2017. The detail on the pathogens isolated from the blood and antibiograms, however, have only been available in the Hospital health information system since 2014.

A blood culture test was considered certainly positive if at least 2 aerobic or anaerobic bottles of blood drawn on the same occasion turned out positive. Tests with only one positive bottle might depend on contaminations. For each patient with blood cultures, we linked positive tests with data regarding the hospitalization during which the blood cultures were collected. Laboratory data were linked with hospital discharge data at the individual patient level through the anonymous stochastic key and through the date of blood collection, which had to be between the hospital admission and discharge dates.

We then analyzed the discharge diagnoses of all hospitalizations during which patients had positive culture tests. In Italy, up to 6 discharge diagnoses could be recorded. They are coded according to the ICD-9-CM. All 6 diagnoses were considered to assess whether sepsis had been recorded in the hospital discharge data. We considered as suggestive of sepsis any of the following ICD-9-CM codes, also used by Bouza *et al*. [2, 4] for bacterial or candida sepsis: 790.7 (bacteremia), 038.xx (septicemia), 995.91 (sepsis), 995.92 (severe sepsis), 785.52 (septic shock), 771.81 (septicemia [sepsis] of newborn), 421 (acute and subacute endocarditis), 003.1 (salmonella septicemia), 020.2 (septicemic plague), 036.2 (meningococcemia), 098.89 (gonococcemia), 112.5 (systemic candidiasis), 112.81 (candida endocarditis).

We assessed the proportion of hospitalizations with positive blood culture tests in which at least one discharge diagnosis corresponded to one of the above-listed codes, overall and stratified by calendar year, by discharge hospital unit (surgical *vs* medical ward), by hospitalization outcome (in-hospital death vs other), and by intensive care unit (ICU) stay during the hospitalization (yes *vs* no). The statistical significance of trends was assessed through the Cochran-Armitage test. The statistical significance of differences among years or units was assessed through the $\chi 2$ test. P-values < 0.05 were considered statistically significant.

We also investigated whether patient's demographic characteristics (age and sex) affected the likelihood of having sepsis coded among the discharge diagnoses through multivariate logistic regression analyses mutually adjusting for sex, age category (0-14, 15-64, 65-79, ≥ 80 years), type of ward of discharge (surgical *vs* medical) and calendar year. Odds Ratios (OR) and 95% Confidence Intervals were calculated.

For hospitalizations with positive blood culture tests but no discharge diagnoses suggestive for sepsis, we described the number of diagnoses that were recorded in the hospital discharge record and the main discharge diagnoses.

Then, we assessed the frequency of sepsis discharge diagnosis codes in cases with no laboratory-confirmed sepsis (i.e. no blood cultures, negative tests, or tests with only one positive bottle). Sensitivity, specificity, PPV and negative predictive value (NPV) of ICD-9 codes were estimated, using either laboratory-confirmed bloodstream infections (≥ 2 positive aerobic or anaerobic bottles) or tests with only 1 positive bottle as the gold standard.

Finally, to assess whether the sensitivity of hospital discharge diagnoses differed according to the pathogens isolated from the blood, we assessed the frequency of sepsis discharge diagnosis codes stratified by genera of the pathogens, for all patients with positive blood culture tests hospitalized from 2014 to 2017. In addition, to assess whether the sensitivity of hospital discharge diagnoses could be affected by antibiograms showing antimicrobial resistance, we analyzed the case of Klebsiella pneumonia and compared the sensitivity in case of isolation of Carbapenem-resistant strains (CRKP) with the sensitivity in case of Carbapenem-sensitive strains from 2014 to 2017, when antibiograms were available for analysis.

All the analyses were conducted using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

This article does not contain any studies with human or animal subjects performed by any of the authors. Since this analysis was based on anonymous administrative data, patient informed consent and Ethical Committee approval were not required in Italy.

RESULTS

From 2011 to 2017, blood cultures were obtained in 27 919 patients hospitalized at the University Hospital of Udine (9.3% of all hospitalizations), totaling 44 533

Table 1
Number and proportion of hospitalizations with positive blood culture test (≥ 2 positive aerobic or 2 anaerobic bottles), University Hospital of Udine, North-Eastern Italy, 2011-2017

Year	Total hospitalizations	Hospitalizations with positive blood culture tests	Hospitalizations with discharge diagnosis suggestive of sepsis
2011	45 224	428 (0.9%)	196 (45.8%)
2012	44 568	453 (1.0%)	218 (48.1%)
2013	43 526	459 (1.0%)	229 (49.9%)
2014	41 795	499 (1.2%)	253 (50.7%)
2015	41 440	549 (1.3%)	292 (53.4%)
2016	41 488	586 (1.4%)	301 (51.4%)
2017	41 671	597 (1.4%)	280 (46.9%)

blood culture tests. In 74.9% of cases, at least 2 sets of blood bottles were withdrawn as recommended [9]. Of all the 299 712 hospitalizations during the 7-year period, 3571 (1.2%) were characterized by positive blood culture tests (i.e., microbial growth in ≥ 2 aerobic or anaerobic bottles). The proportion of hospitalizations with positive blood culture tests showed an increasing trend over the study period (*Table 1*, p-value of Cochran-Armitage trend test < 0.001).

Of all hospitalizations with positive blood culture tests, approximately half had at least one ICD-9-CM discharge diagnosis code suggestive of sepsis (49.5%), with non-significant differences across years (*Table 1*, p-value of χ^2 test = 0.21). There was great variability in the proportion of hospitalizations with ICD-9-CM discharge diagnoses suggestive for sepsis across the hospital units, ranging from 0 to 81.9% (p-value of χ^2 test < 0.001), with proportions all < 50% in surgical wards. In particular, of 713 discharges from surgical wards with positive blood culture tests, only 102 (14.3%) had a discharge diagnosis consistent with sepsis, whereas among the 2858 hospitalizations in medical wards, 1667 (58.3%) had a sepsis-related diagnosis (p-value of χ^2 test< 0.001). The proportion of hospitalizations with sepsis-related diagnoses in surgical wards did not show any trend during the study period, showing a maximum of 17% and a minimum of 10% with an oscillating pattern.

Overall, 595 patients (16.7%) had an ICU stay during the hospitalization. In surgical wards, the proportion of hospitalizations with sepsis-related diagnoses was higher in case of ICU stay than otherwise, although the difference was not statistically significant (17.4% *vs* 13.5% respectively, p-value of χ^2 test = 0.22). On the other hand, in medical wards the proportion of cases with sepsis-related diagnoses was lower in case of ICU stay (51.1%) than otherwise (59.7%, p-value of χ^2 test < 0.001).

In-hospital mortality of patients with a positive blood culture test was 20.7% (n = 740). In medical wards, there was virtually no difference in the proportion of cases with sepsis among the discharge diagnoses for patients who died in the hospital and for the others (57.6% and 58.5% respectively, p-value of χ2 test = 0.67). On the contrary, in surgical wards the frequency of cases with sepsis indicated among the diagnoses was almost double when patients died in the hospital (24.1%) than otherwise (13.4%, p-value of χ2 test 0.02).

Compared with patients ≥ 80 years of age, adults and younger elderly subjects with positive blood culture tests had lower likelihood to have sepsis recorded among the hospital discharge diagnoses *(Table 2)*. On the other hand, no association was observed with patient's sex. After adjusting for patient's demographics and calendar year, being discharged from a medical ward was significantly associated with having sepsis recorded, whereas in-hospital death was not associated with the likelihood of recording sepsis.

Table 2
Association of patient's demographic characteristics, calendar year, hospital discharge ward type, with discharge diagnosis of sepsis among hospitalized patients with positive blood culture tests (≥ 2 positive aerobic or 2 anaerobic bottles), University Hospital of Udine, North-Eastern Italy, 2011-2017

	OR[1]	95%CI
Sex		
Male	1.00	-
Female	0.97	0.84-1.12
Age category		
0-14	0.94	0.31-2.92
15-64	0.84	0.70-1.01
65-79	0.79	0.66-0.94
≥ 80	1.00	-
Type of discharge ward		
Surgical	1.00	-
Medical	8.22	6.56-10.29
Calendar year		
2011	0.87	0.67-1.14
2012	1.00	0.77-1.30
2013	1.08	0.83-1.41
2014	1.08	0.84-1,39
2015	1.22	0.95-1.56
2016	1.12	0.88-1.43
2017	1.00	-

[1] Adjusted for all factors in the table.

Of hospital discharge records not including sepsis among the 6 discharge diagnoses, 354 (19.6%) had all 6 diagnoses filled out; 225 (12.5%) had 5, 310 (17.2%) had 4, 350 (19.4%) had 3, 295 (16.3% had 2, and 272 (15.1%) had only 1 diagnosis recorded. Among those records, the main discharge diagnosis belonged to the infectious and parasitic diseases group in 63 cases (3.5%), to the neoplasms group in 376 cases (20.8%), to the circulatory diseases group in 311 cases (17.2%), to the respiratory diseases group in 159 cases (8.8%), to the digestive diseases group in 243 cases (13.4%), to the genitourinary diseases group in 158 cases (8.7%), to the injury group in 158 cases (8.7%), to the supplemental classification of factors influencing health status and contact with health services in 112 cases (6.2%, almost all V42.7, person with transplanted liver, and V58.11, encounter for antineoplastic chemotherapy). The remaining 226 had other main diagnoses.

In the study period, there were 3491 hospitalizations with at least one discharge code among those considered as suggestive for sepsis, without a laboratory confirmation. Only 213 (6.1%) were discharged from surgical wards. As shown in *Table 3*, sepsis was included among the discharge diagnoses more frequently when a blood culture test was done than otherwise, and more frequently when at least one bottle turned out positive than in case of no growth in any bottle.

Of 2231 patients with positive blood culture tests from 2014 to 2017, we found information on the pathogens that were isolated in 2184 cases. In 594 of them, more than one microorganism was isolated. There was very little difference in the frequency of sepsis discharge diagnoses among patients with only one isolated microorganism (784 cases/1560, 49.3%) and those with more than one microorganism (311/594, 52.4%; p-value of χ^2 test 0.20). *Table 4* shows the frequency of pathogen genera that were isolated from the blood and, for each genus, the proportion of hospitalizations with a sepsis discharge diagnosis. For the most frequently isolated pathogen genera, the percentage of hospitalizations with a sepsis discharge diagnosis was always < 60%. From 2014 to 2017, there were 41 hospitalizations with isolation of CRKP: a sepsis diagnosis was found in 63.4% of those hospitalizations. The frequency of sepsis diagnoses in 159 hospitalizations with isolation of non-resistant Klebsiella pneumoniae was lower (47.2%; p-value of χ^2 test 0.06). However, in the 11 cases of CRKP discharged from surgical wards, only 2 (18.2%) had a discharge diagnosis of sepsis, whereas sepsis was coded in 24 out of 30 cases discharged from medical wards (80.0%).

DISCUSSION

Accurate coding of hospital discharge diagnoses is crucial not only for reimbursement issues, but also for health management and, last but not least, for allowing valid epidemiological estimates. In fact, hospital discharge codes from administrative data are extensively used for studying the epidemiology of a plethora of diseases and conditions and have substantial impact on epidemiological estimates [10]. For this reason, much research is being conducted to assess their accuracy [11-16].

Sepsis is one condition whose epidemiology has also been studied through hospital discharge summaries [1, 4, 17] and diagnosis coding has been shown to have impact on epidemiological estimates [4]. Various measures of validity of discharge diagnosis codes for sepsis have been investigated, showing variable results depending on the particular diagnosis of interest, calendar year, setting [5-7, 18] and attempts to develop optimized ICD-based case definitions have been done to increase validity [8].

In Italy, a study conducted in the Veneto Region described the burden of sepsis-related mortality based on death certificates [19], whereas hospital discharge data have never been used for epidemiological estimates and their validity on sepsis had never been assessed so far.

Through a comparison of hospital discharge diagnoses ICD-9-CM codes with laboratory results, we found that only half patients with laboratory-confirmed bloodstream infections were discharged from the Italian University Hospital of Udine with a diagnosis suggestive of sepsis. Despite the proportion of hospitaliza-

Table 3

Distributions of hospitalizations in the University Hospital of Udine, North-Eastern Italy, 2011-2017, according to blood culture tests and sepsis discharge diagnoses

		Blood culture test with ≥ 2 positive bottles			Blood culture test with 1 positive bottle			Negative blood culture test			No blood culture test		
Year	**Hospitalizations**	**N**	**n with sepsis diagnosis**	**%**	**N**	**n with sepsis diagnosis**	**%**	**N**	**n with sepsis diagnosis**	**%**	**N**	**n with sepsis diagnosis**	**%**
2011	45 224	428	196	45.8	409	113	27.6	2726	134	4.9	41 661	182	0.4
2012	44 568	453	218	48.1	421	139	33.0	2670	136	5.1	41 024	176	0.4
2013	43 526	459	229	49.8	453	144	31.8	2916	155	5.3	39 698	212	0.5
2014	41 795	499	253	50.7	438	143	32.6	2924	162	5.5	37 934	165	0.4
2015	41 440	549	292	53.1	452	142	31.4	3128	165	5.3	37 311	201	0.5
2016	41 488	586	301	51.3	420	135	32.1	3256	187	5.7	37 226	203	0.5
2017	41 671	597	280	46.9	495	160	32.3	3640	226	6.2	36 939	211	0.6
Total	299 712	3571	1769	49.5	3088	976	31.6	21 260	1165	5.5	271 793	1350	0.5

Table 4
Proportion of sepsis discharge diagnoses in hospitalized patients with ≥ 2 positive aerobic or 2 anaerobic bottles, by genera of the isolated pathogens, University Hospital of Udine, North-Eastern Italy, 2014-2017

Genus	Total pathogen isolations[1]	% with sepsis diagnosis
Acinetobacter	9	33.3%
Actinomyces	1	0.0%
Aerococcus	1	100.0%
Aeromonas	6	83.3%
Alcaligenes	4	25.0%
Bacillus	3	66.7%
Bacteroides	28	50.0%
Brevibacterium	4	50.0%
Candida	150	58.7%
Chryseobacterium	2	50.0%
Citrobacter	26	26.9%
Clostridium	16	31.3%
Corynebacterium	14	50.0%
Cryptococcus	1	0.0%
Enterobacter	82	47.6%
Enterococcus	270	51.5%
Escherichia	717	54.4%
Fusobacterium	2	50.0%
Gemella	3	66.7%
Haemophilus	4	50.0%
Hafnia	1	0.0%
Klebsiella	256	46.5%
Kocuria	2	100.0%
Leuconostoc	1	0.0%
Listeria	11	36.4%
Morganella	7	57.1%
Neisseria	1	100.0%
Ochrobactrum	2	100.0%
Pantoea	2	50.0%
Peptostreptococcus	1	100.0%
Prevotella	2	50.0%
Propionibacterium	12	50.0%
Proteus	49	51.0%
Providencia	5	40.0%
Pseudomonas	140	52.9%
Raoultella	7	28.6%
Salmonella	13	69.2%
Serratia	35	37.1%
Shewanella	1	100.0%
Sphingomonas	3	0.0%
Staphylococcus	995	50.6%
Stenotrophomonas	18	38.9%
Streptococcus	175	55.4%
Torulopsis	18	50.0%
Yersinia	1	0.0%

[1] The sum of total isolations is greater than the number of hospitalizations with positive blood culture tests because of the isolation of multiple pathogens in 594 hospitalizations.

tions with laboratory-confirmed bloodstream infection had increased monotonically from 2011 to 2017, no analogous increase was evident in the sensitivity of discharge diagnoses. In our hospital, sensitivity of any of the ICD-9-CM codes we considered suggestive of sepsis was slightly lower than 50%, similar to that observed in Canada using an ICD algorithm from the Canadian Institute for Health Information [8].

In the late 1980s, Romano and Mark, in California, observed that acute conditions with quick resolution, such as mild sepsis, could be missed in the hospital discharge records if other complications, determining prolonged hospital stay, affected the patient [20]. This seems not to be the case in our hospital. Competing high-severity or high-impact diagnoses were unlikely explanations for the omission of sepsis-related codes from list of 6 discharge diagnoses in Udine, since in more than 80% of cases of omitted sepsis codes, less than 6 diagnosis codes were compiled. Among patients with positive blood culture test but no sepsis diagnosis, one fifth had a main discharge diagnosis of cancer. Not even an ICU stay was sufficient to increase the likelihood that a laboratory-confirmed sepsis is reported among the discharge diagnoses.

The undercoding of sepsis was much more common in surgical wards than in medical wards and, in surgical wards, was more likely in case of in-hospital death. Type of hospital ward seemed to be strongly associated with discharge diagnoses sensitivity even in the analysis controlling for patient's characteristics. Higher sensitivity was observed in the 2014-2017 sub-analysis when particular pathogens were isolated from the blood cultures: for example, sensitivity was greater than 60% in case of CRKP and less than 50% in case of Carbapenem-sensitive Klebsiella pneumoniae. Again, however, sensitivity was high only when patients were discharged from medical wards and very low in surgical wards. Audits are certainly worth being conducted in the wards where the undercoding is more evident, and periodical ICD coding training should be provided in our hospital.

In this study, we also observed that diagnoses of sepsis were assigned to patients with a single positive blood bottle, to patients with no positivity, and even to patients with no blood culture tests. The proportion of hospitalizations with a diagnosis of sepsis decreased steeply from cases with double positive blood test, to single positive cases, to negative cases, to no-blood-culture-test hospitalizations. Nonetheless, the absolute frequency of patients with a diagnosis of sepsis with no laboratory confirmation was twice the number of patients with correctly coded laboratory-confirmed sepsis. Of course, not all those cases were necessarily misclassified. A blood culture can turn out negative if a patient has already started antibiotic therapy, or the physician may be aware that the patient is septic because of his/her clinical history, without the need of a concurrent laboratory confirmation. In some cases, though, miscoding or even misdiagnosis can be an issue. A number of clinical conditions, in fact, can mimic sepsis (e.g., non-infectious causes of systemic inflammatory response syndrome, myocardial infarction, pericarditis, myocarditis, massive pulmonary embolism, etc.) [21] and differentiation may be challenging especially in the absence of a microbiological identification of the underlying cause.

The availability of administrative health data including laboratory results allowed a relatively quick assessment of the sensitivity of ICD-9 codes from hospital discharge records on sepsis in the University Hospital of Udine, using blood culture test double-positive results as a strict gold standard. On the other hand, we could not assess the extent of false positive ICD-9 codes, since we could not exclude sepsis in cases lacking two positive blood culture bottles.

CONCLUSIONS

Using ICD-9 discharge codes for epidemiological estimates of sepsis may yield biased results in the Hospital of Udine. We believe that, although this result is only based on data from a single hospital, it can be generalized to other Italian hospitals, since the frequency of errors and the characteristics of hospital discharge records are quite similar across the various Italian Regions [22]. Audits and ICD coding training are worth being implemented since the quality of diagnosis registration and coding is important for scientific research, health planning and risk management.

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Conflict of interest statement

None.

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Impact of the lack of integrated care for older people with urinary incontinence and their family caregivers: results from a qualitative pilot study in two large areas of the Marche Region

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Abstract

Objectives. Urinary incontinence (UI) may have a severe impact on older people and on their family caregivers' quality of life, especially when support services are scanty or inadequate. This study investigated the support needs and expectations of community-dwelling older people with UI and their family caregivers in the Marche Region (Central Italy).

Methods. Face-to-face semi-structured interviews were carried out to eight over-60-year-old patients with UI, four family caregivers, two representatives of the Regional Health System and two pharmacists.

Results. Findings show that the insufficient supply and low quality of continence products and the lack of integrated care services negatively affects the well-being of both older people and family caregivers.

Discussion. Integrated care services and a standardized system for the periodic assessment of sufferers and a more customized service delivery, including the possibility of choosing brand and type of products for users, may improve the current provision in this Italian Region.

Key words
- family caregivers
- integrated care services
- older people
- urinary incontinence

INTRODUCTION

Global population ageing is one of the most important socio-demographic phenomena of this epoch. Across the European Union (EU) Member States, Italy reports the highest share of people aged 65 or older, who constitute 22% of the total population [1]. In association with population ageing, an increasing number of people either suffer from multiple chronic diseases – in Europe circa 50 million of people are estimated to be in this condition, making it the first cause for morbidity [2], or die as a consequence of a chronic disease. Related annual deaths are projected to rise to 52 million by 2030 [3].

Urinary incontinence (UI) is linked to age-related multi-morbidity, and as such is becoming an ever-increasing societal problem. The International Continence Society (ICS) defines UI as an involuntary leakage of urine, which is well detectable and creates social or hygienic problems [4]. On the whole, UI affects from 3% to 23% of men and from 11% to 52% of women [5], and is more frequent among institutionalized older persons, especially if suffering from dementia and limited mobility. Its prevalence in residential settings reaches a rate of 50-80%, and UI is per se also a predictor of institutionalization and of death among institutionalized older people [6].

The levels of shame and embarrassment related to UI are higher than those caused by other widespread conditions, such as depression or cancer [7]. As such, it has a strong "stigmatizing" power [8], and may deeply affect self-esteem [9]. For example, a survey conducted in the UK shows that although 25% of women and 10% of men suffer from UI, only one in ten consults a doctor for this reason [10].

The daily management of UI-related care tasks might represent a heavy burden not only for those who suffer from it, but also for their caregivers. In Italy, indeed, as in many other Southern European countries, fami-

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lies are largely involved in the daily care of older people [11], and family caregivers cover between 50% and 90% of the total (formal and informal) costs for long-term-care provision [12], often not from choice but because of a lack of appropriate public supports. The assistance of an older relative with UI can have negative consequences on the caregivers' physical, psychological, social and financial status, more than in the case of a relative without UI [13], because the UI management requires a greater amount of watchfulness and implies greater financial costs [14, 15]. Many caregivers report physical exhaustion [15], due to the lack of sleep and leisure time [15, 16] and social isolation [17], because of the difficulty in living in a dignified condition that allows them to interact with friends and other family members [18]. The highest levels of burden are experienced especially by family caregivers of older people with UI associated with cognitive impairment [19].

The availability of quality products for UI (also referred to as continence products), such as, for instance, absorbent pads, and of appropriate support services on how to use them to tackle UI-related discomforts, may play an important role in enhancing the quality of life of older people with incontinence (OPI) and of their caregivers, by reducing the stigma deriving from UI symptoms [20]. In particular, pad performance can affect one's self-confidence, self-perception and other psychological dimensions [21]. The use of hypoallergenic and absorbent products can improve the patients' and caregivers' quality of life [22], by reducing the frequency of changing pads, and preventing bedsores and rash [23], thus avoiding the negative events that most affect social contacts [24]. Ensuring a comprehensive and correct information about UI and continence products' features and usage may therefore represent a crucial strategy to enhance users' and caregivers' quality of life. So far, however, only very few national health systems (NHS) in Europe provide this kind of support and training for caregivers on a systematic basis [25].

Very few studies have focused on this issue, and even less provided detailed insights on how the whole process is carried out, for example in terms of user eligibility, assignment of reliefs, and delivery procedures. Especially in the Italian context, where health-care provision is organized at regional level (i.e. the State allocates funds to regions, which are responsible for taking decisions on how to spend them to address the different health needs of regional populations), the few studies in this field were carried out by private foundations [26] and patient federations [27].

The lack of a nationwide homogeneous, appropriate support and the above-mentioned still widespread, stigma-driven silence on UI, show how difficult the situation of Italian caregivers can be: in most cases they cannot count on a strong public and private support network, appropriate information or suitable incontinent products [28]. Long waiting times for receiving the products, administrative procedures for accessing the service, and inadequacy of aids in terms of quantity and quality worsen an already weak provision [26].

To help bridge the gap in this area, the National Institute on Health and Ageing's (INRCA) carried out a pilot study aiming at investigating the process of allocation, delivery and distribution of continence products by the Regional Health System (RHS) of the Marche Region, and at understanding the needs and expectations of older patients with UI living in the community and of their family caregivers. In light of the above, we provide first a description of the methodology employed in the study – including the characteristics of current service provision, to clarify the context in which the survey was performed – followed by an analytical illustration of the main findings and their discussion.

MATERIALS AND METHODS

The study was carried out between January and April 2015 in the urban area of Ancona (i.e. the capital city of the Marche Region). It developed through two main phases. First, the national and regional legislation governing services for continence management and the guidelines referring to the absorbent products' delivery process were analysed. Second, experts' interviews were carried out, where "experts" were considered – following Meuser and Nagel's approach (2009) – both professionals (e.g. representatives of the Regional Health System and pharmacists) OPI and their family caregivers [29].

Sample size and inclusion criteria

In order to identify the different perspectives characterizing all main stakeholders participating in the investigated phenomenon, the sample of respondents was multifaceted and included: eight OPI; four family caregivers; two representatives of Marche's Regional Health System (RHS) administration; two local pharmacists *(Table 1)*.

The first objective of the sampling was to identify and involve persons representative not in terms of statistical power but for the knowledge they brought. Thus, the main criteria shaping the selection of participants to the study was to identify people with knowledge of the management of IU and experience of the public service dedicated to it [30]. In light of this, the individuals best fitting with these characteristics were people aged 60 and over, who suffered from slight leakage of urine or frequent urge or who had no control. They were recruited by means of a sampling among the over-60-year-old patients reporting those symptoms admitted to the "Urology" and "Neurology" wards of INRCA Geriatric Hospital

Table 1
Sample composition

Typology of interviewed stakeholders	Number
Older patients with UI	8
Caregivers	4
Representatives of Marche's Regional Health System	1
Marche Unique Contracting Authority Service (MUCAS)	1
Pharmacists	2
Total	16

UI: Urinary incontinence.

"U. Sestilli", located in Ancona (i.e. the capital city of the Marche Region). When older persons could not answer directly to the interview due to cognitive disability, their main family caregivers were involved in responding both as proxies and as addressees of some additional specific questions. In order to investigate and compare different conditions in which UI takes place, the sample was divided into cognitively able and impaired patients. The first group embedded three sub-groups, reflecting the main types of patients treated by the aforementioned hospital wards: women with stress-related UI; people with UI treatable through sacral neuro-modulation surgery; and people with UI due to other causes.

Four family caregivers, providing care to older people with UI (different from the eight cases above), were also recruited via the same two INRCA hospital wards.

A representative of the RHS and one of Marche's Unique Contracting Authority Services (MUCAS) were identified as expert witnesses, as they play a pivotal role in managing the process of assignment and distribution of continence products. Two pharmacists were selected from local urban areas reflecting populations with different socio-economic status (in terms of income and housing conditions), in order to detect possible differences among citizens in purchasing continence products related to this factor.

Data collection tool and analysis

The topic guide used to administer interviews was adapted to the four different typologies of subjects illustrated above, but keeping the same, basic thematic areas: type of absorbent products; the process of authorization and distribution of products; critical situations encountered; and suggestions for improvement. Informed consent was obtained from each respondent included in the study, and the protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the Human Research Committee Institution. The administration of the qualitative interviews was covered by the approval for a larger, comprehensive and longitudinal study targeting all INRCA hospitals patients in the Marche Region, named Reportage. The latest was approved by the INRCA Ethic Committee on 17th February 2011 (Approval Communication n. SC/10/272) and the approval was applicable also to family caregivers. The interviews were carried out by a psychologist skilled in the treatment of UI-related psychological malfunctions in connection with pelvic-perineal problems, who took minutes and transcribed the most important parts of conversation verbatim.

Data gathered from patients and caregivers were organized following the framework analysis approach, i.e. through case and theme matrixes [31]. This method was used to organize and manage data through the process of summarization, resulting in a matrix output that allowed the researchers to analyse data both by cases and themes.

Through the scrutiny of the raw data, the researchers identified key issues, concepts and themes by drawing on a priori issues and questions derived from the aims and objectives of the study, as well as issues raised by the respondents themselves and views or tales of facts recurring in the data. After that, quotes were sorted out and researchers made comparisons both within and between cases. Data were rearranged according to the appropriate part of the thematic framework to which they related, and the case/theme matrixes were designed. Finally, the charts were used to define concepts up to a second-level analysis that enabled possible causal correlations to be identified among themes emerged from the inquiry. Results concerning OPI and caregivers were reported through a narrative technique, with the support of quotations extracted by the transcriptions.

Data collected from the different subjects involved in the process (from the initial prescription to the everyday use of pads), and information from the legislative framework review, made it possible to understand how and to which extent the public care system dedicated to OPI meets their needs within their social context, and to identify existing correlations among the service characteristics and older persons' behaviours [32].

The analysis allowed the identification of the main issues and the formulation of possible solutions [33]. Given the small sample, the exploratory and piloting nature of the study and the restricted number of the analysts (i.e. 2 researchers), the interviews could be managed without the support of a qualitative software program [34].

RESULTS

Continence care service in the Marche Region: legislative background

Before reporting the findings emerging from the expert interviews, it is useful to illustrate the process through which OPI and their caregivers receive continence products in the investigated regional context. The review of national and regional legislation shows that Marche Region Health System is divided into "Large Areas" (LAs), organized into District Health Boards (DHBs). LAs are autonomous and implement services for people with UI according to the minimum level of health services guaranteed nationwide for free to all citizens by law, within the limits of public expenditure set by law 332/1999. In the Marche Region, the general practitioner (GP) or the relevant specialist prescribes the type of products considered adequate to the patient's disorder, by using specific codes identifying the aid/prosthesis. With regard to continence pads, a monthly maximum of 60 pieces per patient is currently set as the standard amount by the Marche Region (except for patients with recognized special needs, who are entitled to a higher number of aids), for a charge of 19.20 € per month (as set by the State Law with Council Resolution No. 1696/2012). The GP sends this request to the Prosthesis Office (PO), which evaluates the adequacy of certification according to the severity of the disorder, even if in this region there is not a protocol for assessing UI according to validated assessment tools. If adequate, the PO authorizes the delivery of services/products and the user can receive the absorbent aids. Otherwise, the authorization is blocked until the doctor produces a new adequate prescription. Currently, no data are available for this region on the number of days needed for a new request to the PO by the GP and the related authorization. In this regard, it should be noted that the RHS does not allow to choose pads types, nor provides any advisory services or training on how to choose and correctly use the continence products; and there is no system in place for assessing patients' satisfaction. The purchase of the continence products by the RHS is based solely on the criterion of the lowest price offered by competing companies, and the process is not (yet) managed by the Marche Unique Contracting Authority Service (MUCAS), a body which has been recently set up to draft and launch common calls of tender for the whole Marche Region. Until this is no longer the case, each LA remains autonomous from an administrative and economic point of view, and can choose the continence products it prefers, with the only condition being that it respects the general expenditure limits fixed by law.

The perspective of older persons with UI

This pilot study involved patients from two LAs. The LA n. 2 embeds four municipalities (Ancona, Fabriano, Jesi and Senigallia) positioned in the central part of the region. The LA n. 3 includes three municipalities (Camerino, Civitanova Marche and Macerata) positioned in the central-southern part of the region. Out of the eight OPI interviewed *(Table 2)*, three came from Macerata, a town located in the hinterland at about 50 km from Ancona, a district with a potentially different approach to the distribution and provision of services and products for UI. The major part of the sample was represented by women (6 out of 8 cases), married persons (5 out of 8) and subjects with a low educational level (6 out of 8 reported an elementary school qualification). Given the high mean age (over 78), the interviewees were not active in the labor market. The older patients interviewed reported different severity levels of UI. Very often they were not fully aware about the latter, because they had not been officially diagnosed with regard to the functional quality of their disorder, so that its consequences in terms of possible discomfort for them had not been sufficiently investigated. The first three interviewees did not even remember the exact time of the onset of the condition, as initially they did not place much importance on the issue. Several women in the sample showed a sort of 'sacrificial' approach in this respect, as they were used to considering work and the care of their loved ones first, before thinking of their own needs. Therefore, they took on multiple responsibilities and tried to keep everything under control, with the result of losing sight of themselves: *I didn't have time to think about it (UI), I had to work, to take care of my grandchildren and to cook for everybody. I couldn't think of myself* (Case 2).

The older patients with mild and average UI considered it to be "natural" to have slight leakages during a task requiring effort or while laughing, thus regarding this experience to be part of a "regular" process of ageing, as reported by Case 3:*It is normal that when you age even the body becomes old.*

So, it seems to be quite common that, from the onset of the first symptoms to the first visit to a specialist, many years might pass without any evaluation of the severity of the symptom or any intervention: *I do not remember when it started, maybe several years ago, at the beginning I did not care...* (Case 4).

The interviewees decided to go to the GP or to the specialist, after the appearance of a prolapse, or because the pressure to go to the toilet became very frequent. Indeed these symptoms, in the long term, might become irreconcilable with social and working life, and might require intervention by sacral neuromodulation to reduce them. In this case, for example (*Table 2*, Case 6), one patient reported that she felt *enervated* as a result of the necessity of going to the toilet every five minutes. She referred that, since she started to suffer from this disorder, she had *travelled far and wide before finding an answer*, as each specialist had suggested a different solution to her problem. Clearly, her quality of life had worsened considerably and she had developed a strong form of mood disorders like anxiety and depression, for which she had to take psychopharmacological drugs, with several side effects such as gastrointestinal disorders, nausea, headaches.

Table 2
Demographic features of older patients

Case number	Age	Large Area	Gender	UI	Other diseases	M. Status	Children	Education	Occupation	Support received
1	79	LA n. 2 (AN)	F	Low	None	Widow	2	Elementary	Retired	None
2	64	LA n. 2 (AN)	F	Low	None	Married	2	Elementary	Retired	None
3	75	LA n. 3 (MC)	F	Mild	None	Single	0	Elementary	Retired	None
4	84	LA n. 2 (AN)	F	Severe	None	Married	3	No degree	Housewife	Daughter
5	88	LA n. 2 (AN)	F	Severe	Dementia	Widow	2	Elementary	Housewife	MCW
6	61	LA n. 3 (MC)	F	Severe	Mood Disorder	Married	1	High school	Retired	None
7	85	LA n. 3 (MC)	M	Severe	Dementia	Married	3	Elementary	Retired	Daughter MCW
8	94	LA n. 2 (AN)	M	Severe	None	Married	1	Elementary	Retired	Daughter MCW

UI: Urinary incontinence; AN: Ancona (Marche Region, Italy); MCN: (Marche Region, Italy).

Given their different health conditions and levels of UI severity, older patients used different absorbent products. In the case of a very severe UI, some respondents preferred adult nappy pants with fixing tapes, a product that is adopted and distributed by the RHS. In case of not frequent leakages (mild or moderate UI), users preferred rectangular pads. As for quantities, for half of the patients the number of absorbent products provided by the RHS is inadequate or insufficient, and patients suffering from severe UI have to buy additional products out of their own pocket: *I have to spend a lot of money every month to buy pads. That's incredible. I'm disgusted,* said Case 4, and *really I spend too much on buying the products I need* was Case 3's remark. The expenses borne by the interviewed users for filling this gap amounted to about 100-200 €per month. Much more expensive is the cost sustained by the older patients' families in terms of private care work (e.g. migrant care worker or private nurse), hired to provide support in everyday care delivery – including continence care – since for this, three out of five of the interviewed households spent approximately 1700-1800 € per month.

It is finally worth mentioning that there is an evident mismatch between older people's continence needs and the type of products delivered by the RHS: *These kind of pads are no use for me! I need a different model of pad! I can't go outside with these big ones!* said Case 1. This is evident in light of the fact that often patients suffering from mild and moderate leakages prefer buying more suitable products, rather than accepting those supplied by the RHS, even if free of charge, because these pads are suitable only for persons with severe UI. This is partly due to the fact that OPIs usually cannot choose and select absorbent products.

The perspective of family caregivers

Family caregivers were represented by three women and one man living nearby the cared-for person. They started caring for their elderly relatives from the very beginning of the symptom onset, and continued doing so, mostly on a daily basis, for about 5 to 6 years. The main motivations for providing assistance were love, affection and sense of duty. The interviewees often needed support for themselves, including better information on how to deal with UI management. They reported many somatic disturbances, such as crying, anger explosions and insomnia: *I often cry and feel angry* (Case 2).

Daytime tiredness is the consequence of the psychological and physical burden they experience every day. Indeed, most interviewees reported that caring for an OPI affected their own quality of life, contributing to the onset of a prevailing sense of daily sadness. A woman stated: *Yes, to stay in close contact with a sick person is emotionally conditioning, in the sense that you feel sad all the time*' (Case 1), while another complained '*I am exhausted, both mentally and physically* (Case 4).

Changing pads at night is a particularly annoying discomfort, as this activity affects not only the quality of sleep, but also the quality of life during the following day: *I do not sleep well, because I have to wake up several times a night for changing pads or because my mother calls me and screams* (Case 3). Family caregivers also complain about the lack of respite and the interruption of any social activity due to care commitments.

One of the main problems faced by the interviewed family caregivers, however, were the lack of information about the prices and characteristics of the continence products, and the lack of training on how to best apply and manage pads: *We don't know anything about the cost of the pad and its characteristics, we only know that we have to use it because that's the law… we can either accept it or not… that's it!,* said Case 2.

Three out of four caregivers received products at home, but none could choose or indicate the preferred way of delivery, nor the model of pad. Those receiving pads at home considered this delivery modality as acceptable, while the one who had to collect the products in a pharmacy defined this mode of delivery as *non-functional*.

In light of these difficulties, several suggestions were collected from among the interviewees. On the one hand, older patients suggested implementing the home distribution of continence products in the whole regional territory, and underlined the necessity of increasing the number of products supplied per month, because the current number is insufficient for a medium/severe UI level.

On the other hand, family caregivers suggested that help from public services should be increased, especially in the form of more information about continence products' features and their usage: *We need more information about UI in general, about the products to use and how to use the pads, too!*, said Case 5. All interviewees in general complained about the lack of clear eligibility criteria, and the long and difficult procedure needed to obtain the pads supply: a problem that they suggested should be tackled via a substantial simplification of the related bureaucracy.

The perspective of pharmacists, of regional representatives and of the Italian Federation of non-continent persons

In Ancona and its surroundings, the delivery of absorbent aids currently takes place through the pharmacies, where all types of continence products are available. Thus pharmacists represent strategic "expert witnesses", and can provide a more in-depth understanding of service criticalities. For this reason, two pharmacists working in two different urban areas were interviewed, reflecting socio-economically different neighbourhoods.

Pharmacists noted, in the first place, that users often buy products that are not among those covered by the RHS, because out-of-pocket purchased products provide a higher satisfaction, since patients can choose high-quality products that better fit their personal needs.

Secondly, in their opinion, the number of pads currently provided by the RHS should be increased, because this is the only measure that can really enhance users' quality of life. One pharmacist was quite favorable to the adoption of a voucher system (according to which eligible recipients would receive a voucher of a certain value, which they can spend in any pharmacy, possibly integrating its amount with their own resources to choose the type of products they wish). The other interviewed pharmacist, however, believed it would be better not to change the current practice, thus suggesting that the current system should be kept (and amended only in terms of higher quantities of products allocated to users). Both, in any case, would prefer to maintain the 'advisor and consultant' role, a trust-based role that they have been able to build with their customers over the years.

According to the MUCAS, a possible solution for improving the current process of allocation and distribution of continence products might be found via a more effective, standardized system for assessing the amount and frequency of urinary leakages. This position is based on the observation that, currently, a wrong evaluation of the severity of the symptoms by the general practitioner can easily lead to a wrong prescription of continence aids: *What we need is not so much a different way to distribute devices, but rather a different way to assess the congruity of the product. At the beginning of the whole process, the doctor's prescription is often superficial, as he doesn't consider the severity level of UI itself, including for how long the person has been suffering from it, or what kind of UI he/she suffers from and his/her need to reach a toilet etc.*

As a consequence, within the current system in the Marche Region, it repeatedly occurs that a person with a low UI severity ends up receiving the same products as someone suffering from a far more severe UI level.

DISCUSSION

The study results are compliant with previous Italian studies highlighting the delivery process criticalities [26, 27] and the literature concerning the additional burden posed by UI-management for family caregiver [35] on different realms of life [35, 25] and in terms of social isolation [36, 18]. This study confirms that UI is often not recognized as a disorder worthy of attention, either by sufferers or by their caregivers, because both consider it as a component of the 'natural physiological process' following age-related deterioration. This behaviour may conceal the shame that characterizes UI, and confirms the 'stigmatizing' power of the condition, which may have hindered a prompt symptoms' evaluation for a timely and proper intervention [37, 38].

The study shows the interaction between psychological–biological and social factors and proves that UI can lead to the development of psychological disturbances' development, which are exacerbated by the difficulty in finding the right response.

Moreover, the study also underlines the need for a standardized and uniform system for the assessment of the patients' condition and for a customized system for assigning continence products, in order to take into consideration the possibility for users to choose the type and quality of aids according to the severity of their UI.

Furthermore, the lack of a long-term and integrated care system for the assistance of older people with UI and for the support of their family members is evident in the Marche Region. The public service is indeed limited to the free-of-charge delivery of continence products that are insufficient in number and quality. This forces patients to purchase out-of-pocket additional and better aids, with financial consequences. Thus, the current service seems to be disrespectful of OPI's dignity, well-being and economic condition.

The observed lack of information and training services for patients and caregivers suggests, in addition, that ad hoc training opportunities on how to manage relatives with UI and support for the emotional aspects that might derive from the caring activities (i.e. anxiety, fatigue, anger) should be offered especially (but not only) at the point of discharge from hospital wards.

While the qualitative approach of this study allowed to carefully analyse the different facets of the examined issue, the investigation presents also some limitations. The first is the local coverage of the collected data: additional cross-regional research on this issue is needed in Italy, to gain a clearer picture of possibly different regional policy approaches to ensure fair and adequate assistance to OPI and their family caregivers across the country.

The second restriction is the small sample size that, albeit compliant with the qualitative nature of the research design, cannot provide an exhaustive picture of the phenomenon at national level. Nevertheless, this first study gave insights for another quantitative study in the Marche Region involving larger samples, started in March 2016, whose findings are being currently analysed.

CONCLUSION

The study results provide evidence that when integrated and tailored services for UI are missing, OPI and family caregivers can experience emotional and physical upsets and that the insufficient provision of continence product exacerbates this condition. Thus, the main suggestion arisen from the study is to consider UI as a bio-psycho-social disorder needing a multidisciplinary, integrated and holistic approach, for taking care of the entire person (e.g. environment, family and social relationships, psychological well-being, lifestyles), and not only of a single disease. Such an approach, compliant with the principle of human beings dignity and the right to high quality, timely and tailored care, could be applied to the continence care via concrete measures at Regional and National Health Systems level, and it would contribute to positively impact on the different actors involved in the delivery of services for UI. First, OPI might count on better continence products and prevent incontinence related discomforts. Second, family caregivers might reduce physical fatigue and avoid emotional stress. Furthermore, the Regional Health System might limit costs related to non-pertinent prescriptions and allocation of public resources, especially if this is achieved via a standardized assessment of the products' adequacy to users' time-sensitive needs.

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Conflict of interest statement

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iGeneration's social media usage in retrieving information related to healthcare education: a web-based survey among Italian and Romanian undergraduate medical students

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Abstract

The aim of our study was to assess medical undergraduate student's preferences associated with the value of information/learning methods via social media. An electronic questionnaire was developed and applied to undergraduate medical students from two university centers: Foggia (Italy) and Cluj-Napoca (Romania). 1196 answers were collected, 326 from the Italian university, and 870 from the Romanian university. Students use smartphones to access Facebook, from home, in average 1-3 hours daily. Along with school bibliography and Internet, social media is an active part of the academic life of students. Social media is used to search for information about a specific medical topic or to manage daily student activities. Romanians frequently share information with other colleagues or search for topics related to courses taught at school. The medical students use social media for academic purposes similarly in Italy and Romania.

Key words
- undergraduate students
- healthcare education
- social media

INTRODUCTION

Social media (SM) defines the online platforms that enable the user to create and publish information. These platforms have user generated content, a high degree of interaction between creator and viewer, and can easily be integrated with other sites [1].

Currently, five generations could be seen as making up our society, each having an active role: the Silent Generation (born 1945 and before), the Baby Boomers (born 1946 to 1964), the Generation X (born 1965 to early the 1980s), the Generation Y or Millennials (no precise start and end dates; the most commonly used timeframe is early 1980s to the mid-1990s or early 2000s) and the Generation Z (starting late-1990s or mid 2000s) [2, 3]. Students enrolled in universities starting early 2010s fall into Generation Z, also known as iGeneration, iGen or Post-Millennials. They have been raised in this world with Internet, smartphones, and social media, so, this generation has no ability to understand a world without these features [4]. Social media is a medium to connect to the world more than any other channel or communication option for the iGen [5]. The technology savviness of this generation was documented in previous research, showing that social media can be used as an information sharing or collaborative learning tool, and to educate students on a global scale in a virtual form (e.g. teaching through multiplayer virtual world games, podcasts, etc.) [6, 7]. Medical education goes beyond the boundaries of the classroom [8], and social media has been used as an open-learning resource for medical students [9] as well as a tool for active engagement of undergraduate students [9, 10].

Third-year students of the University of Tennessee Health Science Center College of Pharmacy communicate with classmates about course content and connect with professors via social media [11]. In United States, Wiki-based learning proved to enhance nursing education [12]. Specifically, Wikipedia was found to be an appropriate educational tool, judging by learning outcomes [13]. Furthermore, in Canada, the same platform, has shown short-term knowledge acquisition in medical students [14]. Canadian nursing students perceive social media as an educational tool, but their

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faculty members use it much less for this purpose [15].

Similar research questions were addressed to first-year nursing students of one university in a large major city in Australia, and the same outcome was depicted: Facebook (specifically) was found to be a useful avenue for peer-to-peer learning and support [16]. Other researchers within the same geography, showed that medical students positively support the use of social media (specifically Twitter) in medical education as it enables student-staff engagement [17], but more in principle than in practice as they still prefer to print out, highlight, and annotate the lecture material [18].

In 2016, undergraduate medical students in Saudi Arabia, mostly using YouTube, found social media to be beneficial (efficient and effective) for academic purposes, but considered that their tutors did not use SM effectively [19]. In 2017, Al-Jumaili *et al*. showed that Facebook is accessible and easy to use tool for academic communication among Iraqi pharmacy students [20].

A study on Israel nursing students demonstrated the positive and key role of social media in class and the clinical placement. Furthermore, students expected faculty members and nurse educators to use social media to provide support and guidance during the learning process [21]. In 2017, a research conducted at Ludwig-Maximilians-University Munich, Germany, found Facebook groups to be an essential part of the learning environment of their medical students [22].

Social networking sites, in particular Facebook, are popular among United Kingdom (UK) pharmacy students [23]. Twitter, in UK, proved to be a feasible tool for both Plymouth University's nursing students [24] and Southampton University's medical students [25], creating an online support network during learning by enhancing communication methods with teachers and increasing morale among students. Additionally, Facebook pages have demonstrated to be useful tools to support medical students in preparation for high-stakes timed anatomy assessments in the UK [26]. The response of the undergraduate students about the use of social media in medical education is positive, but the efficacy of the teaching strategies via social media lack scientific evidence regarding the outcome of the teaching intervention and thus the benefit from social media as a learning tool [10; 27-29].

The use of social media across Europe was reviewed by different organizations *(Table 1)*. A research among Romanian population of 2014 highlighted the preferred time to use social media as evening time and the preferred place as home [30]. Starting in high school or college, Romanian students are aware that the use of social media has advantages and disadvantages [31].

This study aimed to assess the value of social media usage among Italian and Romanian undergraduate medical students in order to identify the most common resources used in education.

MATERIALS AND METHODS

Participants and procedures

During December 2016-January 2017 in Italy and February-May 2017 in Romania, we conducted a cross-sectional web-based study among undergraduate medical students. We invited all students at the University of Foggia, Italy (n = 1808) [36] and at the Iuliu Haţieganu University of Medicine and Pharmacy, Romania (n = 4218) [37] to participate. The universities included in the analysis are both public universities and have similar educational programs (six years program for medicine and dentistry, five years for pharmacy, four years for midwives and nursing, and three years program for physiotherapy and other medical/healthcare related sciences) with qualifications recognized in the European Countries, as well as similar ranks according to Scimago Institutions Rankings (with the Italian university on the 1173 position and the Romanian university of the 1218 position). The investigated universities have similar paths, and just a cultural difference may emerge.

We built the questionnaire through 6 steps: a literature review, construct definition, writing the survey items, pretesting on prospective respondents, and reconciliation of the definitions found through the literature with the suggestions made by the target audience and final revision by a pool of experts [38]. We examined students' perceptions and attitudes toward social media as an educational tool using 12 items as closed questions (single choice (5), multiple choice (4), Likert-scale (2)), and one open question. The Likert-scale had five points with one being strongly disagree, and five strongly agree.

Table 1

Summary of knowledge about social media usage in Italy and Romania in 2017

Item [ref]	Italy	Romania
SM penetration [32]		
%	52	49
Active users (millions)	31	9.4
Mobile social use penetration [32]		
%	27	41
Active users (millions)	28	8
The most active social media platforms	YouTube, Facebook, Instagram, Twitter, Google+, LinkedIn, Pinterest, and Tumblr (2016) [33]	Facebook, Wikipedia, YouTube, Google+, Twitter, Hi5, and LinkedIn (2014) [30]
The average time spent on SM	2 hours [33]	30 minutes and 3 hours [34, 35] (students)
Why students use SM?		Communication, learning and exchanging information, exchanging photo, video, friend search, and texting [35]

We created the questionnaire in both Italian and Romanian, following instructions available in the Google Forms web site. An e-mail containing an explanatory letter and a link to a self-administered standardized questionnaire was sent to all students. Recipients who agreed to respond were directly linked to the questionnaire by clicking the following URLs: https://goo.gl/forms/LjnBHu2CnxXAuagn1 (Italian) and https://goo.gl/forms/mINZDy8x7nQROLHz1 (Romanian). A reminder e-mail was sent one and two weeks after the initial e-mail. Anonym responses were automatically redirected in an Excel spreadsheet.

The study protocol was approved by the Iuliu Haţieganu University of Medicine and Pharmacy's Ethics Committee (no. 185/10/05/2016).

Statistical analysis

To ease up comparison, all the undergraduate programs of 3 or 4 years (180-240 European Credits Transfer System also known as ECTS) were grouped under the name of college: nursing, midwifery, radiology and medical imaging technicians, laboratory, balneo-physio-kinesiotherapy and rehabilitation, dental technology, speech-language therapy, nutrition and dietetics. Similar answers of the open questions were pooled before analysis. Descriptive statistics were used to characterize responses to the survey. Qualitative data are summarized as percentage and associated 95% confidence interval (values provided in squared brackets) calculated with an exact method [39]. Quantitative data are expressed as mean and standard deviation whenever data proved to follow the normal distribution (tested with Shapiro-Wilk test), otherwise median and the range (min-max) were reported. The Mann-Whitney Test was used to compare quantitative data that proved not to follow the normal distribution among two groups (Italian and Romanian students). The Chi-square test, with or without continuity correction according to the expected frequencies, was used to test the association in the contingency tables. Statistical analysis was performed with Statistica program (v. 8, StatSoft, Tulsa, USA) at a significance level of 5% and a p-value lower than 0.05 was considered statistically significant.

RESULTS

Participant's profile

Overall, 325 (17.98% [16.25-19.85]) students responded from the Italian University, and 870 (20.63% [19.42-21.89]) students responded from the investigated Romanian University.

The majority of respondents were females *(Table 2)*, with younger participants in Romania compared to Italy ($p < 0.0001$). Sixteen participants from the Romanian University did not fill the age, corresponding to 1.84% [1.03-2.99] missing data.

General use of social media

Most of the respondents both Italian (92.92%, 95% CI [89.54-95.38]) and Romanian (98.62%, 95% CI [97.59-99.31]) used Facebook with significantly higher frequency among Romanian respondents *(Table 3)*. They use social media mostly from home, 96.32% Italian responders (95% CI [93.85-98.15]), and 98.39% Romanian responders (95% CI [97.36-99.08]). The average time spent on social media is 1-3 hours for both groups, Italian (57.36%, 95% CI [52.00-63.1]) and Romanian (55.98%, 95% CI [52.64-59.31]) responders *(Table 3)*. No significant differences were observed between Italian and Romanian undergraduate students regarding the use of Snapchat ($p = 0.5475$), LinkedIn ($p = 0.2208$), SlideShare ($p = 0.2687$), or WhatsApp (0.9747). A small but significant number of Romanian students use ResearchGate or Academia (Romania:Italy = 3.45%:0.92%, $p = 0.0178$), Pinterest (Romania:Italy = 1.61%:0%, $p = 0.0214$) or Tumblr (Romania:Italy = 1.38%:0%, $p = 0.0333$).

The most used gadgets to access social media platforms are the smartphones regardless the geographical setting of the respondents (Italians:Romanians = 95%:94%), and a significantly higher percentage of Romanian respondents (87%) access social media using laptops (Italy 30%, $p < 0.0001$). Tablets are less frequently used (Italy:Romania = 25%:23%, $p = 0.4313$) while the desktop are on the fadeaway (Italy:Romania = 15%:19%, $p = 0.1293$).

Academic use of social media

Over 90% of the responders both Italian (95.69%) and Romanian (93.10%) use social media platforms for academic purposes, with no significant differences between groups ($\chi^2 = 2.41$, $p = 0.1209$).

The respondents also use other information sources in their learning process (293/325 of Italians and 833/870 of Romanians) with a significantly higher percentage among Romanian students compared to Italian students ($\chi^2 = 13.61$, $p = 0.0002$). Besides social media, the other most used sources of information are school bibliography (Italians:Romanians = 78%:74%, $p = 0.2147$) and the general Internet *(Table 4)*. Majority of the responders both Italian (78.15%, 95%CI [73.23-82.46]) and Romanian (88.97%, 95%CI [91.26-94.71]) said that they would like that teachers to use social media platforms to communicate with them. Facebook (including the features messenger and groups) was pointed as the most useful platform of communication by both Italian students (49%) and Romanian students (56%), with a significantly higher percentage among Romanian respondents ($p = 0.0223$).

Frequently, both Italian and Romanian students search through social media while preparing for an exam (Italians 26.77% [22.15-31.99] and Romanians 27.36% [24.37-30.46]) or to find administrative information about the university (Italians: Romanians = 34.46%:41.61%). Neither Italians (30.46% [25.54-35.69]) nor Romanians (23.91% [21.15-26.90]) search healthcare professionals through social media. Italians, also, never share their own experience as students (36.00% [30.77-41.54]) or their own opinion on a given medical subject (37.23% [32.00-42.77]), meanwhile Romanians rarely post their experiences (24.94% [22.07-27.93]) or express their opinion (29.66% [26.67-32.76]).

Sometimes, Italian students search for information

Table 2
Main characteristics of the participants

	Italian (n = 325)	Romanian (n = 870)	Stat. (p-value)
Gender, no. (%) [a]			11.42 (0.0007)
Female	188 (57.85)	593 (68.16)	
Male	136 (41.85)	273 (31.38)	
Age, median (Q1-Q3) [b]	22 (20–25)	20 (20–21)	12.43 (< 0.0001)
Study program, no. (%) [a]			229 (< 0.0001)
Medicine	92 (28.31)	416 (47.82)	
Dentistry	0 (0.00)	227 (26.09)	
College	226 (69.54)	223 (25.63)	
No Erasmus, no. (%) [a]	289 (88.92)	849 (97.59)	39.09 (< 0.0001)

% = percentage; a: Chi-square test; b: Mann-Whitney Test.

Table 3
Summary of social media usage, location, time, and devices

	Italian (n = 325) no. (%)	Romanian (n = 870) no. (%)	χ^2 (p-value)
Social media, no. (%)			
Facebook	302 (92.92)	858 (98.62)	27.02 (< 0.0001)
YouTube	64 (19.69)	309 (35.52)	27.60 (< 0.0001)
Instagram	187 (57.54)	557 (64.02)	4.23 (0.0396)
Wikipedia	235 (72.31)	776 (89.2)	51.80 (< 0.0001)
Google +	174 (53.54)	574 (65.98)	15.64 (0.0001)
Scribd	2 (0.62)	225 (25.86)	98.01 (< 0.0001)
Bloggs	1 (0.31)	77 (8.85)	28.30 (< 0.0001)
Twitter	8 (2.46)	119 (13.68)	31.34 (< 0.0001)
Location			
home	314 (96.62)	856 (98.39)	3.64 (0.0564)
public places	105 (32.31)	681 (78.28)	222 (< 0.0001)
school/university	83 (25.54)	612 (70.34)	195 (< 0.0001)
Hours spent per day			14.83 (0.0006)
≤ 1 hour	63 (19.38)	98 (11.26)	
1-3 hours	187 (57.54)	487 (55.98)	
3-6 hours	59 (18.15)	210 (24.14)	

Table 4
Summary of other learning sources and teacher-student communications platform desired by students

	Italian (n = 325) no. (%)	Romanian (n = 870) no. (%)	χ^2 (p-value)
Other Learning Sources			
The Internet but not SM	242 (74.46)	569 (65.4)	8.90 (0.0028)
Books[a]	9 (2.77)	81 (9.31)	14.54 (0.0001)
Course notes	12 (3.69)	9 (1.03)	9.68 (0.0019)
Teachers-students communication platform:			
Email[b]	15 (4.60)	104 (11.95)	14.21 (0.0002)
YouTube	25 (7.67)	35 (4.02)	6.68 (0.0097)
WhatsApp (groups)	22 (6.75)	20 (2.30)	13.94 (0.0002)
Wikipedia	2 (0.62)	32 (3.68)	8.03 (0.0046)
Cloud storage[c]	14 (4.29)	14 (1.61)	7.53 (0.0061)

a: atlases, manuals, books from the library, e-books; b: Gmail, Hotmail, Yahoo, Groups; c: Dropbox, Google drive.

regarding a course taught in school (29.85% [24.92-35.08]) and share information on social media with other colleagues (27.69% [23.08-32.92]). Romanians perform these searches a little more frequently (27.82% [24.83-30.92]) and share with other colleagues more frequently information (40.11% [36.78-43.45]). A specific medical subject (not mandatory to be school related) is a frequent subject to search for the Italian students (29.85% [24.92-35.076]), while Romanians perform this search only occasionally (29.66% [26.67-32.76]). Italian students rarely search for healthcare providers' information (23.38% [19.08-28.31]), but Romanian students sometimes look up more (26.90% [24.02-29.99]).

The differences between the Italians and Romanians remain unchanged if the comparisons were conducted for gender or specialization subgroups as compared to the country batches.

DISCUSSION

The primary objective, namely to explore the use of social media within two medical schools, one in Romania and one in Italy, was successfully achieved. The results indicate that the use of social media for educational purposes is spread in a similar way within the researched groups.

A slightly higher rate of female responders from both countries (57.67% for the Italian university and 68.16% for the Romanian university). This can be explained by the fact that in both countries more women than men graduate the baccalaureate exam [40], so they have better chances of being accepted by universities. The median age of the Italian students was slightly higher than the median age of the Romanian students *(Table 2)* and both fits within the demographics of the two geographies. Most participants in the Italian sample were college students while most participants in the Romanian sample were general medicine students *(Table 2)* reflecting the distribution of undergraduate students at the universities included in the study.

The investigated samples of undergraduate medical students are part of Generation Z [2] with social media as an integrative part of their lives. Facebook was listed as the most utilized social media among both investigated groups not only in this research but in previously reported ones [18, 22]. The students spend from 1 to 3 hours daily on these platforms. Smartphones, convenient gadgets (easy to carry and use), are the preferred method to access social media by the two groups assessed, but not the only one, the students also using their laptops, tablets or desktops *(Table 3)*. Neither the Italian nor the Romanian students have a one-and-only preferred location to interact through social media *(Table 3)*, this generation has integrated technology in their every-day activity and staying connected, no matter if they are at home, at school/work or in a public place, is essence [5].

Having social media integrated into every-day-routine is not a surprise that over 90% of both groups have integrated these platforms for academic purposes *(Table 3)*. Wikis [12], YouTube [19], Facebook [20] proved to be feasible tools for searching about a specific medical subject or performing administrative educative tasks, like planning of the exams, lectures, practical activities, scientific manifestations or extracurricular activities. The administrative feature has been successful previously tested among Israel [21] and UK [24, 25] students. Similar to US students [11], Romanian students also search for topics related to courses taught at school.

As Wikipedia [13, 14], YouTube [19], and Facebook [26] have proven to be useful tools that can enhance the learning outcomes, students from both university centers use, these three, but not exclusively, while preparing for an exam *(Table 3)*. Romanians, like their US [11] or Australian [16] counterparts, frequently share information with other colleagues, through social platforms.

Despite the usage of social media throughout the educational process, technology is not the single point of trough. Students also use other information sources, like the school bibliography, in print version that can be highlighted and annotated [18] or Internet, in general *(Table 4)*.

US [11], Canadian [15], Australian [16, 17], Israel [21] or UK [24, 25] students found social media a useful avenue for communication and support during the learning process. Likewise, the Italian and Romanian students encourage teachers to use especially Facebook to communicate with them. There has been revealed a gap between the academia members and students not only among Italian and Romanian students but also across other geographies like Canada [15] or Saudi Arabia [19].

Limitations

The present study has several limitations that provide opportunities for future research. Firstly, the response rate was reasonable; however, the possibility of bias resulting from non-response cannot be ignored. Cultural or geographical customs may affect to the country generalization of the results reported in this paper. Furthermore, the non-probabilistic sampling used in the design also induce some limitations. A multi-center study to analyze the differences in usage of social media by undergraduate medical students across Europe could bring more insights and more generalizable results.

Additionally, regarding the same audience, it will be interesting to assess whether or not, and how, the information received on social media influences their exam results. Secondly, this study only examined one-way communication, student's interaction. The social media phenomena are tools that support healthcare education. Youngsters are social media savvies, but research aiming teacher's social media behaviors are scarce [15]. Further studies are recommended to evaluate the usage of social media also from the perspective of teachers, and the student-teacher social media interactions. Thirdly, the opinions were captured at one point in time and were self-reported, and several potential sources of bias such as attribution and exaggeration can be listed. Fourthly, the research conducted did not capture complex values and behaviors indicatives of professionalism. Having an identifiable presence on social media can have the same impact on a future healthcare professional's social reputation as being active in any other public venue. In fact, having access to a global audience can magnify this reputation. The most effective use of social media often involves communicating information that is both personal and professional. However, students must retain the same standards boundaries of the professional relationship when dealing with virtual interactions that they would apply in face-to-face interactions [15]. The question thus remains open as to what measure(s) should be used to identify potentially inappropriate attitudes towards professionalism and how guidelines or trainings would increase the responsibly of social media behavior [41, 42].

Recommendations

It is important to acknowledge that, even though healthcare practitioners are known to be late adopters of technology, the next generation of undergraduate students will have grown up in a society where social media technology is inescapable. Enforcing existing recommendations to include social media in the educational process [43], based on the results, social media might be used as one of the tools to fill the communication gap between the two universities and students. We appreciate that the students will well receive the use of this innovative practice in current teaching and it will facilitate interactive learning and their engagement with lectures and lecturers. Health care educators should educate the students on how to utilize social media as support in their daily lives and studies (e.g., learn how to differentiate between real and fake information, how to look for high-quality information).

CONCLUSIONS

The results confirm that the undergraduate medical students are readily using social media platforms as educational support. This creates an avenue to research further the most effective methods to engage these students on their own terms whilst still providing sound and reliable pedagogical structure.

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Conflict of interest statement

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

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Health issues and informal caregiving in Europe and Italy

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Abstract
Informal caregivers are the unpaid persons who take care of a not self-sufficient family member, due to old age or chronic illness or disability. As in all the European countries, the demand for informal cares is further increased as a result of the ageing societies and the social and political fallout of informal caregiving is a very current and important issue. We have overviewed some international scientific literature, with the aim of understanding the key research objectives to be firstly pursued to address this problem. In particular, we focused on the psycho-physical health differences in informal caregivers, subjected to long lasting load and prolonged stress, as compared to non caregiver persons. We also underlined the relationship between caregiver health differences and stress, gender type, kind of the care recipient (autism) and social and political situation in Europe and Italy. The collected data indicate the necessity to prevent caregiver psychological and physical health by appropriate laws, especially supporting women, often most involved in care activities.

Key words
- caregiver
- health
- stress
- gender differences and inequalities
- autism
- social policies

INTRODUCTION

The defining characteristics of informal caregivers (CG) typically include all the providers of unpaid long-term care of a not self-sufficient family member with disability or chronic illness. CG differ from formal caregivers as the latter are paid care providers providing care in one's home or in a care setting. In this review only informal caregivers will be considered.

Psychological and physical health differences have been found between CG and non-CG and the most significant were observed in specific CG groups, such as those for dementia or mental illness or disability patients. Several findings suggest that women suffer a greater burden of care compared to men, also in the presence of the same pathological condition of the care recipient. Moreover, women have a greater perception and react differently to psychological distress than men.

This review reports the main updated results on caregivers' health and the relationship with stress, autism, gender and support services in Europe and in Italy, with the aim to inform and stimulate the scientific community to further investigate this challenging research area, addressing the national policies to the relevance of supporting the caregivers.

CAREGIVING AND HEALTH

In the last two decades, many studies on the relationship between psycho-physical health and caregiving have been reported. In 2003, the results of two meta-analysis [1, 2] showed that CG have poorer physical health than non-CG, as indicated by the subjective perceived health as well as by some objective measures, like hormonal and antibody stress responses.

An additional meta-analysis by Pinquart and Sorensen [3] showed that, among family CG, a number of predictive factors are related to a worse physical health such as: severity of behavior problems and cognitive impairment of the care recipient, intensity of care provided, co-residence, kind of kinship, higher burden and depression, higher age, lower socio-economic status and scarce levels of informal support.

Caregiving can also result in chronic stress, which may influence physical and mental health, being depression one of the common negative effects [4]. Accordingly, an Irish population-based study by Gallagher and Hannigan [5] reported the higher prevalence rates of depression in parents caring for children with developmental disabilities, as compared to parents of typically developing children, where the increased risk of depression was explained by the child behavior problems. Data from the same Irish survey also showed that the increased child problems were predictive of obesity in parents [6]. In addition, Gallagher [7] demonstrated that the antibody response to vaccination is negatively influenced, mostly depending on the behavioral characteristics of the child, while Yamaoka [8] showed that half of parents, taking

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care of children with disabilities, reported psychological distress and mental health problems.

Recently published data, obtained from the Welsh Health Survey 2013, confirmed that most informal CG have a poor quality of life, in that they experienced physical health limits, bodily pains and sadness, regardless of having or not a chronic disease [9]. In addition, a Spanish population-based study by Gonzalez-de Paz [10] reported some associations between informal care and depression, lower social support and higher stress. Sleep disturbances are also prevalent and associated with negative physical, medical and functional outcomes in informal CG [11].

The risk of Coronary Heart Disease (CHD) and stroke is significantly increased in spousal CG, after the diagnosis of cancer in their partner [12] and impaired cardiovagal baroreflex has been associated with long-term caregiving [13]. Indeed a high number of weekly hours of informal caregiving is associated with higher risk of cardiovascular disease, irrespectively of time spent to work [14]. Moreover, in studies on CG of dementia patients, it was observed a more elevated cardiovascular risk associated with increased levels of inflammation biomarkers [15] and higher morning cortisol levels [16], with predisposition to negative health consequences.

Importantly, Lacey [17] has recently published a large UK Household Longitudinal Study reporting that informal caregiving is associated with less favorable lipid profiles that may be the cause of increased health risk. In particular, both men and women CG had higher total cholesterol levels than non-CG and, among women, those providing intensive care also had higher triglyceride levels and lower high density lipoprotein cholesterol levels.

Finally, a definitive finding about the association between caregiving and increased risk for mortality is lacking and even if the study by Schulz and Beach [18] suggested that being a strained spouse CG is an independent risk factor for mortality, other five subsequent studies have found reduced mortality and extended longevity for CG, as compared with non-caregiving controls [19]. The controversial results may be explained by the limitations of the different study designs such as: high heterogeneity of the sample, lack of well controlled population-based studies, size and selection of sample, potential confounds, selective measurements of negative predictive factors without considering the positive ones (i.e. individual and formal resources), lack of rigorous methods for distinguishing stress from the CG status.

In the next future, it will be necessary to identify new biological markers associated with CG health and how do they vary during the time and at the individual level, looking not only for associations but possibly for cause-effect relationships between caregiving and health outcomes.

CAREGIVING AND STRESS

The term stress is often used to refer both to stressors and to stress response. Stress is a process that consists of stressors (i.e. challenging events), mediators (i.e. constructs that enable us to evaluate the nature of a threat and the emotional and behavioral responses elicited by threats) and the stress response (i.e. physical and emotional responses elicited by a stressor). Caregiving may generate chronic stress in situations such as long lasting care, severe illness or disability of the care recipient, lack of the necessary informal and formal support and high levels of unpredictability, uncontrollability and vigilance. Caregiving can produce also secondary stress, such as in work and familiar or social relationships. Therefore, caregiving may be used as a model for studying the health effects of chronic stress [20].

Periods of stress are accompanied by increased activation of the hypothalamus-pituitary-adrenal (HPA) axis and increased production of cortisol: the initial responses of the brain, body and behavior are protective and hormones, cytokines and other mediators, such as neurotransmitters, are used to survive and adapt to the challenge. However, repeated stressful experiences have deleterious effects, in part because the very same mechanisms that help to protect in the short-term are either mismanaged or overused. The existence of glucocorticoid receptors on the surfaces of multiple populations of immunocompetent cells [21] as well as evidence for the production of glucocorticoids in primary lymphoid tissue [22], provides the means by which aberrant levels of adrenal hormones, associated with chronic stress or vulnerability to stress, might exert a negative influence on immune function [23].

Many studies have reported that some physiological abnormalities are associated with caregiving chronic stress. Thus, a greater inflammatory activity and blunted glucocorticoid anti-inflammatory signaling were observed in monocytes of chronically stressed CG [24]. Inflammation may be one possible mechanism induced by caregiving stress to increase vulnerability to inflammation-related diseases, such as Coronary Heart Disease (CHD) [25]. Moreover, in CG of dementia patients, it was observed that the low grade and chronic hypercoagulable state, associated with stress, may be predictor of pro-thrombotic and cardiovascular risks [26] and, in chronically stressed mothers of autism spectrum disorder (ASD) children, it has been shown a reduced number of circulating hematopoietic progenitors, which is considered a predictor biomarker of subclinical atherosclerosis and future cardiovascular events [27].

A milestone study of Epel and Blackburn [28] showed that perceived life stress and the number of years, spent as a caregiver, were significantly associated with determinants of accelerated cell aging (i.e. higher oxidative stress, shorter telomere length and lower telomerase activity), in peripheral blood mononuclear cells (PMBC) from healthy premenopausal women. In particular, caregiving mothers with the highest levels of perceived stress have shorter telomeres, on average by the equivalent of at least one decade of additional aging, as compared to low stressed or not caregiving mothers. Accordingly, Damjanovic [29] demonstrated that chronic stress is associated with altered T cell function, accelerated immune cell aging and excessive telomere loss not compensated by telomerase activity, in PMBC of CG of Alzheimer patients as compared to controls.

It is important to underline here that family caregivers of people with dementia are one of the best examples of the tall of caregiving, if we consider that about 40% of them suffers from depression compared to 5-17% of non-caregivers of similar ages. Rates of depression increase with the severity of cognitive impairment of the person with dementia [30]. Recently, a systematic review by Allen [31] evaluated a broad range of data examining biological and cognitive markers of chronic stress, in CG of dementia patients. In CG versus non-CG controls, the reported results indicated increasing cortisol in a majority of studies, a mixed evidence for differences in epinephrine, norepinephrine and other cardiovascular markers, high level of heterogeneity in immune system measures and poorer cognitive functions. Thus, caregiving of dementia patients has been generally associated with a greater hypothalamus-pituitary-adrenal (HPA) axis activity, as indicated by the elevated cortisol levels during the diurnal cycle of cortisol secretion. Noteworthy, chronic exposure to stress hormones, like cortisol, during the lifetime, may have an impact on brain structures involved in cognition and mental health [32] and also with psychopathology, including depression [33] and irritable bowel syndrome [34]. Accordingly, it was observed that CG of patients with a chronic disease have a higher prevalence of the stress-related gastrointestinal irritable bowel syndrome associated with depression, anxiety and poor quality of life [35].

More recent data by Picard [36, 37] demonstrated that an association exists between daily mood, chronic caregiving stress and mitochondrial functional capacity, suggesting that mitochondrial health may represent a step in the pathway between psychological stress and health outcomes.

Interestingly, Vitaliano [38], for the first time, investigated the causal connections between caregiving and psychological distress in female twins. The main advantage of analyzing twins, discordant for a given exposure, but sharing the same developmental history and the same genetic background, consists in disaggregating the confounding factors. In this study, the measurements of the mental health functioning, as anxiety, perceived stress and depression, confirmed the typical finding that caregiving is modestly, but significantly, associated with psychological distress at the individual level. At the phenotypic level, the association between caregiving and distress is confounded by both common environment and shared genetics, in the case of anxiety and depression, while only common environment is a confounding factor in the case of perceived stress. These data suggest two focal points: i) distress is a function of both exposure to stressors (caregiving) and vulnerable phenotypes (genetics and environment) that increase the risk of distress, and ii) genetics and common environment are relevant to understanding the connection between caregiving and distress. However, this study includes many limitations and, despite 50 years of research, we still need to find optimal ways to identify those CG with higher risk for psychological distress. It is important to underline that CG have also the capacity to demonstrate resilience, displaying high levels of psychological well-being despite high caregiving burden. At this regard, many studies tried to identify factors that facilitate CG resilience and Joling [39] found that being a male, caring for a female, not co-residing with the care recipient and a low caregiving burden were positively related to CG resilience.

CAREGIVING AND AUTISM SPECTRUM DISORDER

Commonly, the CG of people with autism spectrum disorder (ASD) are also their parents. The interest of research in studying this group of CG lies in the fact that this population is not contending with age-associated decline of the endocrine and immune systems. Moreover, ASD and most developmental disabilities are present at birth and, as they last a lifetime, may cause a higher burden of care. In addition, many factors related to the care recipient, such as young age, severity of symptoms, lack of psychosocial autonomy, aggressive behaviors and emotional and communication difficulties, make these CG at higher risk of mental and physical health problems in comparison to other groups of CG [40-45]. All these characteristics may generate a prolonged stress in parents, which are middle-aged and working, with serious consequences even on their social life.

For what concerns the relationship between chronic stress and health outcomes in CG of people with ASD, a study by Ruiz- Robledillo [46] demonstrated a higher electrodermal response to acute stressors in a laboratory setting, suggesting that worse health was related to a malfunction of the physiological adaptive response to the stress. Accordingly, the same authors found that those CG, with a higher cardiovascular response to acute stressors, presented more severe somatic symptoms [47]. Moreover, in parents of ASD children, it has been shown a dysregulation of the stress-induced immune and hormonal responses, i.e. immunoglobulin A and salivary cortisol respectively, which are considered predictors of health problems [48]. Lovell [49] demonstrated also the presence of elevated levels of the pro-inflammatory biomarkers IL-6 and C-reactive protein, independently of the diurnal cortisol secretion. Thus, high inflammatory responses may generate a greater risk for diseases, even in the absence of a dysregulation of the HPA axis. The observed acute stress responses can have a positive significance in coping with stress but could also lead to negative effects on health. According to literature [50, 51], these effects will depend on the intensity and the duration of the stressor: it is likely that the most adaptive reaction to acute stress is a fast one, that subsides rapidly.

Significant predictor factors of ASD parenting stress are the severity of child impairment and parenting self-efficacy, but not gender, while the competence of parenting a child in challenging situations may reduce stress [52]. Recently, Lindsey [53] overviewed the potentially protective factors against distress that should be emphasized when working with families of a child with ASD. Noteworthy, informal social support partially mediated the negative impact of burden on the quality of life, suggesting the importance of informal support networks for the CG of persons with ASD [54]. However, formal support is important too, in that the non-supported CG presented higher somatic symptoms and a lower cortisol awakening response than the supported ones [55]. Moreover, as social support may influence blood pressure responses, it may be considered a key determinant of cardiovascular health [56].

For what concern parenting needs, ASD parents are more likely to report adverse family impact and difficulty in using services as compared to CG of children with others developmental disabilities [57]. Most of them need respite care services, which result associated with decreased stress [58]. Very interestingly, a recent editorial, published in the Journal of Autism Spectrum Disorder, has focused on parenting and caregiving for people with ASD [59]. The key themes, addressed over a hundred of manuscripts, include: intervention and training, mental health issues related to parent and family stress, measurement and assessment and parent-child transactional processes.

There are research areas that need to be further explored in the future. Among them, we can enlist: gender specific health outcomes in the presence of ASD-associated parental distress, understanding caregiving cultural differences in a world with increasing mobility and migration, more studies on fathers of ASD children, since most published studies have been targeting mothers, more investigations on females with ASD, focusing on differences in their behavioral phenotypes compared to males, caregiving extended to siblings of ASD persons and resilience stress-protective factors.

CAREGIVING AND GENDER SPECIFIC DIFFERENCES

There are two factors to be considered in analyzing individual differences: sex and gender. Sex refers to the biological differences between males and females, whereas gender refers to the different roles (gender role and gender identity) that men and women may have during their lifetime.

It is a fact that women, all over the world, are more involved in care tasks than men and this can generate health differences both intra-gender and between women and men.

A meta-analysis by Pinquart and Sorensen [60] reported that gender differences in depression and physical health among CG are indeed larger than those found in the general adult population, being in part explained by gender differences in caregiving stressors. In particular, higher levels of stressors and lower levels of social resources, among females versus males, accounted for elevated gender differences, supporting the stress and coping theories [61] to explain the observed disparities. Del-Pino Casado [62] showed that, both in a Mediterranean environment characterized by a high familism and in countries with low familism, females reported more subjective burden than males, suggesting that this gender difference is a shared characteristic among different cultures. Results support also that kinship (spouses versus offspring) moderates the relationship between gender and subjective burden, suggesting that gender and kinship are placed before subjective burden. Contrary to the countries with low familism, in those with high familism no gender difference was observed in objective burden (intensity of care and patient needs), suggesting that objective burden varies among different cultural environments.

Mothers, but not fathers, of children with Asperger Syndrome and High-Functioning Autism, reported impaired health-related quality of life (HRQL) and presented worse maternal well-being related to hyperactivity and conduct problems in the child [63].

Interestingly, an interaction effect between child diagnosis and gender was observed: mothers of children with autism scored higher than fathers in parental stress, while no such difference was found in the groups of parents of children with Down syndrome and typically developing children [64]. At this regard, Foody [65], in an exploratory study, compared some indicators of chronic stress between mother-father dyads of ASD children. Mothers reported significantly higher levels of parenting responsibility, parental distress, anxiety and depression than fathers, while fathers had significantly higher blood pressure (BP) and heart rate variability (HRV) than mothers. No significant differences were observed between mothers and fathers in relation to systolic or diastolic blood pressure-dipping during sleep, or levels of cortisol secretion and alpha amylase. Thus, the risk of HPA-axis dysregulation may be extended to fathers as well as mothers.

In men, particularly in African American men providing caregiving to their wives, caregiving strain is significantly associated with higher estimated stroke risk than in women, indicating race and sex differences in stroke risk [66]. Moreover, older males caring for spouses with more severe dementia, are at greater risk than females for increased thrombosis and inflammation associated with cardiovascular disease, and this could be the result of having more disturbed sleep [67].

However, it is important to underline that gender differences in the cardiovascular response have shown mixed results to date: one study, conducted on CG of people with dementia, showed a higher BP response to an acute laboratory stressor in women than in men [68], while another one, conducted on CG of people with ASD, showed higher BP and higher HRV in males versus females [65]. Thus, conclusive data are still lacking.

It has also been observed a relationship between gender and social support needs, suggesting that women need social support more than men. In fact, a study concerning ASD parents [69] reported that mothers have a higher number of important support needs and a higher proportion of those that are unmet, than did fathers. Recently, demographics, HRQL and social support data, obtained from the 2009 Behavioral Risk Factors Surveillance System (BRFSS) in US, were used to analyze CG mental health differences between males and females [70]: females reported significantly more mentally and physically unhealthy days than males, but no differences in general health or life satisfaction; men reported that rarely or never received social support but, despite this, the effect of social support on their HRQL was stronger than in women. Yet, females experienced more social stigma and higher burden than males [71]. In a Spanish study, males and females differed in the kind of support received and in the effect on their HRQL: more women used respite care and counseling services, while more men used paid assistance, home help, and other forms of instrumental help [72].

Caregiving can be considered as a social determinant of health inequalities and in particular of gender inequality, being women the most exposed (see next paragraph). A review by Morgan [73] reports that the palliative family caregiving for older adults is mostly given by women and the fact that women experience a greater degree of mental and physical strain than males, is linked to societal expectation that women would provide care at the end of life of their relatives. Moreover, women provide care while managing their other responsibilities, including full-time employment, and this highly impacts on inequalities [74].

A review by Sharma [75] highlights some issues regarding gender differences in caregiving of elderly or mental illness patients. The authors state that, although a large body of evidences indicates that women suffer more than men from the negative consequences of providing care, several other trends indicate that gender differences have not been consistently or conclusively documented and their magnitude and significance are also uncertain. Thus, further analyses will be necessary to search for specific gender health differences.

CAREGIVING AND SOCIO-POLITICAL SITUATION IN EUROPE AND ITALY

In Europe (EU), informal caregiving contributes to over three-quarters of all long term care provided and about 6% of population, aged 50 or over, provide care to an older relative [76].

In all EU countries, the demand for informal care is high and will further increase because of the ageing population, as an ageing society results in heavy pressures on families and also on welfare state regimes.

Social and health policies vary significantly across the EU. Most countries still do not have a process that systematically identifies informal CG or that assesses their needs. Some countries evaluate the needs and supports of informal CG, while others are at an early stage in developing support services.

Frericks [77] compared care policies towards older care-needy people in the welfare states of the Netherlands, Germany and Denmark. Results showed that CG have been formalized to some degree in all the three countries and the care recipient can choose a family member as the care provider to be supported by the welfare state. However, the legal situation and the quality and level of social rights (i.e. eligibility for being paid, social security rights related to unemployment, pensions and sickness, right to leave regular employment, care leave) differ considerably among the three countries, with consequences that may expose CG to social risks.

As reported in the review by Hiel [78], providing informal care may influence aspects of life such as personal development, opportunities to enjoy leisure time and to have a social life. All these effects depend on conditions under which care is given, rather than care itself, and are modulated mainly by the cultural environment. At this regard, the Mediterranean countries form a distinct cluster versus the North European countries, in that the care is almost entirely delegated to the family, mainly to women, due to a traditional gender stereotype and division of work.

The predominant female distribution of caregiving has to be considered a determinant of health inequalities, above all in the Mediterranean countries. To answer this problem, in 2006 Spain has recognized the obligation of the state to provide support to CG by the Dependency Law. The post-law analysis of the health inequalities trends showed different tendencies according to gender and share of responsibility: among women, those who could not share the responsibility of care with others remain the weakest subjects who least benefit from the supports provided by the law [79].

Various forms and levels of support have been implemented across the EU to facilitate the role of informal CG. Financial support is the most common type of support provided, followed by respite care and training [80]. Ultimately, there is an increasing interest in EU on web-based interventions [81] and telehealth technology for in-home caregiving support [82].

Very recently, by the SHARE research program, Calco-Perxas [83] studied the effects on CG of the different health supporting policies, among twelve EU countries. Results showed that the most effective policies were providing free time, helping to deal emotionally with caregiving and giving skills to improve the care situation and cope with it.

Further research is necessary to find and monitor information on family CG, in order to realize adequate support policies and evaluate their impact across the EU.

Among EU countries, Italy is one of the few without a national law that legally recognizes and supports CG. Since 2014, only the Region Emilia-Romagna has adopted a law (the number 2 of March 28, 2014), which recognizes and sustains family CG as a resource of the integrated social, social-health and health systems of the National Health Service. This law identifies the family CG as the person who takes care, in the ambit of the Individual Care Project, of a not self-sufficient family member, for a long lasting time, voluntarily and without being paid. In addition to economic contributions, the law provides for agreements with insurance companies and with the employers, for any accidents relative to the care activity and for flexibility in working hours, respectively. Moreover, psychological support is offered through local health services, such as the necessary help in emergency situations. At the national level, Italy has recently given an initial recognition to this figure, with an amendment inserted in the budget 2018, and has set up a fund of 20 million Euros/year for three years to enhance and support the activity of caregiving (L. December 27, 2017, n. 205, art 1 comma 254-255-256). The current XVIII legislature has resumed the amendment, presenting six Bills that are now in discussion at the XI Senate Commission. "The Bills (DDL S. 55, DDL S. 281, DDL S. 555, DDL S. 698, DDL S. 853 and DDL S. 890) are examined in order to come to come to an agreement on a single text that dictates the rules for obtaining rights but above all places the appropriate financial resources.

In Italy, the number of family CG who regularly take care of elderly, sick and disabled, not self-sufficient relatives in a familiar context is estimated to be over three million of people (about the 8% of the population) (ISTAT 2011). Most of the CG are women (63% up to 75%), 45-64 aged. For their social rights the legal reference is only the law 104/1992 or regional provisions. Thus, Italy is in a backward position compared to EU countries, i.e. France, Spain, Great Britain, Poland, Romania and Greece, which actually provide specific protections for CG such as welfare holidays, economic benefits and social security funding.

For what concern the Italian contribution to research, there are still few groups working in this area. In agreement with the international literature, Fianco [84] observed that a higher care burden is associated to a lower wellbeing, in CG of people with neuromotor and cognitive disorders. Most of the total burden is represented by the subjective and perceived one, which can be mitigated supporting personal and relational resources.

A pilot study by Servello [85] aimed to evaluate the physical health and psychological stress in a group of CG of dementia patients. Results showed an enhancement of some pathological alterations in CG as compared to non-CG, such as decreased ejection fraction, cognitive impairment and depressed mood. However, the limitation of this study was the numerical scarcity of the sample.

Noteworthy, in 2015 the UP-TECH research group was born, with the aim to support CG of Alzheimer's disease patients in Italy [86]. In 2017, based on the promising preliminary results of this group, the first randomized controlled Swedish trial has been developed. This ongoing trial aims to evaluate the effects on burden of new technologies (information and communication technology), among informal CG of people with dementia, by reducing the time spent in supervision [87].

Moreover, also the Italian National Agency for Regional Health Services (AGENAS) has taken seriously the issue of caregiving in Italy by establishing a working group on the family CG. The AGENAS working group has produced numerous documents about the enhancement and support of the family CG [88-92], that not only give a definition of the Italian CG and their relative activities, but also suggest the formal support services that must be provided, by taking advantage of the UP-TECH project results.

CONCLUSION

The aim of this review is to provide an overview of the current state of knowledge about informal family caregivers.

Caregiving may be definitively a positive asset for both people directly involved and for the society. At the same time, it is important to question whether the activity of caregiving may cause health problems in CG and what the consequences might be for those who do not receive the necessary support from informal networks and institutional services.

Some representative scientific literature, on this research area, has been discussed: it is probably partial, but in any case it sheds future light on the problems to be faced. In fact, many suggestions can be deduced for addressing future research. First, the issue concerning CG health prevention, not consistently considered by the actual policies, that needs to be further researched, starting from the available data about CG health outcomes. Second, a greater number of longitudinal prospective studies on larger and well controlled samples need to be set up, in order to find biological markers specific for CG health. Third, the available studies on CG stress have only partially demonstrated a cause-effect relationship between chronic stress and physiological dysregulation at the individual level, as well as the time-frame of these effects. Similarly, basic research, demonstrating cause-effect relationships between stress-related physiological responses and health outcomes, should be supported and stimulated. Attempting to delineate sequential causal relationship in the pathway from CG chronic stress to illness, among all the critical variables, will be an interesting challenge for future research. Fourth, we need to more thoroughly understand the true nature of the gender differences observed in caregiving, in order to inform social and health policies regarding the correct interventions that can reduce gender inequalities. Fifth, it is a future challenge to study the social and health effects of caregiving on men, since more men are now involved in caregiving, compared to the past, also taking into account that women have been so far over-represented in the samples. Finally, there is a great research interest on caregiving of people with ASD, due to the extent of specific care problems and unique difficulties that are associated with high parental stress in subjects that are young- or middle-aged and that often have to combine care activities with a high work burden, as they are in the initial or mid-career.

Conflict of interest statement

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

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Revisiting problems and solutions to decrease *Mycobacterium tuberculosis* pyrazinamide false resistance when using the Bactec MGIT 960 system

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Abstract
Pyrazinamide (PZA) is a first-line key drug used in combination with other agents for the treatment of tuberculosis (TB). Phenotypic and molecular assays for testing susceptibility of *Mycobacterium tuberculosis* (Mtb) to PZA have been developed, with the assay in liquid medium at acidic pH in the Bactec MGIT 960 (M960) system being routinely used in the mycobacteriology laboratories. However, false resistance to PZA by this method was reported to occur by several investigators, mostly due to high Mtb inoculum, which may impair drug activity by increasing the pH of the medium. In this study, a revision of the literature on the issue of false resistance in the M960 PZA assay was performed. In the reports examined, all improvements of the M960 test proposed to decrease false resistant results were based on the use of reduced inoculum densities of Mtb cells, to be easily translated into laboratory practice.

Key words
- tuberculosis
- *Mycobacterium tuberculosis*
- pyrazinamide
- drug susceptibility
- false resistance

PYRAZINAMIDE FOR TREATMENT OF TUBERCULOSIS

Tuberculosis (TB) is the main cause of death due to a single infectious agent worldwide, and drug-resistant forms of the disease are a major risk to global health security [1]. The current anti-TB therapy consists of a combination of the first-line drugs isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA) given daily for 2 months, followed by RIF and INH administered daily for 4 months. Poor adherence to TB treatment leads to emergence of multidrug-resistant (MDR) *Mycobacterium tuberculosis* (Mtb) strains (resistant at least to INH and RIF) and extensively drug-resistant (XDR) strains (MDR strains resistant to any fluoroquinolone and to at least one injectable second-line drug, kanamycin, amikacin or capreomycin). At global level, in 2017 the World Health Organization (WHO) estimated that 558 000 people developed TB that was resistant to RIF, and that of these, 82% had MDR-TB [2].

PZA is a cornestone anti-TB drug active in the first two months of therapy. It is likely that during the early inflammatory stages of the TB disease, PZA kills intracellular and semidormant tubercle bacilli living in the acidic environment of the phagolysosomes of activated macrophages. In the 1980s, the substitution of PZA for streptomycin (SM) in the regimen INH-RIF-EMB-SM shortened the course of TB therapy from 9-12 months to the current 6 months regimen, INH-RIF-EMB-PZA. The ability of PZA to shorten the *in vivo* therapy is of great importance. In this view, this drug is currently being considered in future anti-TB regimens in combination with new agents, including bedaquiline, delamanid, pretomanid, moxifloxacin, levofloxacin, linezolid in phase II and III trials [2].

MECHANISMS OF ACTION AND RESISTANCE OF PZA

The activity of PZA depends on the acidity of the culture medium, with the drug being active at pH lower

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than 6. PZA is a prodrug which enters Mtb cells by passive diffusion. Inside the cytoplasm, the drug is converted into its active form pyrazinoic acid (POA) by the pyrazinamidase (PZase), an enzyme encoded by the *pncA* gene. Then, POA is expelled out of the cell through passive diffusion [3]. Under external acidic conditions, the POA is protonated and enters the cell by passive diffusion and a defective POA efflux mechanism. Following intracellular accumulation, POA kills Mtb by various mechanisms including disruption of membrane energy production, inhibition of trans-translation and inhibition of panthotenate and coA biosynthesis.

Resistance to PZA is mostly generated by mutations in the *pncA* gene, but mutations in *panD* and *rpsA* genes may also be involved [4]. Several studies indicated that MDR Mtb strains were more likely to harbor PZA resistance than non-MDR strains, with estimated prevalences being 16.2% for all TB cases and 60.5% for MDR cases [5]. The estimated global burden is 1.4 million PZA-resistant cases annually, including about 270 000 in MDR patients. Recently, the WHO categorized PZA in the group C agents for use in longer MDR-TB regimens, to be added to group A (levofloxacin or moxifloxacin, bedaquiline, linezolid) and B (clofazimine, cicloserine or terizidone) regimens, and when medicines from groups A and B cannot be used [6].

DRUG SUSCEPTIBILITY TESTING OF PZA

Drug susceptibility testing (DST) of PZA is challenging. Two main phenotypic assays are known, including the automated Bactec MGIT 960 system (MGIT; Becton Dickinson, Sparks, MD) performed by monitoring the growth of Mtb in liquid medium at pH 5.9 containing 100 µg/ml of PZA, and the classic and modified Wayne's methods, which assess activity of PZase on the basis of colorimetric changes at 100 µg/ml and 400 µg/ml of PZA, respectively [5]. The PZA MGIT test is the more commonly used of these two methods, but false resistance in a multicenter study was recently reported, largely due to high Mtb inoculum, which may impair PZA activity by increasing the pH of the medium [7]. For this reason, the WHO considers the DST to PZA not reliable, and considers an acceptable practice to administer the drug in a regimen even when a laboratory demonstrates resistance [8]. However, PZA is counted as an effective agent when DST results confirm susceptibility [6].

In the last years, genotypic PZA assays have also been developed, based on DNA sequencing to detect *pncA* mutations, which have been shown to correlate with PZA resistance [3, 9-10]. The sequencing of *rpsA* and *panD* genes provided only a 2% increase in sensitivity, and from 8% to 10% resistant strains without *pncA, rpsA* and *panD* mutations may point to alternative mechanisms of resistance [10]. Even though *pncA* sequencing is a powerful tool for molecular diagnosis of PZA resistance, a study reported that the countrywide prevalence of *pncA* mutations in Mtb isolates phenotypically resistant to PZA varied from 45 to 100% [11]. Furthermore, in a large investigation of genetic surveillance conducted on 7094 patients in highly endemic countries, the sensitivity for *pncA* sequencing compared with MGIT testing adjusted for the results of the Wayne's test was only 54% [12]. The diversity of single nucleotide polymorphisms across the *pncA* gene complicates the development of rapid molecular diagnostics, because not all mutations confer resistance, and not all susceptible strains lack mutations [5, 7]. For these reasons, also these molecular techniques are not yet approved by WHO for PZA DST [5, 11]. In this view, the whole-genome sequence (WGS) may be useful to improve diagnosis. Indeed, the sensitivity of this technique for PZA DST was reported to be 91.3% in a recent study performed on 10 209 Mtb isolates assayed by WGS and various phenotypic DST [13]. However, this technology is not yet routinely available in most laboratories worldwide, thus in consideration of this limitation, it is still necessary to perform culture-based PZA DST [7].

PREVENTION OF FALSE PZA RESISTANCES WHEN USING THE MGIT SYSTEM

Erroneous results indicating false PZA resistances when using the MGIT system were reported by several investigators.

In 2009, Pandey *et al.* found that the MGIT test showed 54.2% false PZA resistance in comparison with *pncA* sequencing [14].

In 2010, Chedore *et al.* reported that 42% of 57 strains diagnosed as resistant by MGIT were false resistant in comparison with *pncA* sequencing, and with results obtained by the radiometric system BACTEC 460 TB (BACTEC) (Becton Dickinson), that was considered the gold standard [15]. Erroneous results by MGIT were attributed to various reasons including high concentration, volume and heterogeneity of the inoculum. Indeed, i) the concentration of inoculum was 2.5 times greater than in the BACTEC method, ii) the volume inoculated was 5 times greater than in BACTEC, iii) the bacilli were inoculated by a pipette in MGIT and by a fine-needle syringe in BACTEC, resulting in uneven distribution of bacilli due to "clumping". It was suggested to retest all PZA-resistant isolates by the BACTEC, but this system was later withdrawn from the market by the manufacturer to avoid disposal of the radioactive waste, and was replaced by the MGIT system.

In 2011, Simons *et al.* found that in 69 strains resulted to be PZA resistant by MGIT, 68.1% were false positives after a second MGIT analysis, and that *pncA* mutations could identify these false resistances correctly [16]. Also these investigators pointed out that false phenotypic PZA resistance was due to large inocula which increased pH and thereby inactivated PZase. To improve DST, they recommended repeating the MGIT test, giving attention to the inoculum size, and performing mutation analysis as an adjunct to the MGIT assay.

In 2013, the Sweedish Institute for Communicable Disease Control reported that over the course of proficiency testing excercises, two out of six clinical laboratories showed pronounced problems with false resistance results, with a positive predictive value of only 63% and 45%, respectively [17].

Piersimoni *et al.*, in two papers published in 2013 [18] and 2016 [19], respectively, retested a total of 82 PZA-resistant strains by the BACTEC standard assay, by reducing the inoculum volume of the MGIT test tubes from 0.5 ml to 0.25 ml. By this approach, false resistance decreased by 71.1% and 51.4%, respectively, in comparison with standard MGIT assay. It was suggested that PZA resistant isolates should undergo a repeat DST using the reduced inoculum of 0.25 ml. In case of resistance, *pncA* gene sequencing should be performed, otherwise, the isolate should be reported as susceptible. Some investigators also suggested to reassess the critical concentration for PZA susceptibility [20, 21]. In the Piersimoni's studies, both reduced inoculum and PZA testing at 200 µg/ml reduced false MGIT-resistances, however, only reduced inoculum allowed a clear separation between true- and false-resistant isolates.

In 2017, Morlock *et al.,* during the course of a multicenter study coordinated by the US Centers for Disease Control and Prevention, also mitigated false PZA positivities by MGIT through the use of reduced inoculum densities [7]. Twenty genetically and phenotypically characterized isolates were tested in ten independent laboratories by the standard PZA MGIT method (0.5 ml of positive MGIT tubes transferred to test tubes containing 100 µg/ml of PZA) and 1:2.5 and 1:5 dilutions of the positive tubes. By this approach, the percentages of resistant results that were false-resistant declined from 55.2% for the standard MGIT test to 28.8% and 16.0% for the 1:2.5 and 1:5 diluted inocula, respectively. These investigators reported that some strains were "always susceptible" regardless of inoculum concentration while other strains called "predominantly susceptible" showed high degree of false resistance when the standard method was used.

Finally, in 2017, Mustazzolu *et al.* tested 106 WHO strains with known *pncA* mutations by a slightly modified MGIT standard test [22]. A positive MGIT seed tube was allowed to settle for 20 to 30 min, then 1 ml was taken from the top surface, instead of lower down; of this volume, 0.5 ml was transferred to a 100 µg/ml PZA-containing test tube, and 0.5 ml of 1:10 dilution from the positive tube was used to inoculate the growth control tube without PZA. Using this easy variation, 0.9% of strains were falsely resistant and no strains were falsely susceptible. Furthermore, when 10 of those strains were tested by 17 Italian independent laboratories (a total of 68 resistant and 102 susceptible strains), false resistance was reported to be 4.7% by the standard method and 1.2% by the modified MGIT method.

CONCLUSION

Overall, these observations provide compelling evidence that to decrease false resistant results it is necessary to reduce the inoculum in the MGIT PZA assay currently used worldwide. This purpose can be achieved by changing the method of drafting the initial inoculum, or changing PZA critical concentration. As suggested by Morlock *et al.* [7], clinical laboratories should validate their modified method prior to routine implementation. However, large controlled studies using both MGIT and molecular methods should be performed by investigators and/or by the manufacturer of the current test, to modify the MGIT package of the PZA assay.

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Author contribution statement

AM and LF conceived and wrote the study; CP, AI, FG and BC conceived the study and critically revised the manuscript.

Conflict of interest statement

None.

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Tuberculosis outbreak in a grammar school, Serbia, 2016

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Abstract
Serbia has a low incidence of tuberculosis (TB), with a decreasing trend in the last decade. The purpose of this manuscript is to describe an outbreak of TB infection that occurred in 2016 among students of a grammar school in Novi Pazar. A 17-year-old girl, third-grade student of a grammar school (the index case), was diagnosed with smear-positive tuberculosis. Contact investigation was conducted, including chest X-ray examinations of over 1100 persons. After the index case was detected, a total of 16 (10 pulmonary and 6 extrapulmonary) tuberculosis patients were newly diagnosed during 2016. Among 11 culture positive cases, MIRU-VNTR method revealed that all *Mycobacterium tuberculosis* isolates were identical. Diagnostic delay contributed to the transmission of infection.

Key words
- tuberculosis
- outbreak
- grammar school

INTRODUCTION

Serbia has a low incidence of tuberculosis (TB); in 2016, incidence of notified cases was 11.8/100 000 population, with a decreasing trend in the last decade [1, 2]. However, higher rates were reported in some areas: the highest incidence of notified cases was reported in Raska District – 29.0/100 000 population in 2016, with an unfavorable trend in the last decade [2]. The BCG vaccine coverage in newborns was over 95%. Novi Pazar is the largest city located in the Raska District (the urban area has about 66 000 inhabitants, while the city administrative area has about 100 000 inhabitants). The grammar school of Novi Pazar has about 1200 students (in grades I-IV, with 40 classes) and around 100 employees. We described an outbreak of TB infection that occurred in 2016 among students of a grammar school in Novi Pazar.

METHOD AND MATERIAL

In this study, descriptive epidemiological method was used. This study was performed in Novi Pazar (a city in Serbia) during 2017. As a source of data in this paper, the material obtained during the investigation of the epidemic was used.

Case definition

A "TB case" was defined according to the diagnostic criteria proposed by the World Health Organization (WHO) [3], and implemented in Serbian guidelines for definition and classification of tuberculosis [4]. A case of TB denotes a patient in whom tuberculosis has been bacteriologically confirmed, or has been diagnosed by a specialist doctor. A definitive case of TB denotes a patient with positive culture for *Mycobacterium tuberculosis* (MTB) or a patient with two sputum samples positive for acid-fast bacilli. Cases were classified as pulmonary TB (the disease involves lung parenchyma and tracheobronchial tree) and extrapulmonary TB (the disease involves any organs other than the lung, including pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges etc., if lung parenchyma is not affected at the same time). A patient who at the same time has both pulmonary and extra-pulmonary TB was classified as a case of pulmonary TB. In absence of bacteriological confirmation of clinical specimens, TB diagnosed on the basis of clinical signs and symptoms alone, and by a radiologic, pathologic, or therapeutic response, and/or a positive tuberculin skin test that was consistent with active tuberculosis.

Case detection

Detection and identification of mycobacteria using classical, conventional methods is performed in accordance with national recommendations in referent laboratories [5]. All of the isolates were obtained from cultures of respiratory samples. Diagnosis was based on

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direct microscopic detection of acid-fast bacilli in sputum or other samples and isolation of MTB on appropriate medium, or on a pathohistological confirmation based on the finding of MTB in the histological sample and / or cultivation of the biological material obtained by a biopsy. Samples for direct microscopic examination were stained with carbol-fuchsin technique according to Ziehl-Neelsen. Processed samples were seeded on the Löwenstein-Jensen medium. Identification of MBT in samples was carried out using the GenoType® Mycobacterium MTBC (Hain Lifescience) assay. Conventional methods for testing the susceptibility of TB isolates were based on the detection of growth on solid substrates containing antituberculotics [4]. A proportion method, on modified Löwenstein-Jensen solid substrate, was used to examine the sensitivity of TB isolates to first-line anti-TB drugs. The susceptibility of TB isolates was examined for the following drugs: isoniazid, rifampicin, etambutol, streptomycin, pyrazinamide [5]. All TB isolates were susceptible to first line drugs. Response to first-line drug combination of anti-TB therapy was favorable and after some months *MTB* was not detectable on sputum microscopy.

Genomic investigation of Mycobacterium tuberculosis

To determine a detailed picture of tuberculosis epidemiology, all MTB isolates were analyzed by classical genotyping techniques, i.e. mycobacterial interspersed repetitive unit – variable number tandem repeat (MIRU-VNTR) genotyping on 24 loci [6]. MIRU-VNTR genotyping was performed in accordance with the protocol described by Supply *et al* [5]. The chromosomal DNA of the laboratory reference strain MTB H37Rv (ATCC 27294) was used as a control. The MIRU-VNTRplus database (https://www.miru-vntrplus.org) was used for identification by similarity search of the isolated strain [7]. Categorical distance was used as distance measure for strain comparison. The distance cutoff of 0.17 was used for identification.

Epidemiological investigation

Contact investigation was conducted in accordance with guidelines of the European consensus on the tuberculosis contact investigation in low prevalence countries [8]. From June 2016, as part of the investigation by local public health authorities for TB control, additional testing extended to all students who attended the same school during 2016, and to all school staff members. Testing had to be completed before the end of the school term. Contact investigation included chest X-ray examinations of over 1100 persons (students, employees of grammar school, as well as all family members of cases). Contact investigation revealed 10 new cases of pulmonary and 4 new cases of extrapulmonary tuberculosis in third-grade students. There were no tuberculosis cases among family members of sick students and among school staff. Additionally, contact research that included all staff of cafes and grocery shops near the grammar school, recorded absence of the disease among them.

RESULTS

In February 2016, TB pleuritis was identified in a 17-year-old girl who was a third year grammar school student. She experienced fatigue, hard breathing, dyspnea and weight loss. Patient was treated by a pediatrician, but, one month later, she was hospitalized because the severity of symptoms had increased, and MTB was isolated from a pleural fluid sample.

Between April and May of 2016, three students who had attended the same grammar school as the first case-patient, developed pulmonary tuberculosis. In these cases, tuberculosis was confirmed by isolation of MTB. By the end of December 2016, a total of 17 cases of TB were identified among students in the same school *(Table 1)*, including 10 pulmonary forms confirmed bacteriologically, 1 pulmonary form confirmed clinically without MTB isolation, 1 extrapulmonary form confirmed bacteriologically, 2 extrapulmonary forms confirmed pathohistologically and 3 extrapulmonary forms confirmed clinically. Except one case, all patients were students of the third grade of the grammar school. There were no tuberculosis cases among grammar school employees.

BCG scar was recorded in 13 cases. Only a few patients gave information that they smoke cigarettes, use nargile and consume alcohol. Positive family history for TB in the past was recorded in 4 students. Comorbid-

Table 1
General and clinical characteristics of the tuberculosis (TB) cases

Characteristics	**Number (17)**	**%**
Sex		
Male	7	41.2
Female	10	58.8
Grade		
III	16	94.1
II	1	5.9
Symptoms		
Cough	6	35.3
Fever	6	35.3
Fatigue	4	23.5
Night sweating	4	23.5
Breathing difficulty	3	17.6
Weight loss	6	35.3
Chest pain	3	17.6
Without symptoms	2	11.8
Comorbidity	0	0.0
Body Mass Index (<18.5 kg/m^2)	0	0.0
Habits		
Cigarettes smoking	1	5.9
Nargile use	2	11.8
Alcohol use	2	11.8
Positive family history for TB in past years	4	23.5
Contact with colleagues - cases with TB	17	100.0
Clinical findings		
Pulmonary TB	11	64.7
Extrapulmonary TB	6	35.3
BCG scar	13	76.5
MIRU-VNTR*		
Identical strains	11	100.0

MIRU-VNTR = mycobacterial interspersed repetitive unit - variable number tandem repeat; *Only for culture-confirmed TB.

Table 2
MIRU-VNTR profiles of control strain *Mycobacterium tuberculosis* H37Rv, all strains from Novi Pazar and strain identified through the similarity search of the MIRU-VNTRplus database

	MIRU loci																							
Strain	154 MIRU02	424 Mtub04	577 ETRC	580 MIRU04	802 MIRU40	960 MIRU10	1644 MIRU16	1955 Mtub21	2059 MIRU20	2163b OUB11b	2165 ETRA	2347 Mtub29	2401 Mtub30	2461 ETRB	2531 MIRU23	2687 MIRU24	2996 MIRU26	3007 MIRU27	3171 Mtub34	3192 MIRU31	3690 Mtub39	4052 OUB26	4156 OUB4156	4348 MIRU39
H37Rv	2	2	**4**	**3s**	**1**	**3**	**2**	**2**	2	**5**	**3**	4	**2**	**3**	**6**	1	**3**	3	3	3	**5**	5	**2**	2
Novi Pazar	2	2	3	2	3	5	3	1	2	2	2	4	4	2	5	1	5	3	3	3	4	5	3	2
Haarlem, Germany*	2	2	3	2	3	5	3	**3**	2	**4**	**3**	4	4	2	5	1	5	3	3	3	**3**	5	3	2

Abbreviations: MIRU-VNTR = mycobacterial interspersed repetitive unit – variable number tandem repeat.
*Categorical distance < 0.17 (Locus differences compared to the isolated strain are bolded).

ity (immunosuppressive conditions, malignant diseases, silicosis, renal insufficiency, diabetes mellitus, malnutrition) was not observed in patients.

All *Mycobacterium tuberculosis* isolates from students with culture-confirmed TB, analyzed by MIRU-VNTR genotyping techniques, revealed that all 11 strains from Novi Pazar were identical *(Table 2)*. Search of the MIRU-VNTR plus database showed that the MIRU-VNTR type identified in all cases in this epidemic in Serbia matched in 20 loci with a strain which represents the Haarlem sublineage (distance 0.1667) and which was isolated in Germany.

DISCUSSION

We described a high school TB outbreak among students in Novi Pazar, Serbia. Genotyping of *Mycobacterium tuberculosis* isolates of all cases confirmed that all cases in this outbreak were infected with the same strain.

The majority of cases (94.1%) were in the same year at school, which is in concordance with previous findings from a retrospective study of a TB outbreak in one secondary school in the United Kingdom, where a significantly higher risk for being diagnosed with TB was noted in pupils in the same school year as the first case-patient [9]. Previous studies suggested that the risk to school employees teaching children with TB might be very small, similar to what our study showed – no cases were detected among employees in the grammar school [9, 10]. Testing an entire high school for TB is uncommon, although a similar event occurred at a Colorado school in 2011, where 1249 persons were screened [10], alike to the outbreak we reported here, where local public health authorities examined over 1100 persons including students, staff of the grammar school and family members of cases. Investigation of a TB outbreak in a boarding middle school in China found significant efficacy of the vaccine [11], while we recorded a BCG scar in 76.5% of cases in this outbreak, indicating that previous BCG vaccination did not reduce the risk of TB in those cases.

No cases with this MIRU-VNTR genotype had been detected in Serbia prior to this: this MIRU-VNTR genotype suggests the Haarlem sublineage which belongs to the Euro-American lineage which is widespread across the Americas, Europe and Africa [12]. Search of the MIRU-VNTRplus database, as well as a search of the available literature showed that the MIRU-VNTR type identified in all cases in this epidemic in Serbia has not been previously reported as responsible for other TB cases or outbreaks in Serbia or abroad, either in young or adult persons [8, 12]. Our findings could be due to information lacking in the databases or could reflect the unique nature of MTB isolates from Novi Pazar. Because this TB outbreak consisted of a significant number of cases in otherwise healthy young people, more research is needed to obtain a better insight in the TB situation in Novi Pazar.

Risk factors for outbreaks of TB in schools involve constant contact, inadequate ventilation and delay in diagnosis [13, 14]. In this study, the delay in making a diagnosis led to postponement in treatment, which likely was a factor contributing to the TB outbreak [15, 16].

Epidemiological TB contact investigation established direct contact between all cases. Although the source of this outbreak remained unknown, the spread of the disease in grammar school can be linked to high TB incidence in the community, as well as the students' contacts in school and surrounding cafes. Genotyping of MTB isolates of all culture-confirmed cases showed that all of the cases in this outbreak were infected with the same strain.

CONCLUSION

This outbreak indicates the need for timely identification of TB and adequate treatment. Our findings emphasize the need for increasing the TB knowledge and awareness among community members, especially adolescents, as well as health professionals.

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Author contributions

All authors equally contributed to this paper with conception and design of the study, data collection, data analysis, interpretation of the results, manuscript preparation, critical revision and editing. All authors read, reviewed and approved the final manuscript.

Ethical considerations

This study is a part of a larger research approved by the Ethics Committee of the Faculty of Medical Sciences, University of Kragujevac (Ref. No.: 01-1176).

Conflict of interest statement

The authors declare that they have no competing interests.

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Association between epicardial fat thickness and cognitive function in elderly. A preliminary study

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Abstract

Background. Recent studies suggested that the visceral fat could exert a predictive role in the pathogenesis of dementia. The aims of the present study were to evaluate: i) possible differences between groups with different epicardial adipose tissue (EAT) thickness on the included variables; ii) the possible predictive role of the EAT levels on cognitive functioning.

Methods. 65 community-dwelling subjects were enrolled and divided into two groups: EAT < 7 mm (n = 36); EAT > 7 mm (n = 29). The metabolic profile was assessed through the evaluation of the biochemical parameters whereas the EAT thickness was measured through the transthoracic echocardiography. The Mini Mental State Examination (MMSE) was also administered.

Results. The two EAT groups reported several significant differences, included on the MMSE scores. The multiple linear regression analysis showed that the EAT thickness levels and the hypertension had a predictive effect on the MMSE scores.

Conclusions. These preliminary findings support the association between EAT thickness levels and cognitive impairment.

Key words
- epicardial fat thickness
- cardiometabolic risk
- cognitive impairment
- visceral fat

INTRODUCTION

A multifactorial pathogenesis is assumed for dementia. Indeed, while cardiovascular and metabolic factors are acknowledged as being relevant in the pathogenesis of "vascular dementia", growing interest has been reported about the potential role of these factors in degenerative dementia as well. The importance of such factors is still controversial and research on this matter is being carried out. Over the past years, the role of adipose tissue as a possible risk factor has stirred great interest. By releasing different mediators, adipose tissue exerts a negative action on different organs and systems, including the cardiovascular [1] and nervous systems [2]. Adipose tissue can be classified according to its position in subcutaneous or visceral. In the latter type, epicardial adipose tissue (EAT) presents a unique location, being close or in contact with the heart and the coronary arteries. EAT is an energy source regulating the homeostasis of fatty acids for coronary circulation. Moreover, it produces a "cocktail" of cytokines (IL-6, TNF-α), adipokine (adiponectine), microRNA and other cell mediators (leptin, angiotensinogen, resistin), playing a fundamental role in the paracrine regulation of vascular tone, in muscular smooth vascular cell proliferation and migration, and in susceptibility to atherosclerosis [2].

Over time, more and more convincing evidence has led researchers to believe that this tissue could be involved, through a pathogenic pattern of "initial local inflammation", in different cardiometabolic phenomena such as insulin resistance and atherosclerosis. Thus, it can be concluded that EAT represents an authentic cardiovascular risk factor [3]. Nevertheless, the role of EAT in the development of cognitive impairments is still to be clarified. More specifically, can EAT thickness be considered a reliable or predictive indicator for cognitive impairment?

The primary aim of this study is to evaluate possible differences in both cognitive function and several vas-

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cular risk factors (e.g. hypertension, diabetes, metabolic parameters) in groups with different levels of EAT thickness.

Furthermore, a secondary aim of the study is to evaluate the possible predictive role of both the EAT levels and the vascular risk factors on the cognitive functioning.

MATERIALS AND METHODS

65 community-dwelling Caucasian subjects with a mean age of 72.1 years (standard deviation = 8.9; 31 males) followed by our Department for the evaluation of the functional status participated in this study. Exclusion criteria were: infectious diseases, thoracic trauma, surgical procedures in the last 90 days, alcohol or drug addiction, psychiatric disorders, depression, hypo- or hyperthyroidism, anemia by any cause, heart failure, or condition of being chronically ill and treatment with chemotherapeutic or hormonal agents. All procedures performed in this study which involved human participants were in accordance with our institutional research committee (15th of November 2017) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The same day of the enrollment in the study each patient underwent a clinical interview, a physical examination, an anthropometric assessment and the venous blood sampling. Waist circumference (WC) was measured at the level of iliac crest in standing patients. After an overnight fast, standard laboratory techniques were used to determine the plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), triglycerides (TG) and fasting blood glucose (FBG).

Transthoracic two-dimensional (2D) guided M-mode echocardiography was performed in each subject using a Philips iE-33 machine (ultrasound device iE33 by Philips Ultrasound Inc., USA). Epicardial fat was recognized as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium at end-systole in three cardiac cycles. We measured EAT thickness on the free wall of the right ventricle from both parasternal long- and short-axis views. The maximum values at any site were measured, and the average value was considered. Different cut-off points of epicardial fat thickness for cardiometabolic risk prediction have been proposed [3]. Considering the heterogeneity of our sample in terms of cardiovascular risk factors, a threshold value of 7 mm thickness was fixed, in line with Natale et al. that set the normal upper limit to 7 mm [3, 4]. The clinical cut-off for EAT thickness values (= 7) was used in order to divide the sample in two groups: *Increased EAT thickness level* (n = 29, mean age = 73.9; SD = 8.3, 17 M; EAT mean values = 7.9; = 1.1) and *Normal EAT thickness level* (n = 36, mean age = 70.6; SD = 9.3, 14 M; EAT mean values = 5.6; = .82).

The cognitive function was assessed through the Mini Mental State Examination (MMSE) which maximum score is 30. A score below 27 is indicative of an increased risk of cognitive dysfunctions and dementia [5].

Hypertension was defined as a systolic arterial pressure (SBP) > 140 mmHg and a diastolic arterial pressure (DBP) > 90 mmHg or as reporting an history of use of antihypertensive medication, according to the WHO guidelines. Diabetes was defined as the pres-

Table 1
Differences between groups with normal and increased levels of epicardial adipose tissue (EAT) thickness

Parameters (n = 65) Epicardial adipose tissue thickness						
	< 7 mm (36)		**> 7 mm (29)**		**f**	**p**
	M	***SD***	***M***	***SD***		
Age	70.61	9.3	73.93	8.3	2289	0.13 (ns)
FBG	94.89	13.1	107.10	12.1	14983	0.001**
WC	89.17	11.0	100.15	14.3	12203	0.001**
HDLc	57.28	9.74	49.14	17.2	5790	0.02*
TG	114.98	23.8	138.90	45.33	7479	0.008**
MMSE	28.31	1.06	24.67	1.35	16320	0.001**
	n	**%**	***n***	**%**	**χ^2**	***p***
Gender						
Male	14	38.9	17	58.6	2507	0.09 (ns)
Female	22	61.1	12	41.4		
Hypertension						
No	11	30.6	0	0	10666	0.001**
Yes	25	69.4	29	100		
Diabetes						
No	32	88.9	15	51.7	11079	0.001**
Yes	4	11.1	14	48.3		
MetS						
No	34	94.4	2	6.9	49820	0.001**
Yes	2	5.6	27	93.1		

*p < 0.05; **p <0.01. FBG: fasting blood glucose; WC: waist circumference; HDLc: high-density lipoprotein cholesterol; TG: triglycerides; MMSE: Mini Mental State Examination; MetS: Metabolic syndrome.

Table 2

Regression model reporting the predictive effect on Mini Mental State Examination scores of the variables included

Variables	Beta	95% CI		t	p
EAT	-0.494	-1.110	-0.344	-3.800	0.001**
FBG	-0.135	-0.058	0.016	-1.130	0.263
WC	-0.018	-0.039	0.034	-0.156	0.877
HDLc	0.051	-0.029	0.045	0.432	0.668
TG	-0.176	-0.023	0.002	-1.658	0.103
Gender	-0.078	-1.276	0.599	-0.723	0.473
Hypertension	-0.213	-2.398	-0.059	-2.104	0.040*
Diabetes	0.029	-0.999	1.276	0.244	0.808
Age	-0.187	-0.093	0.002	-1.901	0.063

*p < 0.05 **p < 0.01. EAT: epicardial adipose tissue; FBG: fasting blood glucose; WC: waist circumference; HDLc: high-density lipoprotein cholesterol; TG: triglycerides.

ence of the fasting plasma glucose levels of 126 mg/dl (7 mmol/ l) or the presence of non-fasting blood glucose values equal to or greater than 200 mg/dl (11.1 mmol/l) or a history of diabetes treatment [6]. Impaired fasting glucose (IFG) was defined by FBG concentrations within the range 100-125 mg/dL [7]. Metabolic syndrome was diagnosed, according to National Cholesterol Education Program (NCEP) ATP III 2001 criteria [8], by the presence of three or more of the following features: WC ≥ 88 cm in women and ≥ 102 cm in men; HDLc < 50 mg/dL in women and < 40 mg/dL in men; FBG ≥ 100 mg/dL and/or antidiabetic treatment; fasting triglycerides ≥ 150 mg/dL; SBP ≥ 130 mmHg and/or DBP ≥ 90 mmHg and/or antihypertensive treatment.

All statistical analyses were performed using the Statistical Package for the Social Science (SPSS) version 24 for Windows. Data are presented as means and for continuous variables and as frequencies for discrete variables. One-way analysis of variance (ANOVA) was performed to investigate possible differences between groups in continuous variables while the Chi-square test ($\chi 2$) was used to explore differences between groups in discrete variables. A linear multiple regression model was performed in order to verify the predictive role of EAT, FBG, WC, HDLc, TG, MMSE, gender (0 = female; 1 = male), hypertension (0 = no; 1 = yes) and diabetes (0 = no; 1 = yes) on the MMSE scores. All the independent variables were entered simultaneously. Regression coefficients along with their 95% confidence interval (CI) were reported. A p value below .05 was considered statistically significant.

RESULTS

Data analysis showed that the two groups were homogenous for the variables age and gender, whereas significant differences emerged in all the other variables examined *(Table 1)*. More specifically the group with EAT > 7 mm showed higher levels of FBG, WC and TG and lower levels of HDLc and MMSE compared to the group with EAT < 7 mm. Furthermore, the group with EAT > 7 mm reported a significantly higher frequency of patients suffering from hypertension, diabetes and metabolic syndrome compared to the group with EAT < 7 mm.

The multiple linear regression analysis revealed the absence of collinearity problems (tolerance index>.50; VIF< 2). The model explains the 55% of the MMSE scores (R^2=.55; adjusted R^2=.48). The independent variables who showed a predictive effect on the MMSE scores were: EAT (beta = -.49; 95% CI = -1,110 – -.344; p <.001), and hypertension (beta = -.21; 95% CI = -2.398 – -.59; p = .04) *(Table 2)*. The variable MetS was not included in the regression model because the diagnosis of MetS depends on other variables which were included in the analysis.

DISCUSSION

In accordance with the findings of other authors [9], a connection between increased EAT thickness and MetS and its components was reported. EAT thickness enables a more reliable evaluation of visceral fat than WC. Furthermore, in order to calculate visceral fat, EAT is measurable with good sensitivity and specificity by means of ultrasound techniques (lower costs), whereas other techniques are inevitably less manageable and very expensive, such as magnetic resonance (MR) or dual-energy X-ray absorptiometry, DXA [10].

Although vascular risk factors including hypertension, diabetes and dyslipidaemia have been implicated in the risk of cognitive dysfunction [2], only in Mazzoccoli *et al.* an association between epicardial fat thickness and cognitive impairment in the elderly was found [11]. In our study the negative correlation between the EAT thickness and the MMSE was confirmed. The way in which such an interesting correlation is obtained, at least from an ethio-pathogenic point of view, is still to be clarified and investigated. Visceral fat, including EAT, could have an injurious effect on cognitive abilities because of the intermediation of several cytokine and non-cytokine molecules it produces. This is well described in cardiovasculpathic patients [2] but we still lack clinical studies with patients suffering from Mild Cognitive Impairment (MCI) or dementia. There are, nonetheless, known to be differences among patients with cognitive decline, about prognostic outcomes in relation to inflammatory status. In this light, the EAT would play a dual role as a pathogenetic factor as well as a potentially reversible risk factor. Moreover, several studies show a close correlation between EAT and cardiac function, regulated by the autonomous nervous system, with a reduction of the para-sympathetic activity and significant consequences in terms of arrhythmia and, indirectly, brain activity [12]. In this perspective, associating epicardial fat and sympathetic nervous system by utilizing an accurate and easily reproduced method such as the assessment of heart rate variability (HRV), could represent a further item to explore cognitive decline and frailty [13]. Finally, there are genetic factors implied in the regulation of epicardial fat thickness and these factors are also correlated with insulin resistance, forming a sort of model that includes dementia- inducing diseases such as Alzheimer's, as well as metabolic pathologies like diabetes [14]. Familiarity with these genes and understanding of their function could contribute, in turn, to better understanding the role played by EAT in both pathologies, as well as clarifying the mechanisms through which it performs its negative action [15].

The results of this study need to be interpreted in the light of some limitations. Firstly, we did not use the most accurate tools for the evaluation of visceral fat (e.g. whole-body magnetic resonance imaging). Secondly, the relatively limited sample size. Thirdly, our results suffer from a lack of knowledge about the inflammatory status of the patients.

CONCLUSIONS

The results of our study highlight that EAT thickness, measured by transthoracic echocardiography, is inversely related to cognitive function. Based on our study, the transthoracic echocardiography proved to be simple and affordable. For this reason, it is realistic to suggest its application among elderly people whose physical changes can play an important role in determining biases in the anthropometric parameters routinely used.

Author contributions

Verrusio W, Magro VM and Renzi A were the primary researchers and wrote the manuscript. Andreozzi P and Musumeci M provided research and editing assistance to the manuscript. Andreozzi P and Cacciafesta M contributed to overall article design, data collection as well as revising and approving the manuscript.

Conflict of interest statement

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Identikit of the Umbrian traveller: analysis of clinical activity in a travel medicine unit, Italy

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Abstract

A travel medicine clinic is the proper medical centre aimed to provide updated recommendations before any journey. The study aim was to assess the number of accesses during 2016 at the Travel Medicine Clinic of the Local Health Unit in the Umbria Region. An electronic *ad hoc* database was developed. Paper-based data referring to 2016 were recorded in this electronic registry, developed on Microsoft Office Access®. In 2016, 891 subjects came in our clinic in order to get information before travelling. In our sample, 53.3% were male and the mean age was 35.33 years ± 0.58. Almost half had a higher education, and 20% were foreign. Vaccines against food- and water-borne diseases were the most frequently administered. Approximately, 74% of the attenders were suggested to do an anti-malaria prophylaxis (Mefloquine in one-half, approximately). Every traveller received a pre-travel counselling. Performance activity of our clinic and the adherence to preventive protocols in case of international travels, have been assessed.

Key words

- travel medicine
- vaccine
- immunization information system
- travel medicine clinic
- Italy

INTRODUCTION

Over time, the rapid circulation of people and the low cost of travelling are increasing the chances of travelling. In particular, according to the World Economic Outlook of October 2017 by the International Monetary Fund, the improvement of economic conditions plays a role in increasing both the business and leisure travels [1]. World Tourism Organization data have shown a growth in the number of international travels with 1,237 million in 2016 and an estimated increase between +3/+4% for 2017 [2]. However, international travels can represent a potential health risk depending on the duration, type of travel, destination and health status. Health risks associated to travelling are both infective and traumatic [3] including poisoning [4]. Actually, accident is the first cause of death among travellers, whilst infectious diseases, contracted while travelling, could represent a risk of disease spread also in the country of origin. This is particularly true considering both incubation and emerging/re-emerging of new diseases, such as Ebola [5], Zika [6] or Plague [7]. In the majority of cases, these risks are behaviour related and preventable. Prevention could be obtained both reducing the exposure to risk factors and through vaccination. Periodically, WHO provides and updates data on the distribution of the diseases in the world and, simultaneously, the countries where the vaccine against yellow fever is mandatory, as well as all the vaccinations recommended for each country [8].

A travel medicine clinic is the proper medical centre aimed to provide updated recommendations before any journey. According to WHO guidelines, medical consultation before travelling must identify any possible traveller's health need related to the destination and duration of the journey. In particular it should provide vaccination recommendations and anti-malaria prophylaxis. The physician, with the travellers, should investigate the sanitation conditions of the destination and empower the travellers on how to best protect themselves from the risk of acquiring diseases. Moreover, vaccination schedules should be tailored according to the immunization status, destination and type of the journey.

In Italy, the National Institute of Statistics (Istat) estimates that the trips made by Italian citizens amounted to about 66 million, in 2016 [9]. In 17.2% of the cases, trips were in foreign countries. Looking at the extra-European destinations, United States, Tunisia and China were the most visited countries in 2016 [9].

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Analysing the travel reasons, 90% of all trips took place for holidays while 10% for business. Nevertheless, trips abroad are carried out mainly for cultural, monumental and archaeological reasons (30.6%) [9].

We analysed data of the Travel Medicine Clinic of the Local Health Unit 1 (LHU) in Umbria Region, authorized by Ministry of Health. In particular, the study aim was to assess the number and type of accesses during the year 2016. Moreover, travellers' demographics characteristics, travel and health information were collected.

METHODS

Travel medicine clinic LHU1, located in Perugia, provides medical advices and vaccination counselling before travelling for a catchment area of 497 381 people. During the consultation, the physician collects information related both to the travel and the individual, regarding immunization status, health condition, and pharmacological history. In particular: i) demographic characteristics (age, sex, educational level, job and country of origin); ii) travel information (date of departure, duration, destination, purpose, type of accommodation); iii) health history (chronic diseases if any, allergies, adverse events associated to food, antibiotics or other vaccines, pregnancy, breastfeeding and pharmacological therapy); iv) immunization status (vaccination performed in the past). Moreover, the physician provides information related to the most important health risks associated to the travel. In particular, specific factors are taken in account such as destination, duration of travel, purpose of travel, level of sanitation in the accommodation area and health status of subjects, according to WHO recommendations. Informative sheets on vector-borne diseases, such as food- and water-borne diseases are offered to all the travellers. Different types of anti-malaria prophylaxis, if needed, are discussed with the subjects. Until this study, all the data were collected on paper. We then developed an electronic database, which has been designed and organized *ad hoc*. Paper-based data referring to 2016 were recorded in this electronic registry, developed on Microsoft Office Access®. Statistical analysis was performed using STATA SE/12®. In order to facilitate the occupational comparability, we classified our sample according to the International Standard Classification of Occupations 2008 (ISCO-08). In Italy, there are no national data related to travellers: that means no information available on total people who go on a journey per year. Due to the absence of an established denominator, we calculated the rate of access considering the inhabitants, disaggregated for age class and gender, living in catchment area of our clinic. In order to evaluate the yellow fever vaccination adherence, according to the WHO country list, we considered as countries with required vaccination certificate the following [8]: Angola, Benin Burkina Faso, Cameroon, Congo, Democratic Republic of the Congo, Côte D'Ivoire, French Guiana, Gabon, Ghana, Guinea Bissau, Liberia, Mali, Niger, Rwanda, Central African Republic, Sao Tome, Togo.

RESULTS

During the time period from 1st January 2016 to 31st December 2016, 891 subjects came to our travel medicine clinic in order to get information before travelling. In our sample, 53.3% were male and the mean age was 35.33 years ± 0.58. *Supplementary material 1 (available online)* shows socio-demographic characteristics of the individuals. *Supplementary material 2 (available online)* represents access rate x 1,000 inhabitants, according to age and gender. Almost half (48.2%) of the subjects were either graduated or took a postgraduate licence (higher education). In our sample, 179 people out of 891 had at least one chronic disease and the most frequent was cardio-vascular disease (62 travellers, data not shown). Twenty percent of the people were foreign. Ivory Coast, Cameroon and Nigeria were the most common countries of origins among the foreign travellers attending our clinic, in 2016. *Figure 1* details the countries of origin, while *Supplementary material 3 (available online)* specifies the travel reasons. Actually, the first three reasons are tourism, business and visiting friends and relatives, respectively in 29.41%, 18.07% and 17.06% of cases. Other characteristics of journeys are shown in *Supplementary material 4 (available online)*. *Table 1* shows the type of vaccination and the respective dosage, according to the vaccine schedules. Moreover, we performed 214 yellow fever vaccines in people travelling to destinations with no requirement of yellow fever vaccination certificate. Approximately, 74% of the attenders were suggested to do an anti-malaria prophylaxis. Looking at the chemoprophylaxis, in the majority of cases (47.9%), travellers preferred Mefloquine, followed by Atovaquone-Proguanil (11.7%). However in the 21.4% only a behavioural prophylaxis was suggested and in 10.2% both behavioural and auto medication (data not shown). The highest flow of people attending the clinic, as expected, was during the summer (May, June and July) and before the Christmas period (December), with a mean access of 97 people per month, compared to 63 people/month during the remaining months (data not shown).

DISCUSSION

In this retrospective study, we present data available at the Travel Medicine Clinic in LHU Umbria 1, Perugia. Data presented in this paper display the picture of travellers attending the travel medicine clinic and the activity performance of the clinic. In our study, the regular users are young people, male, and with higher education. Moreover, we moved paper-based data to a more efficient electronic archive. About 20% of our population is foreign, in accordance with previous studies, also conducted in Italy [10, 11]. Approximately 49% of attenders were 21-40 years old. These data are in line with the previous publication referred to the Italian population [9]. Actually, people aged 21-60 years were also the users with the highest number of accesses per year. Among 66 users who attended the clinic twice during 2016, 49 were 21-60 years. More in detail, 24 subjects were aged 21-40 years, while 25 were aged 41-60 years. Regarding the health status, the majority of travellers were healthy, however approximately 20% had at least one chronic disease, whilst 3.5% had an allergy and 2 women were pregnant. The average length of stay was 58.06 days. Students, Professionals

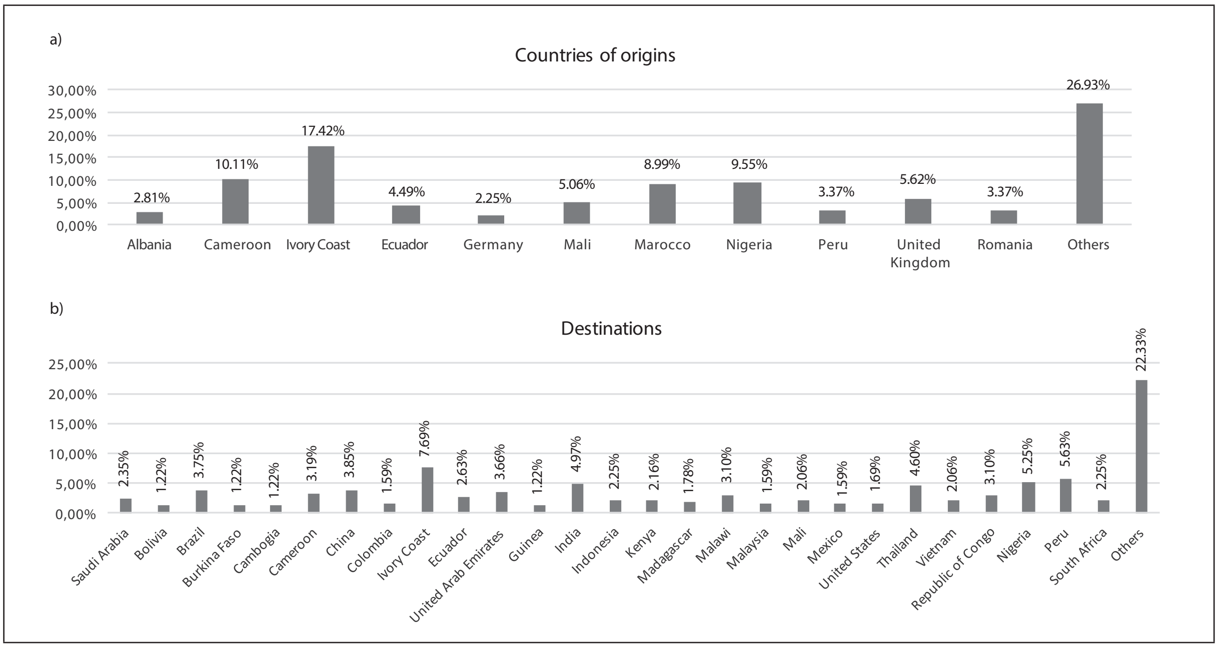

Figure 1
a) Countries of origins of travellers attending the Travel medicine clinic LHU1, Perugia. The figure shows the most common countries among the 178 foreigner travellers, in 2016.
b) Countries of destination.

and Agricultural, Forestry, Fishery and Craft workers were the categories of workers who spent more time abroad. In particular, 53 students stayed abroad more than one month, as well as 35 Professionals and 25 of the Agricultural, Forestry, Fishery and Craft workers. Furthermore, the same three groups are those who came to the travel clinic earlier, related to the date of departure: 61 students, 45 professionals and 32 among agricultural, forestry, fishery and craft workers consulted the clinic at least 30 days before the departure. In our analysis, people attended the travel clinic 38 days before the departure, according with the WHO recommendation that suggests the consultation 4-8 weeks before any journey. Ivory Coast, Peru, Nigeria and Thailand are the preferred destinations. In addition, China and Brazil are chosen respectively in the 3.85% and 3.75% of our travellers. These results are slighting different compared to the national data, where China, Tunisia and United States are the three preferred countries among Italian people [9]. Comparing the travel's

Table 1
Vaccines' injections and appropriate dosage according to schedules

Vaccine	Dosage				
	1st dose	2nd dose	3rd dose	4th dose	5th dose
HAV	516	118	5		
HAV + HBV	56	46	30		
HBV	29	15	15	3	
Yellow fever	325	11			
Rabies	15	11	10	5	3
Men B	18	14			
Men C	2				
Men ACWY	207	6			
Japanese encephalitis	3	3			
Typhus (oral)	560	65	17	6	1
Typhus (i.m.)	10	1			
Cholera	568	26	4		
Diphtheria-Tetanus	143	9	3		
Poliomyelitis	34	3	3	3	

reasons obtained in our study with Istat data, we also confirm the prevalence of travels due to tourism, followed by business [9].

In May 2014, the WHO's Strategic Advisory Group of Experts on immunization stated the life-long protection of one dose of yellow fever vaccine. However, the legal application of this amendment was on 11 July 2016. After this, we stopped performing the booster doses of yellow fever vaccine every 10 years. Actually, our immunization data reflect this change, with only 11 doses of yellow fever booster performed before July 2016 [12]. Among the destinations chosen by our travellers, even though 214 did not have the requirement for yellow fever vaccination, travellers accepted the yellow fever vaccine. In particular, travellers directed to Peru (32 subjects, 14.95%), Brazil (28 people, 13.08%) and Niger (28 subjects, 13.08%) performed the vaccine.

Regarding Malaria, in Italy approximately 2/3 of imported cases occurred among immigrants visiting friends and relatives [13, 14]. Often, immigrants underestimated the risk of malaria infection during travels in their own countries, especially in Africa [15]. In order to prevent imported cases, we suggested a prophylaxis in more than 70% of our sample. During the counselling, we stressed the importance to combine chemoprophylaxis with personal protective measures due to the fact that antimalarial drugs do not guarantee 100% protection. Even though malaria prevention is country-specific, also the drugs interactions and the patients' preference need to be taken into account. The majority of travellers in our sample preferred Mefloquine, in contrast with a previous study, where the preferred drug was Atovaquone-Proguanil [10]. Probably this difference could be due to the longer average length of stay: in the study performed by Troiano et al. the average length of stay was 36.17 days compared to our study, where it was 58.06 days [10]. According to the Centers for Disease Control and Prevention (CDC), Mefloquine should be preferred for long trips. In our case, people favoured a weekly drug assumption instead of a daily one. Moreover, Mefloquine is the cheapest alternative, especially if compared to Atovaquone-Proguanil. On the other hand, Doxycycline was not the first choice probably because in the majority of the cases travellers had planned a sun exposure, and this drug can increase the risk of sun sensitivity; moreover Doxycycline cannot be prescribed in children and needs to be taken daily for 4 weeks after returning home.

CONCLUSION

In conclusion, our results present data on the sociodemographic characteristics of Umbrian travellers, information about the destinations and type of journeys. This analysis allowed to assess the performance activity of our clinic, and to measure the adherence to the preventive protocol in case of international travels. The high number of yellow fever vaccines performed in travellers without compulsory indication, suggests the importance of the travel medicine clinic. In particular, these data highlight the central role played by the counselling for immunization and for all the behavioural prophylaxis. Nevertheless, some issues have to be taken into account when interpreting these results. Actually, due to the absence of an established denominator (total number of travellers), we could not estimate the realistic impact of our clinical activity.

Authors' contribution

VG and IFM conceptualized and designed the study, analysed and interpreted data, and wrote the manuscript. VG contributed to data collection. VG and IFM managed the database and provided statistical support. MM and MG reviewed the last version of the article. All the Authors have read and approved the last version of the manuscript.

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No ethical approval was required.

Conflict of interest statement

None to declare.

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TOWARDS INTEGRATION OF EPIDEMIOLOGICAL AND SOCIAL SCIENCES APPROACHES IN THE STUDY OF COMMUNITIES AFFECTED BY ASBESTOS EXPOSURE

Edited by Pietro Comba and Daniela Marsili

Preface

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The present issue of *Annali dell'Istituto Superiore di Sanità* contains a monographic section dedicated to address the challenging integration of epidemiological, sociological and anthropological studies concerning the communities affected by asbestos exposure in Italy.

This monograph is dealing with the asbestos issue as previous monographic sections and specific articles published by the *Annali dell'Istituto Superiore di Sanità*, because of its relevance as a national and a global public health issue [1-6].

In Italy, numerous municipalities have been facing localized excesses of pleural mesothelioma incidence and mortality due to asbestos exposure in occupational settings and diffuse environmental exposure in the neighborhood of industrial settings. In some of these areas, the increase in mesothelioma incidence and mortality has only recently been identified [7, 8].

The aim of the monograph is to investigate how in different Italian regions communities have been facing the health impact of asbestos related diseases in order to foster a better understanding of the social implications through a multidisciplinary research approach [9]. In this perspective, the four papers composing this monograph highlight the connections among social, anthropological and epidemiological aspects in different asbestos contaminated areas, selected because representative of a large number of asbestos affected communities in Italy. The papers focuses on stakeholder's engagement and the capacity of affected communities to react collectively through social capacity building and social networks [10].

The paper by Marsili *et al.* provides an integrated description and analysis of the epidemiological studies, communication processes and health education initiatives in several municipalities in Italy affected by occupational and environmental exposures to asbestos and asbestiform fibres: the asbestos-cement industrial area of Casale Monferrato in Piedmont, the asbestos-cement industrial area of Emilia Romagna, the area of Mount Pollino in Basilicata and Biancavilla in Sicily affected by the natural occurrence of tremolite and chrysotile containing outcrops and of fluoro-edenite fibres, respectively. The paper sheds light on social aspects concerning communication processes and their implementation depending on the evidence of asbestos health impact and the engagement of local institutional and social actors, scientists, students and teachers, and media. It points out experiences of their capacity to react collectively.

The paper by Parolari describes the outbreak of cancer and asbestosis among former asbestos-amosite exposed subjects affected in the Ledro Valley, Trento Province, since the first occupational health reports in the '70s until the last updating in 2009 including the pioneering and successful environmental clean that took place in the eighties. The paper emphasizes the participation of exposed workers, their families and residents in collecting useful information for the investigations, as well as the role played by local public administrators in response to the asbestos health impact. The paper also reports the efforts dedicated to hold the memory of these events alive for the next generations as an integral part of the community heritage.

Fedrigotti *et al.* also deals with the Ledro Valley community, addressing the asbestos issue from a historical perspective. In particular, the paper summarizes the results of a research project focusing on the asbestos impact on the community from the socio-economic point of view, including the history, the entrepreneurship, the characteristics of industrialization in the Trento Province, individual life stories and women's role in the community, in other words the past, the present and the future of the community.

The paper by Mazzeo illustrates an anthropological research project based on ethnographic fieldwork conducted in Italy (Bari, Casale Monferrato, and Bologna) and in Brazil (Osasco). It discusses the practices by

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which the survivors of the impact of asbestos-related disaster on their lives make sense of their suffering experience and engage in a grassroots health-based movement. In particular, attention is given to the capacity of the affected communities to elaborate their own paths of care by remembering and communicating the asbestos disaster, and underlines many analogies between the Italian and Brazilian settings.

The case studies described in this monograph can be useful to other asbestos affected communities, especially in countries that did not yet ban asbestos [11], in particular in those communities that only recently became aware of experiencing asbestos-related health impacts.

An integrated reading of the different case studies, taking into account epidemiological, public health aspects, anthropological perspectives, historical, socio-economic setting, and communication processes, can help in defining the major steps along the path from scientific knowledge to environmental remediation, victims' support and pursuit of equity. Scientific knowledge starts from observation of adverse health effects deriving from existing epidemiological surveillance systems, by observations of alert physicians or by a direct input coming from the affected communities through their reporting of cases of asbestos-related disease. Workers' unions, victims' associations and local administrators can also contribute to this process.

Formal epidemiological studies are then required in order to provide estimates of the burden of disease and to address its causal attribution with respect to occupational and environmental (both household and outdoor) asbestos exposure. This process is particularly needing in order to define the priorities of environmental cleanup process in terms of health benefits, and it also contributes to orienting compensation activities, and, where appropriate, judicial actions.

While equity-inspired processes of restoration require a major commitment of administrative and political authorities, the communities themselves appear to be the real drivers of the response to the asbestos-related health challenges, by increasing collective awareness, autonomy fostering and development of a strong stakeholder role in all decision making circumstances concerning their present and their future.

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Communication and health education in communities experiencing asbestos risk and health impacts in Italy

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Abstract

Introduction. Numerous municipalities in Italy currently experience asbestos health impact, in particular excesses of pleural mesothelioma incidence and mortality. This paper presents an integrated analysis of epidemiological studies and communication actions in affected municipalities to highlight how communication has been implemented depending on health impact evidence and involvement of local stakeholders.

Methodology. Four case studies are identified concerning industrial and natural sources of asbestos exposure having different diseases burden. This integrated analysis benefited from multidisciplinary skills.

Discussion. Evidence of different stakeholders engagement is presented to emphasize their role in the communication process. Similarities and differences among case studies allowed us to identify lessons-learned to be transferred in other asbestos contaminated sites.

Conclusions. The adoption of communication strategies and practices, since the very early evidence of asbestos health impact, represents a relevant contribution for epidemiological and health surveillance, particularly for those communities where asbestos health impact has only been recently reported.

Key words
- asbestos
- epidemiological surveillance
- communication
- stakeholders engagement
- resilience

INTRODUCTION

Health, environmental and social impacts due to long-term asbestos use in Italy have been requiring continuing efforts both in national priority contaminated sites (NPCSs) and in areas characterized by the presence of natural sources of asbestos or asbestiform fibres [1-6]. Numerous municipalities currently experience specific, localized excesses of pleural mesothelioma incidence and mortality due to a past use of asbestos in occupational sectors and diffuse environmental exposure in the neighborhood of industrial settings. For some of these areas the increase in mesothelioma risk has only recently been identified [7, 8]. The wide use of asbestos containing products over the national territory and the long latency period of mesothelioma concur to maintaining a relatively elevated occurrence of this disease notwithstanding the asbestos ban in 1992, as forecasted [9].

Within a public health approach, health promotion and communication of epidemiological and health surveillance plans and findings to different stakeholders, including the population living in the affected areas, is considered essential [10-13]. Communication with local communities on health risks and impacts affecting their occupational and living environments plays a critical role in contributing to preventive action through informed policies [14].

Epidemiologists can build a relationship with communities by providing evidence about risk in the given context, detecting previously unknown health impacts in specific areas, and improving understanding of risk. In this perspective, a specific concern regards the no-

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tion of population risk *vs* individual risk, typical of the communication of epidemiological findings, also considering possible judicial and economic expectations of the subjects. These problems specifically apply to mesothelioma and asbestos exposure. Communication involves in particular subjects that were directly exposed, people suffering from mesothelioma and, in some cases, relatives of mesothelioma patients.

Local occupational physicians and general practitioners (GPs) play a key role in the process of communication in communities experiencing occupational, environmental, and domestic asbestos exposure. Beyond their specific health activities, they are very useful in explaining with an understandable language the meaning of mortality and morbidity statistics about asbestos related diseases, the content and the usefulness of a health surveillance program (tests, results), how to diagnose and treat asbestos-related diseases. They should be able to convey information about healthy habits adoption (i.e. smoking cessation, precautionary measures to reduce exposures), and to answer typical questions as "Is living here safe now? What about the long-term safety here?", "Is going to school dangerous for my children?", "I have been diagnosed as having asbestosis: what should I do? What should I expect?", "I am concerned about cancer". All medical communication activities should be taken on a regular, predictable basis [15-17].

Awareness and preparedness of affected communities to manage the health impact of asbestos exposure also depend on the effectiveness of communication activities capable to take into account socio-economic, institutional and cultural specificities of the local context. This requires the involvement of social researchers in the communication process playing a critical role in the relationship with institutional and social actors and the affected populations [18, 19]. Communication with asbestos exposed communities though, has not so far been systematically planned. Creating the conditions for an effective communication especially requires the aware participation of multidisciplinary research groups dedicated to increase community resilience versus asbestos health impact. This is particularly needed in areas where asbestos health impacts are still coming to light.

OBJECTIVES

This paper aims to present an integrated description and analysis of epidemiological studies and communication actions in some municipalities affected by asbestos health impact in Italy to throw light on how communication has been implemented depending on the evidence of health impact and the involvement of local institutional and social actors. The goal is to provide useful tools contributing to increased resilience of communities in areas where asbestos health impacts are currently being brought to light, in particular mesothelioma incidence and mortality.

METHODOLOGY

The four case studies identified include both industrial and natural sources of asbestos exposure, with different history and asbestos diseases burden:

- the municipality of Casale Monferrato in Piedmont Region, that experienced major occupational and environmental asbestos health impact due to the past asbestos-cement industrial production;
- a set of municipalities of Emilia-Romagna Region where asbestos-cement production started later than in Casale Monferrato and where a health impact on the population is currently emerging;
- the municipality of Biancavilla in Sicily Region characterized by fluoro-edenite health impact due to natural occurrence of this asbestiform fibre;
- a set of municipalities in the Mount Pollino area of the Basilicata Region characterized by the presence of naturally occurring asbestos fibres in soil.

Times and methods of developing communication processes have been analyzed regarding the scientific evidence of health impact on the affected communities on the basis of both scientific and grey literature, direct involvement of the Authors of the epidemiological studies, and retrieval of newspapers articles.

The integrated analysis of epidemiological studies and communication actions in the different settings here presented benefited from multidisciplinary skills in epidemiology, occupational medicine, social and educational sciences.

CASE STUDIES

Casale Monferrato in the Piedmont Region

The production of asbestos cement started very early in Casale Monferrato. The location of Casale Monferrato was of special interest because of the local production of high quality cement that was already one of the main economic activities of the area. The Eternit plant started operations between 1907 and 1912 and remained active until 1986. It employed a cumulative number of about 4000-4500 blue-collar workers, of which those active on January 1st, 1950 or subsequently hired have been listed and included in a cohort study. The maximum size of the workforce was around 1500 workers in the early '70s. The proportion of women was relevant: out of 3434 workers in the cohort, 777 were women. Female employment mainly occurred during the II World War. The factory covered an area of about 92 000 square metres and was located close to the urban areas of the town [20]. Given these premises, it is evident how relevant the Eternit factory was in the economy of Casale Monferrato, a town of about 40 000 inhabitants. Several books illustrated the complex social and economic relation between the Eternit factory and the town of Casale Monferrato [21-27].

The dangerous effects of exposure to the dust due to the work process started to be known early, but there is little documentation about the awareness of workers and the general population. In the early '70s workers become more conscious of the risks of asbestos exposure, and started fights for improving the workplace, later involving local institutions and citizens. In the early '80s formal judicial denunciations were registered and the institutions were urged to act.

The formal investigations on the health effects of asbestos exposure started in the '80s, with three acts. Firstly, a survey was conducted in 1982 by the Cancer Epidemiology Unit of the University of Turin and by the Cancer Registry of Piedmont, coordinated by Prof. Benedetto Terracini and Prof. Enrico Anglesio, to investigate the frequency of deaths attributable to pleural cancer in residents of Casale Monferrato [28, 29]. Secondly, the frequency of new diagnoses of mesothelioma in the residents of Casale Monferrato was investigated by a junior pneumologist [30]. Thirdly, a court case was started by trade unions against the cancellation of economic benefits for workers affected by asbestosis [31]. The three acts came to similar conclusions. The court accepted the claim and stated that the work activity in the Eternit was dangerous. The survey documented a large increase in the number of pleural cancer deaths. The survey on mesothelioma identified a very large excess of cases, in particular it counted the enormous figure of 61 cases (34 M and 27 F) and showed the large proportion of cases (37/61) that had not worked in the Eternit factory or in other asbestos exposing occupations. These observations induced the regional administration to start an "Asbestos Cement Project" that provided resources for the epidemiological investigations as well as the town and the Local Health Administration (LHA) to start the epidemiological studies and to give a specific role to a hospital doctors team that was assisted in the scientific activity by the Cancer Epidemiology Unit of the University of Turin. The first study, published in January 1987, was the cohort study of workers of Eternit. It documented clearly the large excess of deaths from asbestos related diseases: pleural and peritoneal cancer, lung cancer and asbestosis were the most relevant [32]. The total number of deaths was much higher than expected in a population of the same characteristics but not exposed: 864 observed *vs* 710 expected. One hundred seven deaths were caused by lung neoplasm, 57 by pleural or peritoneal neoplasm, and 89 by asbestosis.

The factory had stopped activities and was declared in bankruptcy in April 1986. The debate on the possible restart of production with a new owner was hot, both in the community and within the trade unions. The final decision to refuse the proposal was influenced also by the results of the scientific research: in 1984 and 1989, two important meetings promoted by the unions were held: their motto was "No to asbestos".

In 1987, soon after the presentation of the epidemiological study on Eternit workers, Mayor Riccardo Coppo issued a historic decree prohibiting asbestos use in town and surroundings [33]. The decree was an advanced application of the precautionary principle, relevant also internationally. It was determinant to stop the opening of a new factory run by Eternit France, being added to the strong refusal expressed by the Chamber of Commerce, the environmentalist associations and a group of 110 local doctors.

The association of the families of victims of asbestos exposure was founded in 1988, with the strong support of trade unions. Its first name "AFLED" was changed in 1998 in AFeVA (Associazione Familiari e Vittime Amianto). AFeVA is the referent organization, with a leading role in the interrelation between workers, affected families, community and politics. Its role is conducted also with the communication activity connecting research and scientific world with the real world of the community affected by asbestos (www.afeva.it/). Its organized pressure for the asbestos ban in 1992 and its role has been prominent in the Eternit trial in the years 2000s and in the debate about the compensation offered to Casale municipality from the Eternit property.

In 1992, the law banning asbestos use all over Italy was issued [34]. The asbestos ban also showed the potential of the positive interaction between science and legislative efforts [35].

In the following years, scientific research continued and produced new evidence documenting the risk of mesothelioma for women with domestic exposure [36, 37] and the risk for residents, because of environmental exposure [5, 38], as well as updating studies on workers [20].

The remediation of industrial buildings and of other occurrences of asbestos presence in houses, playgrounds and other places was started in the early 90's and it is nearly completed, with a cooperation between the municipality, the local health authority and the regional agency for environmental protection, with grants from the Ministry of Environment and the Piedmont Region (www.comune.casale-monferrato.al.it/amianto).

The health assistance of patients affected by asbestos related diseases, and in particular by mesothelioma, was progressively organized and jointly carried on by the Hospitals of Casale and Alessandria, the latter being reference hospital for the area. Two units were formed: the UFIM (multifunctional team for mesothelioma) and the Unit of Simultaneus Care. A website providing information for mesothelioma patients and their families (MaiDaSoli project) is hosted by the website of the Alessandria Hospital (www.meso.ospedale.al.it/).

Communication between researchers, local administrators and the local community, including the trade unions, was frequent and intense but did not follow a well-defined plan that had not yet been devised. Communication towards local administrators had the form of reports and auditions, usually open to the press. Communication to the local community occurred also with scientific presentations, organized in cooperation between local and external scientists and local institutions, including trade unions and association of victims. Local newspapers were usually very cooperative and interested in reporting the scientific evidence to the public.

The town of Casale Monferrato later took the lead in the technical information to residents and a website was created, located in the institutional website. It informs on the results of the sampling campaigns on the concentration of asbestos fibres, which were repeated 3 times in the '90s and 2000s. It also provides practical information on the survey on asbestos in buildings of Casale Monferrato, on the correct removal of asbestos cement, and on the economical supports. A special information desk was opened in 2001 at the Town Office of Casale Monferrato to provide information on asbestos risks and appropriate procedures for removal. The general context of the activities against asbestos exposure and for the detection of asbestos related diseases were defined by the Regional legislation "Piano Regionale Amianto", that was first issued in 2001 and renovated in 2016 (DGR 124-7279 of 1 March 2016). Moreover a Regional Board (Centro Regionale Amianto) was defined in 2008 (DGR 80-6707 of 3 August 2007, DGR 64-3574 of 19 March 2012) within the regional law on asbestos (L.R. 30 of 14 October 2008). An impulse came from the national legislation on priority areas for remediation (Law 9 December 1998 n. 426 and following laws) that provided resources for the asbestos removal. It is of extreme relevance that these procedures, including the location of a dedicated landfill for asbestos in 2001, could be conducted without oppositions or antagonistic debate. This is an empirical proof of the effectiveness of the communication process.

The education system has always been very sensitive to the issues regarding asbestos exposure and damages. The most important activity is the multimedia classroom built at the "Natale & Italo Palli Institute", promoted by AFeVA and the Network of all schools in Casale Monferrato and nearby villages. The name of the classroom is "Amiantoasbesto – the courage to know, the need to go beyond". In this special classroom we can look back at the memory, at the present still difficult, but also at the possible future of Casale Monferrato in the fields of culture, environmental innovations, work, and enhancement of the territory, as acknowledged by UNESCO. The most important reason of this Classroom has been the need to deal with the hidden presence of asbestos in the town, in the courtyards, in the attics, in the health facilities, in the gutters, in aqueduct network. It cannot be treated just with reclamation, even if it is necessary, but with the generalized awareness in every inhabitant, particularly in young people, of the danger that might derive from a wrong manipulation of asbestos materials. Multimedia Asbestos Classroom presents an innovative structure in the definition of contents and stories. It is the result of the collaboration between many subjects: volunteers, artists, technicians, journalists, experts, intellectuals, unionists, university, Ministry of Public Instruction, Foundations, Piedmont Region, with a strong global consent on the contents reported. The multimedia interactive "Ecofficina Ltd" unified the collected materials in a really effective project from the communicative point of view.

The classroom is interactive on three walls: one has two LIMS (interactive whiteboards) of advanced technology, another is a big colorful and bright screen, and the third represents an Eternit worker's house, with twelve symbols – objects, one for each chapter of Multimedia Classroom. The visitors enter the black box of the environmental disaster of asbestos in Casale. Through the objects, it is possible to travel from the past to the future of asbestos. The path develops through twelve specific chapters: remediation, asbestos mineral, disease, court trial, history of the factory and of awareness of citizens, initiatives that school students realize together with associations and institutions. Flexibility is an essential resource to create paths of knowledge suitable for any educational need, also by using key words. The great interactivity allows a strong involvement of visitors who actively participate in the process of acquiring and deepening knowledge, and become protagonists. The constant use of the social networks (Facebook, Instagram in particular) is essential for getting young people involved: every project, every interview, every event connected with asbestos is immediately posted and inserted among contents of the website (www.amiantoasbesto.it). Students and young people are the protagonists and their active participation is essential for the project: the students receive a specific training through lessons, then they are able to meet visitors, give lessons and apply peer education methodology. Near 200 boys and girls between 14 and 19 years old are able to animate and fill with life the multimedia Classroom experience. In fact, every time it is possible to notice emotions, positive exchanges of knowledge and humanity, as shown in the customer satisfaction questionnaires. Since November 2014 to June 2018, 3500 persons visited the Classroom: classes of students from Casale and other small towns from the area as well as from municipalities from Northern Italy, university researchers, groups of people engaged in the asbestos issue and interested in awareness raising projects, and tourists. The activity is supervised by a permanent group of teachers from all schools of Casale. A group of students carries on management and organization of activities on asbestos, as well as on environmental education.

The multimedia classroom offers the opportunity to remember the environmental disaster caused by asbestos, its victims and their suffering. At the same time, it is a new way of knowledge and environmental education. It creates network and allows all the schools of the town, the Town Council, the Region Piedmont, the Associations (Libera, Legambiente, AFeVA, ItacaMonferrato, etc.) to work together in national and international level. This Classroom inside the school keeps the consciousness of our students alive on a personal and common responsibility towards environment and people, developing real competences of active citizenship and a free and critical thinking.

The multimedia classroom is a resource also for the population of Casale Monferrato. It is a place of the memory but also a place where the status of remediation is reported and an area of debate about the status of environment and of remediation from environmental contaminants. It is a teaching area on environment and on the use of the web as well. Currently, students use it to explore and debate past events but also the possible future of the area with sustainable initiatives and economic development.

Communication has not always been an easy process, given the expectations and the extremely relevant topics [29]. In particular, an effective mesothelioma therapy is still lacking and it is difficult to explain the victims, their families and the population how complex is to find a treatment for a disease like mesothelioma. On the other hand, the need for a proper remediation is now clear for everybody. As a final balance, in Casale Monferrato a formal communication plan has not been prepared, at least not until recent years; nevertheless, the interested subjects have been able to overcome this deficiency thanks to a close cooperation among them and to the credibility that they have been able to maintain during the long period of activity.

Municipalities of Emilia-Romagna Region

The main characteristics of Emilia-Romagna Region asbestos cement production is that it started later than elsewhere (between 1952 and 1973), with a relatively higher proportion of female workforce. Women were specifically employed in producing "small" pieces, also using by-products of the main productions. Otherwise, they shared with men the same work environment.

All asbestos-cement factories, except one, utilized crocidolite in varying proportions (4-30%). One factory specialized in pipers used large amounts of amosite. Sixteen out of 20 factories operating in Emilia- Romagna were in the Reggio Emilia Province.

Company records were available for 10 factories, 8 of which in the Province of Reggio Emilia. A cohort study was thus set up, including 2712 men and 632 women, followed-up through 30/6/1987 [39], detecting five pleural malignant neoplasms and one of peritoneum. The extension to 1998 [40] detected 18 pleural and 4 peritoneal malignant neoplasms. Finally, the extension to 2012 showed 63 pleural neoplasms (49 men and 18 women) and 8 peritoneal (7 men and 1 woman).

The first communication interventions took place in the '70s and mainly concerned occupational exposures to asbestos and to other hazards. Subsequently to the 1992 ban of asbestos use in Italy, initiatives of general population information have taken place in case of demolition, cleanup and restore of industrial building.

Public health interventions have been focused, in more recent years, on removal and management of asbestos-containing materials, especially if friable, in a wide variety of settings.

Victims' Associations have been playing a major role in this context. In particular, the collaboration between AFeVA and Schools (teachers and students) allowed to developed initiatives to increase awareness of asbestos risk among the young people. In this collaborative frame, students from Bologna High School "Liceo Artistico Arcangeli" have set up an exhibit on asbestos and wrote a book [41].

The currently adopted Emilia-Romagna Regional Asbestos Plan includes a communication strategy aimed at promoting safe behaviors with asbestos in place, training professionals, informing stakeholders and in more general terms fostering networking between public institutions and general population A major aspect of this plan is the establishment of outpatient wards for ex-exposed subjects, free of charge, and of a therapeutic plan for mesothelioma patients. Communication activities targeted to ex-exposed subjects and mesothelioma patients are foreseen [42].

Biancavilla in Sicily

Biancavilla, a town with 24 000 inhabitants in Sicily, experienced a localized excess of mesothelioma [43, 44]. The town inhabitants diagnosed with pleural mesothelioma had no relevant exposure to asbestos during their professional lives. No consistent occupational exposure to asbestos was detected and the main activity was devoted to the production of prickly pears, citrus fruits and vegetables. The incoherent building materials extracted in a local quarry and used in building industry and road paving were investigated and a new-identified amphibole (fluoro-edenite) was found and approved by Commission on New Minerals and Mineral Names of the International Mineralogical Association in 2001 [45].

High concentration of the amphibole fibre in outdoor environment was found, namely in the unpaved roads because of passing cars and lorries. Out-door workers personal samplers showed the highest concentration when jobs were performed near to unpaved roads and crossing.

In 1998, the quarry activity was terminated. In 2002, Biancavilla was recognized as a site of national interest for environmental cleanup. Remediation activities started by covering the quarry area with spritz bitumen, and paving with asphalt all the roads that were considered the main sources of population exposure. Since 2009 the Regional Environmental Protection Agency has been performing regular monitoring of airborne fibres weekly. Bruni *et al.* documented the significant decrease of airborne levels of fluoro-edenite fibres [46].

Since 1988 different reports and studies clearly showed that mesothelioma occurrence in Biancavilla was steadily high: 62 cases were reported between 1988 and 2011. The collection of the cases became systematic since 1998 because of the work of the Sicilian Region Mesothelioma Register. The overall SIR was 576 (95% CI 376-844) respectively, 369 (95% CI 197-632) in men and 1308 (95% CI 697-2200) in women in 1998-2011, based on 26 cases. The highest overall SIR was found for peritoneal cases (SIR 792, 95% CI 96-2000), based on two observed cases. With regard to pleural mesothelioma, when SIR estimates were stratified by age, extremely high figures were shown in the younger age groups: the overall SIR in subjects less than 50 years old was 2134 (95% CI 693-5000). The results in the less than 40 years age group were impressive (overall SIR 6288, 95% CI 1300-18 000, based on 3 cases) [47]. Analysis of mortality and hospitalization from pleural mesothelioma confirmed excesses for both mortality (men SMR 379, women SMR 1128) and hospital discharges (men SHR 261, women SHR 780) [48].

In 2014, the International Agency for Research on Cancer (IARC) assessed the carcinogenicity of fluoro-edenite concluding that there is sufficient evidence in humans that exposure to fluoro-edenite fibrous amphibole causes mesothelioma, and sufficient evidence of carcinogenicity in experimental animals. Fluoro-edenite was included in Group 1 (the agent is carcinogenic to humans) [49].

Since the beginning of the epidemiological investigation, a main point of concern was how to provide clear information to the population. Early, pragmatic indications were provided by the Mayor with the support of Istituto Superiore di Sanità (ISS) [50]. A meeting organized by the Mayor in 2002 with local authorities, researchers, experts, and other stakeholders represented an important mutual knowledge-exchanging event. More recently, in 2015, the scientific collaboration between ISS and the Sicilian Regional Health Authority allowed to implement communication paths in a Biancavilla prevention model. Different groups of stakeholders were involved in the communication path:

physicians and other health workers, local authorities, teachers and local media [51]. Communication initiatives and seminars dedicated to health workers with the participation of family doctors, health personnel and professionals in the Prevention Department of Local Health Unit were aimed to update professional skills and information on fluoro-edenite related-diseases, and contributed to improve mutual understanding among doctors, patients and attendants. Adequate diagnostic and therapeutic pathways have been implemented to help families and patients with fluoro-edenite related diseases.

Communication with local authorities aimed to provide tailored information for defining rules and modality of building activities and minimizing dispersion of fluoro-edenite fibres in the environment as well as to prevent workers and population exposure. Training has still to be performed for workers of external companies involved in construction and other dust-creating activities.

The health education at the different levels of schooling was considered the most important formative path, making it possible to avoid risky behaviours for schoolchildren. Teachers have a pivotal role for the active involvement of students according to their level of literacy, because of their continuous and qualified presence. In this perspective, initiatives have been undertaken in the High Schools involving students in learning about fluoro-edenite fibres characteristics and exposure modality. Students from the Biancavilla Technological High School – Istituto Tecnico Tecnologico "M. Rapisardi" – illustrated their schoolwork on fluoro-edenite and related-mesothelioma in Biancavilla during a town event on 19th February, 2015.

The Sicilian Government has recently approved a plan of health interventions in Biancavilla favouring cooperation between national, regional and local health institutions with the common goal of improving the quality and appropriateness of diagnostic and therapeutic procedures offered to the community by the health services.

Municipalities in the Mount Pollino area in Basilicata Region

The area of Pollino National Park in Basilicata region (Southern Italy) represents another case study of natural sources of asbestos fibres exposure, including natural outcrops of tremolite-containing rocks, for their health-related impact. The study area includes twelve municipalities, seven of which (Castelluccio Superiore, Castelluccio Inferiore, Episcopia, Lauria, Latronico, San Severino Lucano, Viggianello) are characterized by the presence of asbestos outcrops close to areas where people live or work [52]. Awareness of public health risk raised since the early 2000s when the Regional Centre of the National Mesothelioma Registry (Registro Nazionale Mesoteliomi, ReNaM) identified three cases of mesothelioma mortality occurred in the Lauria and Castelluccio Superiore municipalities [53]. In 2005, joint efforts of national, regional and local health and environmental Authorities allowed the organization of a Consensus Conference on health surveillance of resident population exposed to tremolite in that area [54]. The Consensus Conference delivered guidelines for epidemiologic and health surveillance of the residents in the area of Lauria and Castelluccio Superiore municipalities as well as a communication initiative providing information on asbestos risk and promoting personal and collective behaviours for reducing asbestos exposure [54]. The Consensus Conference guidelines were adopted in the Regional Regulation [55]. Several media and newspapers articles informed the public about the Consensus Conference and the surveillance system guidelines [56, 57]. Local health Authorities, in charge for the epidemiological and health surveillance of the resident population, disseminated information material on asbestos risk for human health in lay language, as well as on the health services provided including a toll-free-number for the resident population. They also collaborated with the local church representatives in realizing tailored initiatives for increasing asbestos literacy of the affected communities [58].

In 2012, studies aimed to assessing asbestos exposure in both occupational and environmental settings highlighted a relevant tremolite exposure both in construction workers [59] and in farmers employed in those areas compared with a group of residents engaged in activities that did not require contact with the soil [60]. The analysis of personal samples showed the presence of tremolite fibres in concentrations higher than these found in natural ground in 100% of the construction workers as well as in two out three cases of farmers, with a peak of 26 ff/l over the background value of 2ff/l. These studies increased the awareness of local Authorities on both safety measures to be implemented and communication initiatives to be undertaken with the resident population.

The recent epidemiological study by Caputo *et al*. [52] concerning the Pollino sub-area in which asbestos fibres are close to dwelling and settlement observed: i) a significant excess of mesothelioma incidence (SIR: 208; CI 95% 111-355; 13 observed); ii) a non-significant excess of hospitalization for malignant pleural neoplasm (SHR 176; CI 95% 93-355; 9 observed); iii) a significant excess for mortality and hospitalization for pneumoconiosis (SMR: 534; CI 95% 345-824; 20 observed – SHR: 245; CI 95% 149-405; 15 observed); iv) a significant excess for hospitalization for asbestosis (SHR: 852; CI 95% 290-2506; 3 observed). This study clarified that in 7 out of 12 municipalities characterized by the presence of naturally occurring outcrops of minerals containing among else tremolite and chrysotile, health risks were ascertained as the outcrops were close to areas with dwellings, quarries, cultivated areas and pastures. Areas where anthropic activities were apt to determine mechanical solicitations to outcrops resulting in fibres release and diffusion, with respect to evidence available in 2003-2005, appeared to be much wider than previously suspected [52].

This study provides recommendations for both fostering environmental monitoring and safety measures concerning those situations considered at high asbestos risk and implementing epidemiological surveillance as a permanent activity by periodically updating mortality and hospitalization analyses for all asbestos-related diseases and incidence of mesothelioma. In this frame, the Authors recommended starting a communication plan with the relevant stakeholders: local administrators, general practitioners, health and environmental professionals, schools, media, local associations and the resident population, in order to implement epidemiological surveillance and contribute to asbestos-related disease prevention [52].

DISCUSSION

The analysis of the communication experiences in the case studies presented in this paper allows the identification of similarities and differences useful to shed light on a few relevant lessons learned.

In all case studies the communication process started with dissemination of basic information concerning the results of the first epidemiological studies. This information was provided to both the workers of the industrial settings and the resident populations (associations, trade unions, local administrators) and concerned the preliminary evidence of health risks of exposure to asbestos and/or asbestiform fibres. The subsequent epidemiological investigations, while providing further scientific evidence of the health impact of exposure to asbestos and /or asbestiform fibres, allowed the establishment and/or strengthened the relationships between the researchers and the affected communities. In particular, they contributed to the development of different types of communication and forms of engagement of social and institutional stakeholders.

According to this common kickoff of the communication activities in the four case studies, we list in the following some evidence of the engagement of different stakeholders, emphasizing their role in the whole communication process:

- trade unions in cases of industrial activities focused on information on asbestos risk and reclaimed better safety conditions for the workers. They promoted the establishment of associations of former exposed workers and family members of asbestos victims in the affected communities. The associations of former exposed workers and family members of asbestos victims, as well as other territorial subjects (the local church representatives in the case of Pollino area), developed local communication networks that really increased knowledge and awareness on asbestos risk and impacts. Local media often contributed to raising the level of attention on asbestos risk and impacts in the affected communities;
- regional and local administrators, because of the scientific evidence of the asbestos health impact in their communities, played a role according to their responsibilities for planning the most urgent prevention interventions and in responding to the requests and needs of their communities;
- local operators of health prevention and environmental remediation progressively increased relationships with researchers involved in the studies and acquired a better knowledge for undertaking proper actions;
- researchers involved in the studies acquired greater awareness of their role in the development of communication processes starting from the relationships with the trade union representatives, the association of former exposed workers and victims as well as with local health and environmental operators, thus contributing to strengthen the resilience of the affected communities;
- the involvement of the School has been more recently developed in all the selected case studies. School action has been characterized by the adoption of learning methodologies "train to trainers" and "peer to peer education", and the undertaking of interactive and multimedia communication. The adoption of these methods has favoured the preservation of the histories and memory of the communities related to asbestos and promoted awareness on the asbestos health related-impact in the communities. The students are involved in the network of relationships of their community and play an active role in increasing the collective reaction of the communities.

Similarities and differences characterizing the four case studies selected in this paper allowed us to identify criticalities and extract the lessons-learned to be transferred through shared communication strategies in other asbestos contaminated sites. *Figure 1* illustrates through a synoptic sketch the key actions/processes and the stakeholders engagement to foster awareness and increase resilience.

CONCLUSIONS

The integrated analysis proposed in the present paper focusing on the four selected case studies allows us emphasizing key points for improving communication processes and building effective relationships between the researchers involved in the investigations and the affected communities. In particular, epidemiological surveillance of asbestos affected populations has been playing a critical role in the perspective of public health. Epidemiologists, occupational physicians and social researchers involved in the studies of asbestos impact on the affected communities should participate in the process of relationships among the others involved stakeholders (the case of Casale Monferrato is an example of good practice). This process of social relationships characterizes the communication practices among relevant stakeholders and strengthens resilience of communities *(Figure 1)*. A strong relationship between the professional figures, epidemiologists and occupational physicians is useful to transfer concepts such as risk at population level versus individual risk by using lay language, without ignoring the complexity and socio-emotional implications of the messages. The communication practices, designed in shared communication plans, certainly benefit by joining multidisciplinary skills and strong relationships within community networks. In this frame, the involvement of the School in participative communication paths is essential to create awareness of the youngest population in order to promote their active role to increase the preparedness of communities.

The analysis of the four case studies selected in this paper indicates that the different local contexts require tailored communication processes able to take into ac-

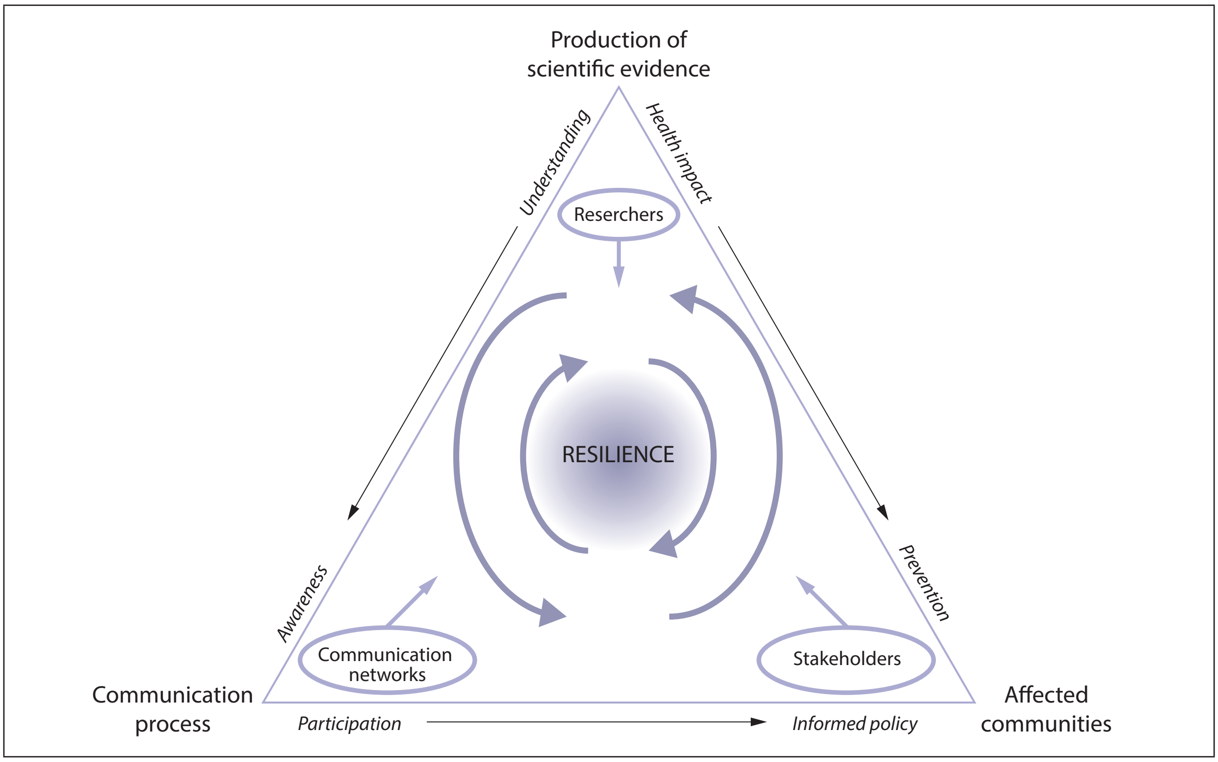

Figure 1
Key actions to foster awareness and increase resilience through communication processes involving relevant stakeholders of the affected communities.

count diverse levels of literacy on asbestos of the involved institutional and social stakeholders and communities.

Although regional asbestos plans recently adopted in Italy envisage communication activities, no experiences of structured communication plans have been implemented to date. The lessons learned from the case studies indicate that the definition of communication strategies and the adoption of communication practices since the very early evidence of local asbestos health impact can represent a relevant contribution for epidemiological and health surveillance of the affected populations. This is especially for those communities in which the health impact has only recently been reported.

The communication process is an effective way to manage the relationships among researchers, local authorities and society at large. The adoption of participated communication practices can foster aware policy-making, health prevention and environmental remediation actions, which in turn represent an effective way to increase the resilience of affected communities.

Conflict of interest statement

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

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An outbreak of cancer and asbestosis among former amosite-exposed subjects in Ledro Valley, Italy. From discovery to environmental cleanup

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Abstract
Here are reviewed the studies conducted on asbestos-amosite pollution and its effects on the health of workers exposed from 1928 to 1973 at the Collotta-Cis factory of Ledro, Italy. The methods adopted to conduct the initial research, involving the population itself and the local administrations are described. The data summarized include: epidemiological studies of mortality carried out in 1977-85 and updated in 2009; results of the investigations carried out throughout the 1980s on the health consequences on workers, their families and residents near the factory; process of environmental cleanup from asbestos of the industrial area, completed in 1989, and the pollution risk assessment in the whole Ledro Valley. Although this was a small community of about 400 workers, these studies show that exposure to asbestos is responsible for the death of 81 people (22 mesotheliomas, 21 asbestosis, 38 malignant tumors of the lung, digestive system, ovary), for 1400 years of life lost, and for about 100 invalidity pensions, as recognized to former workers by INAIL.

Key words
- asbestos-amosite
- cancer
- mesothelioma
- environmental cleanup
- population involvement

INTRODUCTION

Since 1900 the factory Collotta-Cis of Molina di Ledro, Trentino, Northern Italy, produced various compounds containing magnesium carbonate. However, in 1928 a new line of manufacturing was started, which marked the future of the factory and of the entire Ledro Valley forever: on one hand by bringing new jobs, bread and wellbeing, but on the other by causing suffering and grief both among those who worked in direct contact with asbestos, but also among those who unconsciously inhaled the fibers for years despite never setting foot in the factory.

The new product of the manufacturing was a compound called "super-insulator", a highly effective thermal insulator composed of a mixture of magnesium carbonate – extracted from local quarries, and amosite fibers – imported from South Africa by sea in bags of jute and transported to the Ledro Valley by truck. The final product was commercialized as slabs, smaller segments, pipe casings and a powder applicable by spray, all of which were subsequently transported to various destinations, including the ports of Monfalcone, Porto Marghera and Genoa, where the insulator was loaded on cargos and often shipped overseas.

Asbestos-containing products were manufactured at Collotta-Cis for 45 years until 1973, when the production was interrupted due to the overwhelming competition of mineral wool as a cheaper insulating alternative.

What follows is an account of the events that occurred in that factory and valley, in the attempt of taking into account the socio-economic context while describing the manufacturing methods and workers' conditions, as well as the methods of data collection, the results of the mortality studies, the current state of health of both factory workers and non-worker exposed subjects, and what has been done to identify and eliminate the risks deriving from the persistence of asbestos inside and outside the factory.

THE DISCOVERY

The first reports

The first to realize that something was wrong, that the people in that factory were dying young "of tumors and lungs", were the workers themselves. But in those times reporting work-related health risks could potentially be more dangerous than the risks themselves.

Ledro was a poor valley; even the land was stingy [1, 2]. Securing a job in the factory meant safety for entire families, it meant bringing bread on the table, getting out of poverty: the only alternative was the emigrant's

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suitcase. Everyone held on tight to his or her job. A daily reminded of its importance were the two lines of people in front of the factory: of those at the gates looking for work, and of those leaving the valley to seek their fortune elsewhere. Losing a job in the factory was a risk that nobody could run, not even those who wanted to ask for safer working conditions.

At the time, the knowledge about asbestos was very limited, even among doctors: it was known as a health threat in the universities, but much less in peripheral hospitals [3, 4]. Yet, it was in these local hospitals that Collotta-Cis workers were hospitalized, starting as early as in the 1960s and 70s. By then, the Anti-Tuberculosis Dispensary (DAT) already had in archive several chest X-rays with diagnosis of asbestosis; the National Institute for Insurance against Accidents at Work (INAIL) had already recognized a few cases of asbestosis; the first few deaths from asbestosis, mesotheliomas and various other malignant tumors were starting to alarm the workers and their relatives. Nevertheless, it wasn't before 1977 – when the works with asbestos had already been suspended – that it was possible to start digging up the dirt.

It was in that year that the local Public Service of Occupational Medicine was founded, and the author of this manuscript started receiving the first few reports from factory workers and hospital doctors from the area.

Data collection with the participation of the population and administrators

The first mortality investigation thus started in 1977 with a painstaking yet swift work of identification of a first group of factory workers [5]. It began with meetings with the mayor of Molina di Ledro, Agnese Rosa, who became a valuable ally ever since, and continued in the home of a retired town-hall clerk, Candido Zendri, who provided a first list of workers that he had compiled – safe in the knowledge that our office would have reached out to him, sooner or later. The investigation was continued together with the population of the town and the entire valley, reaching out to former workers and relatives of the deceased, to the Office of Vital Records and the Church records for death certificates, and to the hospitals for medical records.

In the following years all the exposed subjects were finally identified through the most varied sources: interviews with co-workers of former employees who had emigrated or died, town-hall clerks and employment officers, but also through the Industrial Sickness Fund, trade unions, the Anti-Tuberculosis Dispensary (DAT), the National Agency for Prevention of Injuries (ENPI) and local hospitals [6, 7].

Data were collected for each of the 429 workers who worked at Collotta-Cis from 1928 to 1973: on one hand on their personal records, including residence, contacts of relatives, cause of death and clinical documentation (hospital health records, histological examinations) for the deceased, and health condition for the living; on the other hand related to the work they performed in the factory, including years spent working, in which departments and performing what tasks, on their level of exposure to asbestos and habit of tobacco smoking, along with other general working conditions in the factory: division of work, type of asbestos used, pollution levels in the different departments [7, 8].

The area of the factory was mapped to identify the asbestos still present, while the levels of pollution were investigated in the homes of the workers and the general population [7, 8].

The collection of these data was facilitated by: 1) the geo-morphological isolation of the Ledro Valley – not easily accessible from the nearby valleys; 2) the fact that all the workers had lived within one of the 6 municipalities of the valley, altogether amounting to less than 5000 inhabitants; and 3) the support of the Mayor of Molina di Ledro who, with the help of several very active elderly workers, organized meetings with other former workers and the relatives of the deceased; this was a remarkable collective effort that lead to compile all the names of workers, length of their exposure and places of emigration of the many emigrants, to inform former workers of the risks they ran, to convince them to take part in the health checks, and to encourage those who were intimidated. This body of information was collected also via questionnaires sent to former workers and their relatives, at times even to those who had left the valley but who still wanted to provide their contribution to the reconstruction of the history of asbestos.

It was therefore an experience of great collective participation, in which the investigations by the Public Service of Occupational Medicine of Riva del Garda, Trento, enjoyed the support of experts from several institutions, including the Medical School of the University of Verona, the National Cancer Institute of Milan, the Higher Institute of Health of Rome, the Occupational Clinic of Milan, the Center for the Study and Oncological Prevention of Florence, and the Armanni Pulmonology Hospital of Arco, Trento.

The support of these institutions was also helpful to break the resistance of the powerful Asbestos Users Association [9] (informally known as the "eighth sister", after seven companies monopolizing the oil trade in those years) and their emissaries sent to the Province of Trento to block the epidemiological research in different ways, including by telling the general public that asbestos was harmless if used well, and that there was nothing true in what that young physician was saying…

However, the impact of the research in the Ledro Valley became clear a few years later, in 1985, when we organized a national conference in Arco, Trento, titled "The Neoplastic Risk from Asbestos in the Workplace and in the Living Environment". Close to 200 scholars attended the meeting, in which the results of the Collotta-Cis studies were presented and published in the official proceedings [7], and the asbestos issue was finally discussed. It was an unprecedented opportunity to shed light on this public health issue, to encourage healthcare representatives from the rest of the country to start investigations in their own districts – if they hadn't already, and to join forces in defense of the health of both workers and the general population, similarly to how it was happening in the Ledro Valley.

These were challenging times not only for the workers, but also for Occupational Health physicians, who were the first to go on trial for reporting the deaths at the workplace – sometimes even before the factory owners themselves. Indeed, this is what happened with Collotta-Cis: the author of this manuscript, as principal investigator in the studies, was the sole person to be ever summoned by the Courts of both Trento and Rovereto, Italy, upon charges of defamation. Both proceedings, however, were dismissed in the preliminary phase.

Exposure to asbestos

The only type of asbestos ever worked at Collotta-Cis was amosite; this was first reported by the factory owners and workers, and then confirmed by all the analysis performed in the 1980s by the National Institute of Health in Rome, the Provincial Chemical Laboratory of Trento, and the Pavia Clinical Labor Foundation [3, 8].

No evidence suggests that the levels of asbestos' dust were ever measured in the work environment before then. Asbestos-amosite fibers were heavily dispersed and ubiquitous throughout the factory, although the concentration was different in different production departments. Intuitively, the steps of production that exposed workers to higher concentrations of fibers were those carried out in direct contact with asbestos, that is: emptying bags of the product of the fibers' preparation and crushing, manual pouring of asbestos into the filters to be mixed with magnesia, drying of the "super-insulator" product, cutting and shaping of the final product with planers, and milling of the production scraps to obtain the sprayable powder for thermal insulation. According to workers' reports, during these processes the amount of asbestos-containing dust in the air was at times so elevated it impaired visibility.

The ventilation and protection systems used by individuals or installed by the factory, if any, were inadequate and ineffective; no separations were placed between different departments, nor between the inside and outside the factory. All things considered, there is no evidence to suggest that the company ever took valid preventive measures.

For these reasons, even workers and inhabitants outside the factory were exposed to asbestos, including farmers working in surrounding fields and workers in nearby workshops, the village's shoemaker, truck drivers transporting the materials, the family members sharing their homes with the workers, and those living nearby the factory.

From the investigations emerged that on average 84 workers were employed by the factory at any given time, peaking at more than 120 in 1960/63; of these approximately 70% were men and 30% women. While women tended to work for shorter periods (average 5.7 years) compared to their male counterparts (9.7 years), they started working on average at a much younger age (18 years *vs* 32 years), sometimes as young as 14-15 years [7].

For each of these workers it was measured the Cumulative Exposure Index (CEI) by multiplying the years/months of work by a variable coefficient representing the level of exposure: ×1.0 for workers in the departments directly processing asbestos; ×0.5 for those in adjacent departments and in general maintenance; ×0.1 for those in departments further away and in courtyards; ×0.0 for those outside the factory (woodcutters for fuel, miners for extraction of dolomite) or office clerks [7]. The average CEI so calculated was nearly identical in both sexes (3.8 in men and 3.3 in women), which means that – since women worked for shorter periods – they performed tasks with higher exposure to asbestos.

THE INVESTIGATIONS AND RESULTS

Mortality studies

The first mortality study, which dates back to 1977, was carried out immediately after the first few reports reached the Department of Occupational Medicine of Riva del Garda [5]. This represented a preliminary scientific confirmation to the suspicions of the factory workers, who had noticed an alarming high number of deaths by asbestosis and cancer amongst those who had worked asbestos in that factory over the previous 45 years.

During the following years, after the whole cohort of the exposed workers was identified, it became possible to calculate the cumulative exposure levels to asbestos for each individual and thus carry out a complete epidemiological study of mortality. This was initially presented at the International Symposium on Occupational Tumors of the International Labour Organization (ILO) in Helsinki in 1981 (Parolari G, Merler E, Riboli G) [10], and later at the National Convention in Arco, Trento, in 1985 (Parolari G, Merler E, Bertazzi PA, Zocchetti C, Carnevale F, Berrino F) [11]. These works confirmed a significant increase of tumors and asbestosis among Collotta-Cis former workers, and were in line with both the preliminary data on the same cohort published in 1977, and those on a different cohort of US workers also exposed to amosite published by Selikoff *et al.* [12].

The mortality study was subsequently updated in 1990, 1995 and 2009 [13-15].

As of 2009, of the 429 known workers who were employed by Collotta-Cis in the period 1928-73: 372 resulted to be exposed to asbestos (218 men, 154 women), 48 were not (woodcutters, miners, office workers), and 9 were not identified. Of the 372 workers exposed to asbestos, 281 had died in the 70 years from 1940 to 2009: 105 for cancer, 18 for asbestosis, 158 for other causes [15, 16] (*Table 1*).

There are a number of reasons for which there was value in keeping up to date the mortality studies on the Ledro Valley cohort. First, this is one of the few epidemiological studies in literature on workers exposed exclusively to amosite, a commercial type of asbestos of the amphibole group, the one with greatest carcinogenic power [12, 17, 18, 19]. Second, in this cohort it was identified a correlation between asbestos and tumors of the digestive system, of particular interest in the field [20, 21]. Third, it was the first cohort studied in Italy and has thus been kept under observation for 40 years. Finally, although small, the Ledro Valley's cohort includes subjects at very high exposure, a large number of women, and shows high mortality rates for several causes [3, 10, 11].

Table 1
Collotta-Cis: mortality study, updated to 31 December 2008. Modified from [15]

	Males	Females	Total
Workers in the study	218	154	372
Living	24	67	91 (24.5%)
Deceased from 1940-2008	194	87	281 (75.5%)
Died for cancer	73	32	105
Respiratory system (excluding pleural mesothelioma)	*19*	*2*	*21*
GI tract (excluding peritoneal mesothelioma)	*36*	*5*	*41*
Pleural mesothelioma	*3*	*7*	*10*
Peritoneal mesothelioma	*1*	*2*	*3*
Ovarian tumors		*3*	*3*
Tumors in other sites	*14*	*13*	*27*
Deceased due to asbestosis (not complicated by cancer)	13	5	18
Died for other causes	108	50	158
Cardio-vascular diseases	*63*	*32*	*95*
Respiratory diseases (excluding asbestosis)	*20*	*9*	*29*
GI tract diseases	*8*	*2*	*10*
Traumas	*6*	*0*	*6*
Other causes	*11*	*7*	*18*

During the 1980s, it was analyzed the mortality for cancer among the Ledro Valley inhabitants who had never worked at Collotta-Cis, which showed no difference when compared to that population of Arco, Trento, a neighboring but non-exposed area [22]. However, within the valley, an unusual number of mesothelioma cases were described among family members of Collotta-Cis workers, residents near the factory, and external workers exposed to the factory's asbestos.

Epidemic of tumors and asbestosis among workers, dose-effect relation

These epidemiological studies showed that exposure to asbestos-amosite increased mortality of Collotta-Cis workers, both among those directly involved in processing the "super-insulator" and those indirectly exposed to asbestos.

In the comprehensive 1985 study, the mortality of Collotta-Cis workers was compared to that of Italy and of the neighboring city of Trento – matched by gender, age and time period [11].

The Standardized Mortality Ratios (SMR) so obtained showed a significant increase of incidence for all tumors (SMR 1.93, 95% Confidence Interval (CI) 1.37-2.65 in comparison with the Italian population) (SMR 2.00; 95% CI 1.45-2.71 in comparison with the population of Trento), for tumors of the digestive system (SMR 2.44; 95% CI 1.51-3.73 – Italy) (SMR 2.03; 95% CI 1.25-3.10 – Trento), and for lung tumors (SMR 2.38; 95% CI 1.14-4.38 – Italy) (SMR 1.70; 95% CI 0.81-3.63 – Trento).

For tumors of the digestive system, the measured risk was also several times higher, especially for esophageal (SMR 8.47; 95% CI 2.71-19.44 – Italy) (SMR 5.25; 95% CI 1.71-12.26 – Trento) and rectal tumors (SMR 5.84; 95% CI 1.56-14.63 – Italy) (SMR 4.71; 95% CI 1.28-12.05 – Trento) [11] (*Table 2*).

For pulmonary tumors, mortality rates increased with cumulative exposure to asbestos and with tobacco smoking, although the number of tumors was significantly increased only for latencies greater than 20 years from the initial exposure [11].

Mortality due to non-neoplastic respiratory causes was also high, statistically significant and correlated to the exposure levels.

As of the 2009 study updates [15, 16], 39.9% of deaths among the exposed Collotta-Cis workers (105/263) were caused by cancer (excluding those from asbestosis) – 40.3% (73/181) in men and 39.0% (32/82) in women. This number was even higher when considering only the most recent period (1991-2008), accounting for to 43.8% of deaths (39/89) –46.8% (22/47) in men and 40.5% (17/42) in women (*Table 3*).

At the same time-point, 18 deaths were attributable to asbestosis; this is likely an underestimation for two reasons: 1) before 1980 this disease was underdiagnosed and rarely reported; 2) when deaths were caused by both cancer and asbestosis, they were reported as caused by cancer alone.

In addition to the overall increase, it was observed a clear dose-effect relation between exposure to asbestos-amosite and mortality: the Standardized Mortality Ratio (SMR) directly increased as a function of the duration of exposure alone, but increased even more when both duration and intensity of exposure were combined as Cumulative Exposure Index (CEI). In particular, for high cumulative exposure (CEI > 6) the SMR for all tumors in males (SMR 2.59; 95% CI 1.42-4.35 – compared to the Italian standard population) was higher than in the medium – (CEI 2-6: SMR 2.22; 95% CI

Table 2
Collotta-Cis: standardized mortality ratio (SMR) and 95% confidence intervals (95% CI) as compared with the population of Italy and of the city of Trento, 1985 [11]

		Standard: Italy	Standard: City of Trento
Pathology code		**SMR** (95% CI)	**SMR** (95% CI)
140-209	All tumors	1.93 (1.37-2.65)	2.00 (1.45-2.71)
150-159	Tumors of the GI tract	2.44 (1.51-3.73)	2.03 (1.25-3.10)
150	Tumors of the esophagus	8.47 (2.71-19.44)	5.25 (1.71-12.26)
154	Tumors of the rectum	5.84 (1.56-14.63)	4.71 (1.28-12.05)
162	Tumors of the lungs	2.38 (1.14-4.38)	1.70 (0.81-3.63)
200-209	Tumors of the blood	2.61 (0.52-7.31)	2.55 (0.53-7.46)

Table 3
Collotta-Cis: frequency of deaths due to cancer, 2009. Modified from [15]

Date of death	Males		Females		Total	
< 1975	28/77	(36.4%)	6/18	(33.3%)	34/95	(35.8%)
1976-90	23/57	(40.4%)	9/22	(40.9%)	32/79	(40.5%)
1991-2008	22/47	(46.8%)	17/42	(40.5%)	39/89	(43.8%)
Total (1940-2008)	73/181	(40.3%)	32/82	(39.0%)	105/263	(39.9%)

1.07-4.09) and lower-exposure groups (CEI < 2: SMR 1.44; 95% CI 0.79-2.42). A similar observation was made for tumors of the digestive system (CEI > 6: SMR 3.75; 2-6: SMR 2.63; < 2: SMR 1.63), for lung tumors (> 6: SMR 2.73; 2-6: SMR 3.64; < 2: SMR 1.50) and for non-neoplastic respiratory diseases (> 6: SMR 2.50; 2-6: SMR 1.76; < 2: SMR 1.40) [11].

As of the 2009 study updates, 52.1% (25/48) of workers had died of tumor in the high cumulative exposure group (> 6), 39.4% (41/104) in the medium- (2-6) and 35.1% (39/111) in the low-exposure groups (< 2). As expected, no increase in mortality due to tumors was observed in the group of non-exposed workers (woodcutters, miners, office employees; 18.9%; 7/37) compared to controls. No significant differences between genders were observed [15, 16].

If we consider the combined mortality from cancer and asbestosis, the correlation between exposure and mortality is even more striking: 17 of the 20 (85%) most exposed Collotta-Cis workers died of cancer and/or asbestosis – 9 of cancer, 6 of asbestosis, 2 of asbestosis complicated by cancer; of the 11 tumors: 3 were mesotheliomas, 3 lungs, 4 GI system, 1 ovary [15, 16].

Mesotheliomas, deaths attributable to asbestos, and years of life lost

If asbestos had never been processed in the Ledro Valley, based on the standard Italian incidence, there shouldn't have been any case of mesothelioma among the 400 Collotta-Cis workers and their families (expected cases: 0.21) [23, 24, 25]; instead, 22 people died of mesothelioma (17 of the pleura, 5 of the peritoneum) in those years: 4 before 1985, and 6 in each of the following decades (1986-95, 1996-2005, 2006-15).

Of these 22 cases, 16 were former Collotta-Cis workers (including 1 driver) and 6 were indirectly exposed (4 relatives of workers, 1 environmental, 1 professional outside the factory). Among the non-factory workers was the shoemaker of Molina di Ledro, who was exposed to the asbestos fibers while repairing the worker's shoes and sewing the factory's jute bags; a woman who had lived in her youth near the factory; 4 family members (2 wives, a daughter and a sister) of 4 different Collotta-Cis workers who inhaled asbestos while brushing their relatives' work clothes, cleaning their shoes, sleeping on the pillow where the husband had laid his contaminated hair. The strong emigration from the valley in the years made it often complicated to identify these victims, to confirm if they were alive or dead, and if so to attest their cause of death. However, for these 22 cases of mesothelioma, it was possible to confirm the diagnosis as certain (histological confirmation available) in 15 instances, as probable in 1 (cytological confirmation available) and as possible in 6 (radiological, clinical, death certification) [3, 16].

While the small numbers of this cohort advise against drawing hard conclusions, it is interesting to highlight a trend suggesting an inverse correlation between cumulative exposure levels and average latency of mesotheliomas, which was shorter in the group at high-exposure (41 years) when compared to all other groups (averaging 50-52 years) – whether directly or indirectly exposed. As of 2015, the incidence of mesotheliomas among the Collotta-Cis workers was 0% (0/57) for subjects with latency up to 25 years, 5.6% (4/72) in those with latency 26-40 years, 7.3% (6/82) for latency 41-55 years, 8.7% (6/69) for 56-70 years, and 0% (0/15) over 70 years. It will be useful to monitor over time the approximately 50 former workers still alive, who have by now reached on average almost 60 years from the beginning of the exposure [3, 26].

It is also worth noting that mesotheliomas affected more the ex workers (mainly women, 11 out of 16) who started to be exposed to asbestos at an early age. In fact, of the 16 cases of mesothelioma, 6 occurred in workers who began their exposure at 15 or younger (6/48), 6 between the ages 16-19 (6/55), and 4 between 20-30 (4/74); no case of mesothelioma occurred among the 138 workers deceased by 2015 (123 men and 15 women) who started to be exposed to asbestos when older than 30yo. The same observation applies to the cases of mesotheliomas among non-factory workers: they affected predominantly women (5/6) who started exposure at a young age. The period of latency of the disease was on average 49 years, ranging between 29-68 [3, 15, 16].

As for cancer cases, if the cohort of Collotta-Cis workers exposed to asbestos died with the same frequency of the control populations (Italian and remaining population of Ledro Valley), only 54 should have been deceased by 2009; however, the deaths for cancer were 105 in this group, which suggests that these 51 tumors in excess are attributable to asbestos exposure. Adding them to the 18 deaths due to asbestosis, 69 former Collotta-Cis workers died as a result of exposure to asbestos, that is one in four of the 281 dead workers. With the addition of the 6 mesotheliomas among the exposed non-workers, the death count goes to 75 [15, 16]. As of today, 3 more deaths for mesothelioma and 3 for asbestosis have been described, bringing to 81 the number of people who lost their lives in the Ledro Valley due to the work with asbestos at Collotta-Cis factory [3].

Finally, we compared the life expectancy at 40 years of age of the exposed workers with that of the rest of the Ledro Valley population (until 1990) and of the overall Italian population (after 1990): by 2009, Collotta-Cis workers lost a total of 1382 years of life, that is they lived on average 5.2 years less [15, 16]. With the addition of the years of life lost due to the cases of mesothelioma in the non-factory workers, the count exceeds 1400 years.

Health status of living workers, surveys on residents, occupational disability pensions

During the early 1980s, 167 former Collotta-Cis employees (of the 248 then alive) were subjected to health checks: medical examination, chest X-ray, spirometry, measurement of the diffusing capacity of the lung for carbon monoxide (DLCO), and research of corpuscles of asbestos and siderocytes in the sputum. Of the 87 new cases of asbestosis diagnosed (52.1% of former workers visited), 56 (33.5%) were cases of pleural plaques, 17 (10.2%) of pulmonary asbestosis and 14 (8.4%) of the two joint diseases [27, 28, 29].

From the chest X-rays emerged a correlation between the intensity of exposure to asbestos (both in years of exposure and CEI) and the frequency of pulmonary asbestosis and/or pleural plaques. The habit of smoking tobacco clearly reduced the threshold-dose necessary to induce asbestosis, as well as the latency time for it to radiate. These health checks were an excellent opportunity also to make known to all workers the particularly negative effects of tobacco smoking on subjects previously exposed to asbestos, and thus reduce that unnecessary additional risk factor. In almost 40% of the 36 workers who had previous X-rays available, it was also shown a trend for pleural plaques to increase in volume and to calcify, even 30-40-50 years after the beginning of exposure [27].

With the Pulmonary Function Tests it was highlighted a strong correlation between reduction of the Vital Capacity and increase of the CEI, increase of the latency period, and presence of X-ray alterations. The measure of Vital Capacity interestingly proved to be even more sensitive than the diffusing capacity of the lung for carbon monoxide (DLCO). Additionally, tobacco smoking showed to be remarkably effective in accentuating signs of obstructive disease. Finally, the presence of asbestos corpuscles in the sputum revealed to be a good indicator of exposure to amosite, even several decades from the last exposure [30].

The health checks also involved 33 people who had lived for years nearby the factory. Among these, we identified 5 cases of pleural plaques, 2 of suspected pulmonary asbestosis (ILO Profusion Score 0/1), but none of certain pulmonary asbestosis; however, 3 cases of asbestos-induced pleural plaques had already been diagnosed a few years prior by the local Anti-Tuberculosis Dispensary on 2 farmers and 1 mechanic who had worked near the factory [27].

All these studies were presented at the Arco Convention in 1985 [27, 30].

Asbestosis and tumors of suspected occupational origin have been thereafter reported to INAIL, which allocated about 100 disability pensions for work-related illnesses, reparations that gave back some degree of justice to workers and their families. Among these reimbursements were those to workers exposed before 1934 (before the rules on insurance against occupational diseases entered into force), thanks to a law approved by the region of Trentino-Alto Adige, with which the region entrusted to INAIL the management of those practices and provided the financial backing [15, 16, 31].

ENVIRONMENTAL CLEANUP

Mapping of asbestos pollution inside and outside the factory

Even after its closure in 1979, the light fibers of amosite were raised in the air at any gust of wind and transported from the factory area and from the polluted structures still present. This represented a constant danger not only for those who entered the industrial area, but also for those who lived or worked nearby, and for those who passed on the nearby road connecting the Ledro Valley and Lake Garda.

The necessity to decontaminate the polluted area became clear, and thus the first risk mapping was carried out in 1981 by collecting samples both inside the factory and in the courtyards. The analysis showed the presence of asbestos fibers in more than 30 of the sampled locations, in high levels in the areas previously used for processing the insulating material and in moderate quantities even in the departments used to produce magnesium. The map obtained was used as a starting point for the subsequent cleanup operations [7, 8, 32].

In the same year, an investigation was also started in the homes of inhabitants of the valley to assess the diffusion of asbestos as insulating material, production waste or other polluted materials. After interviewing 143 among former factory workers, inhabitants and artisans, it turned out that the use of this insulating material in the valley was only sporadic for a number of reasons: it was not customary to use insulating materials at all, its cost was high, its removal from the factory too risky, and the production waste – made of a mix of magnesium and asbestos – was all milled at the factory to be sold as powder for industrial or civil spray applications.

Jute sacks instead, which had contained asbestos and were still heavily contaminated, had been widely used in the valley as containers for potatoes or hay, and as work aprons [8, 32].

Environmental cleanup of the industrial area and surroundings

The first cleanup operations involved the most polluted areas of the factory and were carried out by the Municipality of Molina di Ledro in 1981-82. Lacking any regulation on the matter, the city performed them swiftly following the few recommendations then available, and with the collaboration of the factory workers themselves. These workers, who until a few years earlier had handled asbestos without much protection, found themselves puzzled to be performing those same tasks, yet this time equipped with overalls and disposable shoes, masks with adequate filters, taking showers at the end of the work. The asbestos and polluted material were removed from the factory, sealed in polyethylene bags and sent to an authorized landfill in France. These procedures reduced greatly the health risks due to the dispersion in the air, as well as any possible contact with the fibers for those who may have entered the abandoned property, out of curiosity or to play, as it often happened with the children in the area [7, 8, 32].

Meanwhile, the complete cleanup of the factory and surrounding land was being planned; this included the white mountain made of tens of thousands cubic meters of calcium carbonate, the production waste of decades of work that had been piling up in the courtyards near the factory, nearby a stream. From the geological analysis, it turned out that this build-up was sitting on an aquifer: the presence of these large volumes and unstable weights, located upstream of several towns and of Lake Garda, represented a grave health threat and influenced the decisions to further expedite the interventions.

In 1988 the full cleanup of the walls, beams, planks and roofs was carried out; the only exception were a small shed and a house located at the edge of the industrial area, still existing today, where asbestos had never been deposited or worked. While performing this task, Industrial Technologies of Milan used safe working methods for workers and for the neighboring residents, according to the procedures defined in the works contract, followed by regional and national recommendations and EEC Directives that had meanwhile entered into force [33-37] (*Figure 1*).

Figure 1
1988. Environmental cleanup operations of the Collotta-Cis Area (Industrial Technologies Milan).

Once the cleanup phase was completed with the dispatch of the material to the authorized landfill, the building was razed to the ground in 1989. During the works a constant rain of water was sprayed on the structures, so as to prevent dust and fibers to lift up in the air, yet without washing them away in the aquifer and stream. The demolition waste, together with the most superficial 50 cm of soil of the surrounding land, was brought to the tunnels where decades before the dolomite was extracted to produce magnesia: the ideal shelter for that material, still potentially polluting.

The trucks, after the surface of the loaded wastes had been sprayed a with glue-containing solution, were sealed with tarps to prevent the dispersion of dust during the passage near the inhabited areas. The industrial area was thus decontaminated in conditions of maximum safety, under constant environmental monitoring, and was subsequently reconverted to industrial use.

The first Italian cleanup of an asbestos factory was thus completed in Molina di Ledro in 1989 [3, 16].

As for the jute sacks, which were still polluted with asbestos, they had already been completely discarded by the citizens as soon as they had heard of the carcinogenicity of asbestos, together with the little insulating material they used in their homes. When providing questionnaires to residents, the chance was also seized to provide further indications on how to carry out possible small procedures of cleanup in the homes while minimizing health risks [3, 32, 38].

The fact that the asbestos pollution outside the factory was modest, as assessed by the complete mapping of the Ledro Valley, was also confirmed by the lack of mesothelioma in the general population, which would have certainly been different in case of widespread pollution. The pollution from asbestos outside the factory and its harmful effects on health seem therefore to have been limited to the Collotta-Cis workers' homes and to the areas in close proximities to the factory.

CONCLUSIONS

The investigations on the Collotta-Cis factory of Molina di Ledro were instrumental to research and inform the public about the damages caused by asbestos fibers on the health of workers and residents, to describe what happened in the factory and outside, and to answer the many questions of workers, family members and public administrators. The final results of which are a count of 81 deaths from cancer and asbestosis caused by asbestos, 1400 years of life lost, and about 100 disabled workers recognized by INAIL. This is something really surprising, considering it all occurred in a small community of only 400 asbestos workers.

These studies confirmed the danger of asbestos-amosite, the increased incidence of mesothelioma and tumors of the lung, digestive system and ovary in those exposed, as well as a clear dose-effect relation. Of particular relevance in this cohort is the high number of tumors affecting the digestive system, also observed in other cohorts of exposed to amosite. Although the case of Ledro Valley is small, and consequently the number of mesotheliomas is limited, the studies here summarized have indicated possible trends on the incidence of mesotheliomas, including a reduction of latency in cases of high cumulative exposure, and a change in incidence with the duration of latency. Additionally, exposure to asbestos at an early age was correlated with higher incidence of mesothelioma, in particular among women, while, conversely, no cases of mesothelioma was observed among those who started exposure after 30 years of age; this interesting observation is worth further investigations.

The studies here reported have led to the cleanup of the industrial area, which during the 1980s was completely cleaned and subsequently repurposed to productive area, with positive effects on the health of residents and workers in the neighborhood, and on the local economy. The results of the first studies have also encouraged many families to put in place small cleanup projects, which immediately removed further dangers from their homes. It has been 30 years now since Ledro Valley has been free from the asbestos-amosite of Collotta-Cis.

These studies were an opportunity to suggest former asbestos workers some hygienic behaviors to prevent further aggravation to their health (e.g., tobacco smoking). They have also brought justice to many whose only fault was having worked in that factory and who, for this reason, have gotten seriously ill, lost their lives, or lost a father, mother or child. Justice not only for being able to know what happened or was happening to them, but also for having received a disability pension. And, as we know, suffering is more tolerable if mitigated by some level of gratification, or at least by the reduction of financial concerns.

Finally, these investigations are useful to keep memories of these events alive for the next generations, so that such experiences are not forgotten, but remain integral part of our heritage, in the hope that what happened in the Ledro Valley will not occur again. Not only in our land, which in the meantime has evolved into a modern country where work with asbestos has been banned, but also for the countries where these dangerous processes are still practiced with the same procedures and in the same conditions as in Molina di Ledro 60 years ago. Countries where there are no bans, rules, attentions, checks and where, in a few years, some young occupational doctor will unfortunately have to count the dead, as it happened in Ledro Valley some 40 years ago.

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Conflict of interest statement

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

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"Candido's List": the workers of Collotta Cis & Figli at Molina di Ledro in Trento Province, Italy. A tale of magnesia, asbestos and work

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Abstract
The study entitled "Candido's List" (*La Lista di Candido*) is not the work of the three authors alone. A good part of the community is entitled to feel itself coauthor, each for his/her own part, of a research project that has succeeded in blending a variety of different ingredients: history, entrepreneurship, the industrialization of the Trento Province with all its high and low points, personal life stories, medicine, genius, work, women's emancipation, the past but also the present and future. The research comprises an eloquent collection of memories and a variety of iconographic materials; it has now become a book and a travelling exhibition containing the accounts of the people who worked at the Collotta-Cis factory in Molina di Ledro. It starts with the brilliance of Pier Antonio Cassoni, who in 1816 deposited the first patent in the world for the extraction of magnesium carbonate, and closes with the decontamination of the factory site in the late 1980s. A needful section has been set aside for the painful facts relating to the processing of asbestos fibre; a final space, midway between an artistic reading and an interpretation for the future, has seen the involvement of the Circolo Fotoamatori di Ledro, with a photographic itinerary enabling the reader to "virtually' enter the remaining worksites and listen to these spaces "tell" their stories after years of silence. A story in black and white, where the two tones are also messages for reading a complex story, one that it is important to remember.

Key words
- asbestos-amosite
- cancer
- mesothelioma
- environmental cleanup
- population involvement

RESEARCH

The research project has been planned and carried through by the Araba Fenice association in Arco. *La Lista di Candido. I lavoratori della Collotta & Cis di Molina di Ledro tra magnesia, amianto e lavoro* [1], has resulted in the gathering of over thirty filmed interviews and a large number of hitherto unpublished photographic materials, as well as historical and archival contributions. The work has benefited from the support of the Fondazione Caritro and the collaboration of the Circolo Fotoamatori Valle di Ledro. Inspiration for this title comes from *Schindler's List*, the film illustrating the story of the list of Jews that Oskar Schindler supplied to the Nazis to have them work in his factory in order to save them. In our local echo of this story, in the 1980s, Candido Zendri, a retired councilor of Molina di Ledro, instead gave a young occupational doctor named Giuseppe Parolari a list of names of the workers of Collotta Cis & Figli (hereafter Collotta-Cis) to enable him to start arranging interviews in a systematic way and so understand why so many of these workers had health problems and suffered early deaths. We started from here, with the people who used to work there, with the elderly who had preserved their memories. Working back through time, we delved through the documents preserved in the historical archive of the Municipality of Ledro which reconstruct the urban development of the area. With the help of *Circolo Fotoamatori,* we explored and photographed the ruins of what remained and in one room we tracked down and, incredibly, recovered a "treasure": the office of the Cis Colletta and its small archive (1960s-1980s) which would otherwise have been destroyed.

In Valle di Ledro a strong contrast developed in the last century and survived into the beginning of this century, lingering in the minds of the local population: the contradictions between gratitude towards a factory that

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had given work for decades and helped many families overcome misery and hunger on the one hand and, on the other, an aversion to that same factory which, because of the asbestos processed there over a period of 45 years, had generated suffering, grief and fear in so many families. This contrast could be overcome only by facing both sides with serenity and calmness, because they belong to the same, single history of both factory and the valley. The research then, and the resulting book *(Figure 1)* as well as the exhibitions on the subject, have had and have an almost cathartic purpose; the aim has been to set in motion a process of collective and individual "liberation" from conflicting situations, enabling the re-emergence of the reasons for the contrast and suffering from the memory of the people of Ledro so these can be faced and finally erased.

Figure 1
The cover of the book shows a worker in headscarf shaping the pats of insulation containing asbestos fibre.

THE HISTORY

1816 in the southern part of Tyrol, a short distance from Garda Lake. This area is still part of the Austrain-Hungarian Empire. For the first time in the history of chemistry, in his laboratory in Valle di Ledro, Pier Antonio Cassoni extracted magnesium carbonate from dolomite rock [2]. He then equipped his laboratory with the means to prepare magnesium carbonate, which was obtained by treating dolomite rock, in which Valle di Ledro is rich, with a chemical process. The procedure consisted of calcining dolomite and dissolving the magnesium part in carbonic acid. A similar procedure would be adopted a few years later by the Englishman Pattinson, from whom it derives its name, since Cassoni never patented it (Pattinson Method). Right from the outset, Cassoni brought to bear his skills to give life to different products, such as Magnesia fluida Dolomina; he also opened the magnesia thermal baths offered in single cabins equipped with a bathtub.

This marked the beginning of an epic which, fueled by the entrepreneurship of a number of Valle di Ledro's citizens [3], led within a century to the blossoming of about a dozen industries dedicated to the transformation of dolomite rock. They were small factories that nevertheless gained international recognition. They were new in the local work market and soon become a workplace for several dozen inhabitants of the valley, which is small and out of the way with respect to the main trunk roads of the Trentino.

Cassoni began his activity in 1816, while the *Ditta Eredi Cassoni*, also in Pieve di Ledro, dates from 1849. In 1875, the first production centre opened in Molina di Ledro, and Pietro Silvestri inaugurated the second one in 1878. In 1880, partly because of a rise in tariffs, a factory was opened "in Italy" at Brenzone. Meanwhile, Comboni had been in production since 1862 on the opposite Garda shore at Limone sul Garda, made possible by industrial espionage that had brought the "recipe" for the production of magnesium carbonate to the territories of the Kingdom of Italy. In 1900, the production of Collotta Cis & Gigli began in Molina.

After the upheavals of the First World War, that brought South Tyrol within Italian borders, and following the death of one of the partners, Gigli, it became *Collotta Cis & Figli* [4]. This factory would give employment to over 400 workers in the years between 1922 and 1978, and it launched the production of magnesium carbonate on a global market. A huge range of products is representative of this active, dynamic factory, which during the decade between 1960 and 1970 was connected with all five continents [5]. Collotta-Cis "put food on the table" for many families in the Ledro valley, and witnessed the years of the first strikes, of the emancipation of women. It also indelibly linked its history to that of the processing of asbestos fibre, which performed so well on the market but was, at the same time, so carcinogenic and deadly for a number of the factory's workers [6].

New arrivals joined the workforce while very young, especially the women who often inherited their grandmother's place. The pay served to make meagre ends meet in the family budget, but the help it gave was paid for dearly in terms of work, life, safety and health. However, it was the only possible way to avoid the inevitable choice between poverty and migration. For many people, working in a factory was seen as a dream; the company also represented the meeting point of the valley. Social cohesion was created here and love and new friendships forged. The first factories redeemed most of the population of the mountain valleys from isolation, thus avoiding a process of wretched depopulation and consequent further impoverishment of the mountain region. Indeed, when Collotta-Cis was founded, the Ledro valley was poor and the soil yielded little to peasants. A place in the factory assured security for many families [7].

After the closure of the establishment the aftermath of the unhealthy work that had been done there continued for many years on the backs of those who had worked there, in the form of lung tumors and diseases derived from rock dust and asbestos, while the ghost of the factory remained standing as a memorial of the past times.

Thanks to the stubbornness of a young occupational doctor, Dr. Giuseppe Parolari, and of Molina di Ledro's mayor, Agnese Rosa, the way was opened for the first health surveys. This led to a series of epidemiological investigations and environmental monitoring, and eventually to the total dismantling of the plants [8], see also the paper by Parolari, in this same issue, for a thorough reconstruction of epidemiological, industrial hygiene and occupational medicine studies.

MEMORY: BLACK AND WHITE

Black and white. Two colours that can be useful in telling this story, which is one of products, of men, places and tales; but also, metaphorically, as the colours serve to illustrate contrasting feelings and reflections. Black and white.

The white of magnesium carbonate. An alchemy leads to the separation of the magnesium carbonate from the calcium carbonate present in dolomite rock. Dolomite, the rock of these mountains: it too is dazzling white if pure. Baking, calcination, boiling, drying. In a few moves you can make the white pats of matter that end up laid out on racks. The white is that of a product that for practical purposes was called "borotalco", ground with a special mill from Breda and transported in tankers; it was also the white of the fine "grit" for pottery transported in tipper trucks; and finally it was the white of the so-called "grain of rice". The black, on the other hand, was that of the dangerous shadow cast by asbestos. It offers high performance and is an exceptional material for insulation, but it comes with a black shadow. Asbestos is itself not physically black, but black is an apt colour for what is still happening internationally today, in a world divided into two broad sectors. A rich sector that can afford to maintain certain standards, and the poor or impoverished world that cannot afford these things. The production and use of asbestos has been forbidden since 1992 in Italy, as has anything that might expose individuals to it. It has been banned in almost all industrialized nations even though there are still countries with huge mines that extract it and export it to third-world countries.

In *La Lista di Candido* there is white, an image of human genius, the beginning and nourishing of an industry that shaped the Ledro valley. It is the genius of Pier Antonio Cassoni who in 1816 started the production of magnesium carbonate. It is human genius, mixed with the entrepreneurship of local families: the Collotta, the Gigli, the Cis, the Zecchini, who enabled the flourishing of the magnesia industry in Valle di Ledro. First Pieve, then Bezzecca, Molina, again Bezzecca; these were joined by Brenzone and Limone (then in the Kingdom of Italy). In just over a century, at least eight businesses linked to magnesium carbonate developed in the Ledro district. This was a story written at home, in the community, not dropping "from above" but strongly rooted in the territory. A genius that was replicated in the production processes, that were innovative and cutting-edge for those times, especially if we consider just where the factories were located: in an isolated valley in the Trentino, not in a place imbued with an industrial culture like the big towns in a major valley or on the Po plains. Those were years of hunger, of great hunger, during which the valley, exhausted by poverty, survived thanks to migration. As soon as they were formed, families were destroyed because the men had to look abroad for the sustenance that was lacking in the valley. They came back old, with a tiny nest egg that assured their old age. And in those times of frightful misery, the Collotta-Cis factory represented a truly incredible fortune: those able to find work there counted themselves very lucky.

In *La Lista di Candido* there is black within, reflecting the drama that unfolds as awareness grew that the product being processed was also a cause of death. The year 1928 saw the start of a production that would indelibly mark the factory; while on the one hand the new product brought job opportunities and well-being to over a hundred workers and their families, as well as an appreciable export for a factory located in an outlying valley, on the other it marked the lives of those who worked the asbestos fibre, and of those who breathed it in even though they never set foot in the factory. Cases of asbestosis reported to the National Institute for Insurance against Accidents at Work (INAIL - Istituto Nazionale Assicurazione Infortuni sul Lavoro) already recognized as an occupational disease (although not systematically), began to be attributed to Collotta-Cis. Medical records, X-rays, tumors (the first mesotheliomas) sometimes alarmed the workers themselves and the people of Molina. Therefore, in our story there is the black of the disease, arising from a job that had given bread to our people, but a bread that came with a high cost in terms of health and suffering.

This suffering was alleviated in a certain sense by the financial payouts given to about a hundred families. These have benefited from the studies that have given some justice to all those who had become seriously ill or lost their lives simply as a result of having worked in that factory, alleviating the lot of many workers and their family members who had received no justice until then. A justice recognized through an invalidity pension or widow's or widower's benefit.

The white of our story is also that of the face and hair and smocks of the *fabricote* (the factory's female workers), who were daily covered with a layer of dust that did not stop on the surface of their clothes. From a testimony: "*You know that Giulia comes home always white. So give her a smock! Like the masks, too: those they use nowadays have orange sponge and elastic bands. You could put a handkerchief inside it, but even so, when you took it off, you had all the white marks of the dust*".

There is the white of the factory floors when the magnesia pats fell wet to the ground coating the Stella department; the white of the racks during full production; the light pats rested on boards while awaiting further processing. It is the black "*of the Negri, of Pistorel, of Vito Zecchini. They were black from tip to toe because they would come to take the trolleys and would actually go into the oven: they were surrounded by a smell of gas. It was an acidic smoke, but all the work was done without a mask*".

There is the white that emerges from the decision to pick up the thread of the story, which arises from the act of writing down the interviews. This is how the story has the opportunity to tell everything. Beautiful things, sad things, facts one may wish to be able to forget or facts that should be framed and hung on the wall because even after tens of years they can raise a smile or a trigger a sad memory. The colour of the pages yet to be written is white too because *La Lista di Candido* – book and exhibition – is not a finished-and-done project but an important part of a work that we can patiently continue together. There is also the black of silence that could have been maintained regarding this important piece of Ledro's history. The black of the shadows that could remain such if we were not to try together to recount what has been unsaid but that weighed heavily. There has been no pre-packaged recipe for the work. The initial silence was subdivided into many detailed aspects that were recomposed only at the end, like in a huge puzzle. There is the black of a social and scientific subject that is difficult to deal with. It could have been black and instead it has turned out white, thanks in part to the fact that the manners adopted to tell the story were simple, but not simplistic.

Black is the colour of the carbon paper that emerged together with hundreds of other sheets from the forgotten archive of the Collotta-Cis, incredibly rediscovered and saved, almost as though to tell us that the story must certainly be preserved but must above all be told: because the risk exists that all those folders – images of the past – remain where they are and that the dust that ages and ruins things will no longer be removed from them. So it is a matter of telling the past to preserve the memory of places, facts and voices. It is the white of the need to have instead an awareness of the wealth of knowledge and memory that must help the community throw light on its past but above all on its future. Could the ruins that remain not constitute a shared architectural itinerary aiming at a revival that focuses on the workers' labour? It is the black of the quarries, of the tunnels and underground warrens that risk becoming an unrecognizable place, without identity, agreeable, almost something to be kept hidden.

Is the result of all this a grey story? No, we believe that what has resulted from the project is a story that is above all true and, precisely for this reason, black and white. These colours have left their clear mark on the different moments of conveying the study to the community. On the one hand, the expectation for the publication of the book has always been palpable, as also for the inauguration of the exhibition; equally evident was the emotion caused by remembering those "no longer with us", an emotion triggered by a recalled memory, an object, a photo. Contrasting feelings seemed to have filled the hearts and minds of those who spoke to us: on the one hand the desire to "hear themselves telling their own story"; on the other the awareness that something sad might emerge. Black and white are not just metaphors: they have mixed and given life to the eloquent historical photographs or those taken in an artistic and modern key by the *Circolo Fotoamatori Valle di Ledro*. Black and white together make up the X-rays of the factory workers' chests. Black and white together have been the story of a place in which material was produced for pharmaceutical purposes but also one that killed. This is a story in which black and white mix, even today, but mysteriously they remain separate colours, each of the two highlighting the other.

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Conflict of interest statement

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

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Narrating and remembering as practices of care, community, and commitment in asbestos contaminated contexts

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Abstract
In contexts of social and environmental disasters, practices of memory and narration can become actions implemented by the affected groups to cope with the suffering related to the disaster experience, to mobilise in the name of social justice, and to favour those dynamics by which the survivors develop their sense of being part of a community. This article is based on qualitative data collected through an anthropological study based on ethnographic fieldwork conducted in Italy and Brazil. It discusses the practices by which the survivors of the impact of asbestos-related disaster on their lives make sense of their suffering experience and engage in a grassroots health-based movement. Attention is paid on the social aspects of the health impact of asbestos exposure, and the role of the affected communities in the elaboration of their own paths of care by remembering and communicating the disaster is considered.

Key words
- asbestos
- grassroots activism
- health hazards
- ethnography

INTRODUCTION

In contexts of social and environmental disasters, practices of memory and narration can become actions implemented by the affected groups to cope with the suffering related to the disaster experience, to mobilise in the name of social justice, and to favour those dynamics by which the survivors develop their sense of being part of a community.

This article is based on qualitative data collected during a "multi-sited" [1] ethnographic fieldwork conducted in Italy and Brazil with communities living in asbestos contaminated urban sites.

For a description of asbestos health impact, the reader is referred to the paper by Marsili *et al.* [2] in the same issue. According to the list provided by the International Ban Asbestos Secretariat (www.ibasecretariat.org/), 65 countries have prohibited asbestos to date. Italy has prohibited it in 1992, while Brazil, with an asbestos chrysotile mine still in function, has banned asbestos only by law in December 2017. Due to the burden of asbestos worldwide, the health effects of asbestos exposure can be considered as a public health disaster of global dimension.

This article refers to the practices by which the survivors of the impact of a similar disaster on their lives make sense of their asbestos-related suffering and engage in a grassroots "health-based social movement" [3]. The data discussed below emerged from an ethnographic fieldwork conducted in four research settings: Bari, Casale Monferrato, and Bologna in Italy, and Osasco (São Paulo) in Brazil. The data show in what extent, in the investigated contexts, remembering and narrating the past coincided with practices of socio-political commitment in a movement aiming at the recognition of an invisible disaster and at the global prohibition of asbestos. Moreover, the act of narrating represented a possibility of encounter and openness to the "other" that became a possibility of care for a suffering that was perceived as individual and private as social and collective.

This article aims at paying attention on the social aspects of the health impact of asbestos exposure and considers the role of the affected communities in the elaboration of their own paths of care by remembering and communicating the disaster. By discussing various practices of memory and narration as strategies of care and activism rooted in distinct socio-cultural contexts, this article shows the importance of understanding existing differences across languages, meanings, and actions as a crucial and preliminary step towards effective communication among stakeholders from civil society, researchers, and public health professionals from distinct backgrounds and with distinct expertise. In fact, bridging cultural gaps among all the social actors involved in a disaster process is essential to understand, face and prevent health disasters, especially those that are slow, invisible and often not recognized as are the disasters provoked by the toxic market of asbestos.

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MATERIAL AND METHODS

The material here presented consists of quotations from fieldnotes and in-depth semi-structured interviews conducted with anti-asbestos activists from the four research settings where the Author performed an anthropological study on the relationship between a person's experience of asbestos-related suffering (i.e. illness, contamination, and grief) and the engagement in the anti-asbestos movement. The encounters with the study participants occurred between 2009 and 2018, and took place in occasion of various steps of fieldwork (each lasting from two to ten months) and field trips due to ongoing research.

Participant observation was performed during attendance of the local anti-asbestos Non-Governmental Organizations (NGOs) organised by asbestos exposed and their relatives, with whom the researcher has been collaborating in all settings.

Upon the free and informed consent of the interlocutors, the interviews have been digitally recorded, then transcribed, analysed and translated by the Author since the interviews were performed in Portuguese and Italian languages, without the support of an interpreter.

Historiographical and archival research have been performed to contextualise the collected data in each local socio-political and cultural context.

Bari

In Bari, the capital town of Apulia region, Southern Italy, the main asbestos polluting source was the "Fibronit site", a 100 000 m^2 area situated in a densely populated neighbourhood where an asbestos-cement plant, the Fibronit, has been functioning from the early 1930s to the late 1980s [4]. The plant was then abandoned and kept contaminating the environment until the 2007, when the site, recognized as a contaminated site of national priority for remediation, was partially reclaimed. In 2017, the work for complete reclamation, demolition and construction of a public garden finally began.

Fieldwork in Bari was performed in May-October 2009, and the research focused on the illness experience lived by men and women who developed malignant mesothelioma because of environmental exposure to asbestos. According to interlocutors' narratives, the diagnosis was often achieved with relevant delays implying serious consequences in terms of treatment's effectiveness and patients' distrust towards biomedicine. Moreover, an apparent non-existent connection to the factory prevented the persons with malignant mesothelioma contracted by environmental exposure from relating their own suffering to asbestos exposure, and from counting on a social support by the local unions.

The following quote is from a Skype interview occurred in May 2012 with a researcher's key interlocutor from Bari, who was one of the founders of the local anti-asbestos NGO. The interview is discussed in further detail elsewhere [5].

She [the interlocutor's wife] *decided to launch a blog where we would post all the information that we were collecting about malignant mesothelioma, asbestos, and the recovery of the Fibronit site. However, in the beginning, she was not completely sure… she was very angry when she got the diagnosis, and I was more active on the blog. When she began to feel better, after the surgery and the first cycles of chemo and radiotherapy, she began writing about her experience and her feelings. She thought that in that way she could help others going through similar experiences. Many began to contact us. The blog was offering a sort of help to people feeling frustrated, disoriented, and abandoned as we were.* […] *We wanted to promote a network through which people could share information, and be advised about what to do once received the diagnosis.* […] *I still have my wife's phone with all the numbers of men and women with malignant mesothelioma with whom she was in contact. Many of them were from other cities. They talked about their experiences by sharing opinions, fears, and hopes.*

Casale Monferrato

In Casale Monferrato, a town of 35 000 inhabitants, the largest asbestos-cement plant owned by the Eternit firm in Italy operated over 80 years, from 1906 to 1986 [6]. In the same Region, Piedmont, the largest asbestos mine in Europe, the quarry of Balangero, provided the national and international asbestos market with almost four million tons of asbestos produced throughout the 20th century, according to the World Mining Data 2008 [7]. The ReNaM reports 3560 malignant mesothelioma cases registered between 1993 and 2012 in Piedmont Region [8]. Asbestos-cement production at the Eternit in Casale Monferrato is recognised as the main cause of the death of almost 2000 men and women from asbestos-related diseases contracted by occupational and/or environmental exposure to asbestos in the city, since the start of the activities at the Eternit factory to the recent years [6].

Starting from the early 1980s in Casale Monferrato, the increasing number of people diagnosed with, and dying from, asbestos-related diseases triggered a worker and civil mobilization that led to the promulgation of the first law prohibiting asbestos containing products in Italy [6]. Over the years, the anti-asbestos movement in Casale Monferrato has reached other important achievements with a social relevance on the local, national, and international level. Among them, there is the organization of the first trial against an asbestos-cement corporation accused of environmental disaster manslaughter [6].

An interactive laboratory designed to narrate, in parallel, the tragedy of the disaster and the local mobilization of citizens and workers begun in the early 1980s to denounce the health effects of asbestos exposure was inaugurated in November 2014 in Casale Monferrato. Teachers, students, and the local anti-asbestos NGO have been the main social actors lobbying for the foundation of the laboratory. A comprehensive review of epidemiological studies performed in Casale Monferrato and the social, educational and community-oriented initiatives is presented in the paper by Marsili *et al.* [2], in this same issue.

In Casale Monferrato, ethnographic fieldwork was conducted by the Author in May-June 2012. Afterwards, several fieldtrips occurred. Below, a quote from an interview conducted in June 2016 with an anti-asbestos activist who collaborated with the team of professionals who realised the interactive laboratory is reported:

Our main concern was to leave a testimony. Our prior objective was to pass the baton to someone else willing to collect this testimony and to become him/herself a spokesperson not just of what happened in relation to asbestos, but in a broader sense, in relation to a different idea of development. It should be questioned whether it is worth pursuing a development that brings immediate profit for few people, and leaves a terrible legacy for millions. It should be promoted the idea that you cannot achieve economic development without thinking of the consequences that it leaves on the environment, and we should let these ideas sprout up among younger generations, among those who will take decisions in the future. […] I am deeply touched when I see students' passion and commitment. They learnt to share emotions, not just the contents. This is the result of years of work and awareness campaigns, but it is also the sad consequence of the disaster. Among the most motivated, in fact, there are those who lost the grandpa, the father, or the mother. Unfortunately, the personal experience of the suffering is decisive in triggering one's engagement.

Osasco

Osasco is a city with approximately 700 000 inhabitants bordering the megalopolis of São Paulo. Since the 1940s until the late 1970s, Osasco lived a frantic industrialization and became home of various national and multinational industries, including the largest asbestos-cement plant of the Eternit brand in Latin America, operating from 1943 to 1993 [9]. The local anti-asbestos NGO was founded in 1995 by a group of former asbestos exposed workers, the majority of whom had worked at the Eternit, who found themselves contaminated with asbestos after the factory's closure in 1993. In a country such as Brazil where asbestos has been prohibited by law only recently (in December 2017), but it is still used, the anti-asbestos mobilization focused on the promotion of a dialogue with biomedical professionals from local occupational health centres, national research institutes and public hospitals, while pursuing the national asbestos ban. To achieve that, Brazilian anti-asbestos movement is still engaged in the deconstruction of the paradigm stating the safety of asbestos controlled-use, and to contrast the phenomenon of asbestos-related diseases' under-diagnosis as it happens to be a frequent phenomenon in countries currently using asbestos [10]. In Osasco, an ethnographic fieldwork of ten months was conducted in two phases, in August-October 2014 and February-October 2015.

In Osasco, every year, on an early Sunday morning of April, i.e. the month internationally dedicated to occupational health, a group of men and women of various ages and religious beliefs gather in the shadow of majestic trees, in a tiny circular square. The square is bordered by a wall on which the bystanders sit and, at the centre of which, a stone altar stands. The square is called *Praça Aquilino dos Santos - Vítima do Amianto* [Asbestos Victim], in memory of the first asbestos exposed worker who died after the local anti-asbestos NGO's foundation in 1995. The meeting represents the final event of a week of activities organised by the local anti-asbestos activists to raise awareness of asbestos dangers among general population.

The Author participated to the campaigns and actions performed in April 2015. During the collective commemoration, anyone could take the floor and remember a beloved one deceased due to an asbestos-related disease. Fragments of life then resurfaced from the words and emotions of those who survived and were still mourning an irreplaceable loss. At the Eternit in Osasco, the workers were all men with the exception of few women working in the administrative sector. This explains why the majority of the recalled names and fragments of life referred to a lost husband, brother, or father.

Below, a quote from the Author's doctoral dissertation [11] resulting from her fieldwork in Brazil is reported, and it is based on the fieldnotes written soon after the above-mentioned commemoration. *Figure 1* was taken by the Author on the morning of the collective commemoration and refers to the following quote.

During the ceremony, I felt like I was witnessing (and participating in) a sacred ceremony. I was particularly struck by the photographs of the activists who had died and whose portraits were exhibited and hanging just behind their survivors. The glances of those men and women about whom I had hear from their loved ones' narratives seemed to assert their presence and participation beyond their physical and irreversible absence. Part of the ceremony was dedicated to the commemoration by spontaneous sharing of memories and feelings: everybody could speak and say something about a friend or a relative who had died. […] Remembering was painful, but was felt as necessary and conceived of as a moral and political commitment.

Bologna

In Bologna, in Casarini Street, number 25, there are the Officine Grandi Riparazioni-OGR, one of the largest railway repair factory owned by the national railway company. Among the disparate uses of asbestos in Italy before its prohibition, there was a massive utilization of asbestos in the railway industry, especially in the brake systems' production, wagons' insulation, and repair. At the factory set up in Bologna in 1908 and closed in

Figure 1
Commemoration of asbestos victims, April 2015, Osasco (São Paulo, Brazil). Photograph by Agata Mazzeo.

2018, thousands of workers have repaired hundreds of damaged trains throughout the 20th century. The Author visited the OGR on April 28, 2017, on the day internationally dedicated to the victims of asbestos exposure. At that time, the company had already decided to dismantle the factory and the huge site seemed a ghostly industrial landscape.

During the ceremony in memory of asbestos victims, in addition to a sorrowful commemoration of comrades and colleagues who had already passed away, asbestos exposed workers, the majority of whom were members of the local anti-asbestos NGO, pronounced discourses evoking the role of another important subject of their individual and collective stories, the OGR site itself. That was the place where they had nurtured their aspirations and dreams as young men enthusiastic of their job, and which turned to be associated with the most awful of their nightmares in the present. The threat that their past and memory might be vanished together with the tangible proof of their endured injustices triggered in the exposed workers the urgency to elaborate and put into practice new strategies of struggle. To date, they are currently mobilising to defend their "cultural space of memory", and their right to live the "remembering experience" [12]. In particular, the mobilization is currently aiming at entering the decision-making process on the future use of the site to be recovered and preserve a museum set up by workers in a part of the factory throughout the years.

The ongoing collection of ethnographic data in Bologna started in November 2014, when the Author began a collaboration with local anti-asbestos activists to raise awareness of asbestos dangers by organising educational projects at local public schools. A quote from an interview conducted with a worker who was one of the main museum's curators and who is now lobbying for the museum's reopening in the name of the workers right to remember and narrate their story is reported below. *Figure 2* was taken by the Author in occasion of a visit to the workers' museum on April 28, 2018.

Figure 2
Objects from the collection of the museum set up by the workers of the Officine Grandi Riparazioni-OGR, April 2018, Bologna (Italy). Photograph by Agata Mazzeo.

I fell in love with the factory's story, a story of sweat and fatigue, but also of pain. I began collecting everything that recalled that story: objects, documents, and photographs. I needed to find a place where memory could be saved. I had to do that because of my friends and co-workers with whom I had shared a piece of my life and who died in their 50s. […] I terribly suffered for their loss, and every day I renovate my commitment not to forget them.

Over the years, the museum has become the proof of what everyone tried to deny, that was the extermination of many friends and colleagues. All the documents from the medical surveys and the judicial trials as well as the objects we had collected made impossible for anyone to deny the history of the factory and delete the memory of our friends and coworkers. […]

Since the closure of the factory, in June 2018, I feel a deep and indescribable void exacerbated by the impossibility to visit the museum, to see with my eyes and touch with my hands what was part of my life. I miss touching a screwdriver or a plane, looking at the yellowed photos hanging on the museum wall, or taking a moment to reflect while looking at the self-made equipment used to try to protect ourselves from asbestos in those that should be our safe working places, but they were not. […]

In the museum, I could see the tangible achievement of my main purpose, which was to break the silence about our story. For me, there will be no peace until the museum will be reopened and made accessible to everyone. I will fight until my body and my mind will support me to see the museum opened again and the factory's site turned into the shrine of the martyrs, my friends and colleagues, executed in the name of profit. The museum then will be a sort of compensation for the victims of that massacre, a place of meditation and warning for the future.

DISCUSSION

A narrative performance is always influenced by the context in which it occurs, by the objectives pursued by the narrator(s), and by the affects exchanged with the audience [13-15]. It is always relational, contingent, and negotiated. It can use various languages, styles, and registers. It helps to build an individual as well as a collective identity [16]. It can become a "tool", strategically and politically used, to save memory, to promote actions, and to make the suffering lived by entire communities visible notwithstanding the lack of general recognition of it.

The above-presented data show the entanglements among the (collective and individual) disaster experiences, the meanings attributed to "places of memory" [12, 17] and narratives, and the socio-cultural context from which they emerge.

In Bari (Italy), the social actors involved in the disaster experiences had to make sense of an exposure that had persisted ignored until the diagnosis of the fatal cancer, the malignant mesothelioma. Data analysis showed that this aspect deeply influenced the local anti-asbestos activism, one of whose main purposes was overcoming the loneliness and the abandonment perceived by people with malignant mesothelioma and their relatives while facing the uncertainties related to the diagnosis, and the difficulties associated with painful and ineffective treatment.

In a similar context, the first action ideated by the founders of the local anti-asbestos NGO was to narrate and divulgate narratives of asbestos-related illness experiences through a blog. The blog soon became a reference point for whom was searching information about malignant mesothelioma on the Internet, and new relationships – and "biosocialities" [18] – emerged from sharing experiences, knowledge, and emotions triggered by a bodily condition of suffering.

As extensively discussed in the paper by Marsili *et al.* [2] in this same issue, in Casale Monferrato, the interactive laboratory has been conceived of as a "black box" containing proofs, memories, and stories of disaster as well as of the workers and citizens' mobilization. Differently than in Bari, where the links with the world of the factory were narrated as completely unperceived by the study participants, in Casale Monferrato the local anti-asbestos NGO operated in strong collaboration with the local trade unions. The processes through which the disaster extended from the factory to the whole city had been made visible in Casale Monferrato thanks to a grassroots activism able to mobilise and strategically use local social structures and expertise in collaboration with unionists and public health researchers from local unions and hospitals.

The high awareness of asbestos dangers developed among Casale Monferrato's inhabitants represents one of the most important achievements reached by the anti-asbestos activists. The stories of suffering and struggle have come to be narrated not just by local social actors personally involved in the disaster experience, but also, for example, by journalists, writers, photographers, and video-makers communicating the disaster and the workers and citizens' mobilization to a large audience.

The team of professionals including architects, designers, and photographers who realised the interactive laboratory, took almost one year and a half to set it up. At the laboratory, the twelve chapters through which the collective story of Casale Monferrato as the "city that fights against asbestos" [19] is narrated have been "written" after having consulted local social actors and experts in subjects approaching asbestos-related issues from multiple perspectives, e.g. historical, biomedical, and geological. At the laboratory, there is also a section where twenty stories of men and women remembered and narrated by their loved ones are collected.

In Osasco (Brazil), the subversive tension intrinsic to the acts of remembering through narration dissolved the fracture between past and present, and represented practices of a prolonged individual and collective mourning turned into a form of resistance. On this regard, the anthropologist Zhang [20] has highlighted how "the refusal to end mourning becomes a political action of protest against the social injustice responsible for the loss of life. In this light, death is no longer accepted as the end of a life, but is scrutinised as the beginning of the pursuit for justice. The gravity of mourning moved away from death toward life along the axis of moral responsibility for the loss" [20, p. 271].

In Bologna, a "community of memory" [12] is currently aiming at turning a contaminated/contaminating site, dense of meanings for those who had worked there, into a living memorial in the name of social justice. Local anti-asbestos activists assumed the moral commitment not to forget their friends and colleagues who died of asbestos-related diseases. By borrowing from Foucault [21] the effective and suggestive concept of "heterotopies", the space devoted to the memory will then become a heterotopy of resistance where the past/present fracture will be subverted. The past and the absence related to irremediable losses will then become an intense presence, and a place of death will turn into an affirmation of life, since "survival [to a disaster] is the most intense life possible" [22]. The industrial site is meaningful for the community of survivors that, in the present, is able to identify in it the symbols of its story and the traces of its past [17]. From keeping a shared past alive, a community that has been affected by the disaster can elaborate its identity and imagine new practices and meanings to give sense to a destroyed world. The places and the objects then become symbols of a shared past and the tangible proofs of the subtle violence endured over the years. The possibility of touching or looking at the traces of the past allows the survivors to reflect on their individual and collective stories and elaborate their own narration as the retired worker interviewed in Bologna mentioned.

CONCLUSIONS

In all settings here presented, the practices of memory and narration appeared to be crucial: remembering and narrating the disaster represented a strategy of struggle and favoured the elaboration of a "collective memory" [23] based on which a community was emerging and building its identity [17]. Halbwachs highlighted how dynamics and relationships that take place in the present influence memory [23], and the Italian anthropologist Ugo Fabietti recalled Halbwachs' qualification of memory as "communicative" to emphasise its being always a social, and relational practice [17, 23].

Practices of memory and narration are simultaneously practices of care, community, and commitment in the extent to which social actors involved in asbestos-related experiences of suffering due to disease, contamination and grief refer to a collective and individual past to reconcile with (and change) a familiar world that has become a source of sorrow, loss, and threat. By engaging in the activism, the "sufferer-activists" [11] reinvent the world wherein they act, negotiate their identity, and establish new affective relationships.

Remembering and communicating memory correspond to intentional acts and are dependent upon a will that is always historically and culturally informed [17]. The practices of memory and narration show their therapeutic effect for the disaster survivors as both individuals and members of a community. In a similar pathway of care, the "places of memory" [virtual or physical i.e. an industrial site, a museum, a collective ceremony, or an Internet blog) are crucial in the extent to which they favour the "remembering experience" [12] and become cultural spaces for the collective and individual narration of a shared story. In this way, individual experiences of suffering are situated in a broader story of injustice and disaster, and acquire meaning in a continuity with the past.

Taking into account the specificities of each context, the communities living in the four asbestos contaminated sites considered in this article have all been affected by the silent and slow disasters associated with the toxic market of asbestos. Beyond the distinct meanings and words of the collective and individual narratives elaborated by the community members with whom research was performed, a common aspect has been grasped. "Sufferer-activists" [11] from each context conceived remembering and narrating as necessary practices to adhere to a moral commitment assumed in front of the next generations while they were still mourning the irremediable loss of their beloved ones who died of asbestos-related diseases.

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Conflict of interest statement

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

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BOOK REVIEWS, NOTES AND COMMENTS

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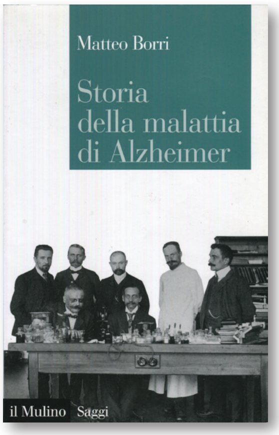

STORIA DELLA MALATTIA DI ALZHEIMER
Matteo Borri
Bologna: Il Mulino Editore; 2012.
184 p.
ISBN 978-88-15-23365-3.
€ 16,00.

[History of Alzheimer's disease]

Alzheimer's disease is a progressive, sometimes early-onset neurodegenerative disease, which is increasingly challenging public health systems, particularly in wealthy countries where longevity has been progressively elongating in the last fifteen-twenty years.

With the cogent presentation of the well-known science historian Paolo Rossi, this book *Storia della malattia di Alzheimer* by Matteo Borri may profitably enlighten physicians, social scientists, caregivers, and all the composite world of people involved in managing patients affected by this and similar neurodegenerative and neurocognitive disorders.

The text starts from Alzheimer first clinical case (patient: Auguste Deter) hospitalized at Irrenanstalt Psychiatric Hospital in Frankfurt am Main, on November 25, 1901. The physician Alois Alzheimer was the director of a section within that institution. He characterized and depicted the cluster of symptoms and presented his clinical observations in November 1906 at a minor local German meeting held in Tubingen. His talk went practically unnoticed. The book illustrates very convincingly which was the changing framework in which Alzheimer's scientific work thrived, including the role played by the "Zurich school" and Carl Gustav Jung's methods for approaching psychologically a composite variety of mental pathologies.

Such a presentation of this critical tract of the history of neurology and scientific characterization of neurodegenerative traits is one of the most original parts of this book. Also the concomitant laboratory contributions by Ugo Cerletti at Rome University "La Sapienza" are well reported. The converging histopathological studies by Franz Nissl also contributed to some characterizations of the causative neurodegenerative processes. Finally, the role of the Italian scientists/physicians Francesco Bonfiglio, Gaetano Perusini and Umberto Sarcheschi are shortly but vividly presented and critically illustrated. In that, this book really adds an original contribution to the field.

In the second chapter this approach, describing the general framework around the understanding of neurodegenerative diseases, progresses by analysing the medical textbooks used in those years, which revealed an unexpected degree of interdisciplinary connections. Hyper-specialist and technologically-assisted clinical approaches were inexistent or very limited, however the attitudes towards confronting different theoretical and even philosophical deterministic theories were usefully enhanced. Such an integrative melting eventually produced new and original insights leading to the firm establishment of sound nosographies, still representing fundamental steps in the present-times management of neurodegenerative conditions in their variable spectrum of pathological severity.

It is also quite interesting to note, from one hand, how epistemological evolution and transformation was sometimes very slow, sometimes quite abrupt and, from the other hand, the relevant role played by the progresses of the emerging structural neuroanatomy discipline on those years.

The effort by Borri to disentangle the various components (e.g. in paragraph 3 of chapter 2, page 99 *The formation of a physician (and of) a scientist)* provides a vivacious description of Alzheimer's original figure. The importance of the early stages of his studentship and clinical and scientific career well explains his successive capabilities and performances in providing neural and mental disciplines with original and pivotal contributions.

A book depicting the history of the "discovery" and characterization of a widespread and now increasingly common disease are a relevant, often indispensable, step in the formation of a clinician or of a scientist. Public health in general should not dismiss more holistic approaches which eventually result not only in a better understanding of the causes and determinants of a given disease, but also of the social-anthropological contributions which regularly represent a non-secondary component of its solution or way to fight or at least to confront it.

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PUBLICATIONS FROM INTERNATIONAL ORGANIZATIONS ON PUBLIC HEALTH

Edited by
Anna Maria Rossi

EUROPEAN FOOD SAFETY AUTHORITY (EFSA)

European Food Safety Authority (EFSA), Zancanaro G, Antoniou SE, *et al.* **SIGMA Animal Disease Data Model. A comprehensive approach for the collection of standardised data on animal diseases.** *EFSA Journal* 2019;17(1):e05556 doi:10.2903/j.efsa.2019.5556 The European Commission is routinely asking EFSA for scientific and technical support in the epidemiological analysis of animal disease outbreaks (i.e. African swine fever, lumpy skin disease and avian influenza) and to report or assess surveillance data (i.e. *Echinococcus multilocularis* and avian influenza). For this purpose, EFSA has over the last years carried out several data collections and gathered specific information on outbreaks, surveillance activities and concerned animal populations (i.e. poultry, domestic pigs, cattle and wildlife such as wild boar). EFSA aims to work together closely with Member States in order to (i) reduce the Member States' manual input of the data to be submitted to EFSA; (ii) avoid double reporting to EFSA; (iii) provide the Member States with tools to produce automatically their own draft national reports on animal health and surveillance in a protected environment to ensure data protection; (iv) increase the quality of the data received from the Member States; and (v) shorten the time to retrieve up-to-date data, relevant for risk assessment purposes. With this purpose, EFSA launched a project called SIGMA. It is important to highlight that the SIGMA – Animal Disease Data Model (σ-ADM) focuses on data which are known to be already collected by several Member States under different legal frameworks and for different purposes. The version presented in this report, will be subject to modifications and updates derived from the feedback during the implementation phase.

European Food Safety Authority, Hart A, Maxim L, Siegrist M, et al. **Guidance on communication of uncertainty in scientific assessments.** *EFSA Journal* 2019;17(1):e05520 doi:10.2903/j.efsa.2019.5520 This document provides guidance for communicators on how to communicate the various expressions of uncertainty described in EFSA's document *Guidance on uncertainty analysis in scientific assessments*. It also contains specific guidance for assessors on how best to report the various expressions of uncertainty. The document provides a template for identifying expressions of uncertainty in scientific assessments and locating the specific guidance for each expression. The guidance is structured according to EFSA's three broadly defined categories of target audience: 'entry', 'informed' and 'technical' levels. Communicators should use the guidance for entry and informed audiences, while assessors should use the guidance for the technical level. The guidance was formulated using evidence from the scientific literature, grey literature and two EFSA research studies, or based on judgement and reasoning where evidence was incomplete or missing. The limitations of the evidence sources inform the recommendations for further research on uncertainty communication.

European Food Safety Authority, Foster D, Locker A, *et al.* **Publication of scientific data from EU-coordinated monitoring programmes and surveys.** 2019 (*EFSA supporting publication;* EN-1544) 43 p. doi:10.2903/sp.efsa.2019.EN-1544 Open government data are about wide and free availability of public information created or collected by public entities. The International Open Data Charter and Findable, Accessible, Interoperable And Reusable Data (FAIR) data principles were selected as the guiding principles for the development of this report. A review of open data maturity reports indicated that most of the EU28+ are making significant progress in open government data, however there are different levels of adoption in food and feed safety organisations. EFSA's Scientific Data Warehouse (SDWH) access rules were defined in 2015; 0this report extends them to an open-by-default approach. Precautions are specified to ensure people, products or food businesses are not identified, and that information deemed confidential is protected. A proactive scientific data publication process that is open, timely, comprehensive, comparable, interoperable, accessible and usable is defined. Publication can be performed on behalf of data providers by EFSA (Supported publications) or by organisations according to their own open data policy (self-publishers). Structural metadata to support interoperability and comply with data protection requirements is defined as are the minimum descriptive and administrative metadata to support accessibility and usability. Datasets will be published in the open evidence community Knowledge Junction and assigned a Digital Object Identifier to ensure persistence and allow tracking of reuse. API technology and Data Catalogue Vocabulary Application Profile (DCAT-AP) will be used to ensure integration with the EU open data ecosystem. Attribution and citation to give credit to parties that have contributed to the creation of datasets are emphasised. The working group identified many benefits of open data and proposes mechanisms to overcome perceived barriers. Upon endorsement, EFSA should proceed with the scheduling of the publication of data from the SDWH. New data collections with a requirement to store data in the SDWH would be subject to this open data approach.

INTERNATIONAL SCIENCE COUNCIL (ICSU)

ISC, WMO, IOC of UNESCO. **Review of the World Climate Research Programme (WCRP).** Paris: International Science Council. 2018, 72 p. doi: 10.24948/2018.03 This report provides strategic directions for the future development of the World Climate Research Programme (WCRP), reviews its scientific achievements and impact since 2009, and assesses the appropriateness and effectiveness of the governance, operational structure, management and resourcing of WCRP. It looks at WCRP's structure and governance in the current context, considering the effectiveness of its operations and relationship with key partners, as well as its contributions to major international policy processes. Finally, the report looks ahead to the future of WCRP and makes a number of recommendations for WCRP to fulfil its mission in the context of 21st century challenges.

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (OECD)

Navrud, S. **Assessing the economic valuation of the benefits of regulating chemicals: Lessons learned from five case studies.** Paris: OECD. 2018, 14 p. (*OECD Environment Working Papers*; 136) doi:10.1787/9a061350-en This paper reviews and compares five case studies on quantification and economic valuation of benefits in cost-benefit analyses (CBAs) of regulating phthalates, mercury, PFOA (perfluoro-octanic acid) and its salts, NMP (1 methyl-2-pyrroloidine) and formaldehyde. The case studies had all been carried out as part of the SACAME project, and the purpose of the present paper is to draw out cross-cutting findings from these studies. Health impacts, rather than environmental impacts, were the focus of the benefit assessments covered in the five case studies. This is mainly due to a weaker scientific evidence-base for impacts on the environment and ecosystem services. The case studies show that there are major challenges in estimating the benefits of regulating chemicals. There are very few detailed applications of the full IPA/DFA, even for mercury, which is the chemical with most available assessments among those covered here. The case studies also document that the values used for morbidity impacts are often incomplete, in most cases covering only lost productivity, lost earnings or cost-of-illness, but mostly disregarding the disutility costs of pain and suffering from the illnesses. Finally, benefits transfer estimates are simplistically applied.

Karousakis, K. **Evaluating the effectiveness of policy instruments for biodiversity: Impact evaluation, cost-effectiveness analysis and other approaches.** Paris: OECD. 2018, 45 p. (*OECD Environment Working Papers*; 141) doi:10.1787/ff87fd8d-en This report provides an overview of methodologies to evaluate the effectiveness of policy instruments for biodiversity, covering impact evaluation, cost-effectiveness analysis and other more commonly used approaches. It then provides an inventory of biodiversity-relevant impact evaluation studies, across both terrestrial and marine ecosystems. The report concludes with lessons learned, policy insights and suggestions for further work.

Moreira, L. **Health literacy for people-centred care: Where do OECD countries stand?** Paris: OECD. 2018, 54 p. (*OECD Health Working Papers*; 107) doi:10.1787/d8494d3a-en In the 21st century care, the old paradigm "because the doctor said so" no longer holds. Individuals are now seeking ways to understand their health options and take more control over their health decisions. But this is not an easy task. Professionals continue to use medical jargon, drug instructions are not always clear, and health information in clinical settings continue to be complex and challenging to navigate. Widespread access to digital technologies offset some of these barriers by democratising access to health information, providing new ways to improve health knowledge and support self care. Nonetheless, when health information is misused or misinterpreted, it can wrongly influence individuals' preferences and behaviour, jeopardise their health, or put unreasonable demands on health systems. This paper finds that health literacy can help steer individuals' behaviour in the right direction. Health education and empowerment help people become partners in the coproduction of health by enhancing communication and decisions in clinical settings, as well as increasing self care. This may contribute to better health outcomes. Ignoring health literacy can come at a high cost. In 18 OECD countries, at least one third of the population shows poor health literacy levels. In 12 of those countries, that proportion rises beyond 50% of the population.

UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION (UNESCO)

Behind the numbers: ending school violence and bullying. Paris: UNESCO Publishing. 2019; 70 p. ISBN 978 92 310 0306 6 School-related violence in all its forms, including bullying, is an infringement of children's and adolescents' rights to education and health and well-being. No country can achieve inclusive and equitable quality education for all if learners experience violence in school. This publication provides an overview of the most up-to-date evidence on school violence and bullying. It includes global and regional prevalence and trends, factors that influence vulnerability to school violence and bullying, and consequences. The publication brings together for the first time in one place a wealth of quantitative data from two large-scale international surveys: the Global School-based Student Health Survey (GSHS) and the Health Behaviour in School-aged Children (HBSC) study. The surveys cover 144 countries and territories in all regions of the world, and from a wide range of other global and regional surveys. The publication also includes an analysis of factors that contribute to effective national responses, based on a series of case studies commissioned by UNESCO of countries that have succeeded in reducing the prevalence of school violence and bullying or have maintained low levels of school violence over time.

WWAP (United Nations World Water Assessment Programme)/UN. **The United Nations world water development report 2018: Nature-based solutions for water.** Paris: UNESCO Publishing. 2018; 139 p. ISBN 978 92 310 0264 9. The 2018 edition of the World Water Development Report seeks to inform policy and decision-makers, inside and outside the water community, about the potential of nature-based solutions (NBS) to address contemporary water management challenges across all sectors, and particularly regarding water for agriculture, sustainable cities, disaster risk reduction and water quality. Water management remains heavily dominated by traditional, human-built (i.e. 'grey') infrastructure and the enormous potential for NBS remains under-utilized. NBS include green infrastructure that can substitute, augment or work in parallel with grey infrastructure in a cost-effective manner. The goal is to find the most appropriate blend of green and grey investments to maximize benefits and system efficiency while minimizing costs and trade-offs.NBS for water are central to achieving the 2030 Agenda for Sustainable Development because they also generate social, economic and environmental co-benefits, including human health and livelihoods, food and energy security, sustainable economic growth, decent jobs, ecosystem rehabilitation and maintenance, and biodiversity.

WORLD HEALTH ORGANIZATION (WHO)

Global Vaccine Safety Initiative. Report of a meeting. Santiago, Chile, 8-9 October 2018. Geneva: World Health Organization. 2019, 89 p. The seventh meeting of the Global Vaccine Safety Initiative (GVSI) was held in Santiago, Chile, on 8-9 October 2018. It was hosted by the Institute of Public Health of Chile, together with the Ministry of Health of Chile. The meeting provided a platform for exchange, interaction and information sharing between Member States and partners, as well as opportunities for partnership-building and planning. The meeting enabled Member States and partners to discuss progress in the implementation of national and global vaccine pharmacovigilance activities. Participants had opportunities to share ideas, explore new frontiers in vaccine safety, and initiate collaborations. Attendees included immunization program managers, pharmacovigilance staff from national regulatory authorities, representatives of UN agencies, academic institutions, umbrella organizations of pharmaceutical companies, technical partners, industry representatives and funding agencies. This report provides an overview of presentations and key points discussed during the meeting.

Global status report on road safety 2018. Geneva: World Health Organization. 2018, 424 p. ISBN 978 92 415 6568 4 The report, launched by WHO in December 2018, highlights that the number of annual road traffic deaths has reached 1.35 million. Road traffic injuries are now the leading killer of people aged 5-29 years. The burden is disproportionately borne by pedestrians, cyclists and motorcyclists, in particular those living in developing countries. The report suggests that the price paid for mobility is too high, especially because proven measures exist. Drastic action is needed to put these measures in place to meet any future global target that might be set and save lives.

Global tuberculosis report 2018. Geneva: World Health Organization. 2018, 277 p. ISBN 978 92 415 6564 6 WHO has published a global TB report every year since 1997. The main aim of the report is to provide a comprehensive and up-to-date assessment of the TB epidemic, and of progress in prevention, diagnosis and treatment of the disease at global, regional and country levels. This is done in the context of recommended global TB strategies and targets endorsed by WHO's Member States and broader development goals set by the United Nations (UN). The 2018 edition of the global TB report was released on 18 September, in the lead up to the first-ever UN High Level Meeting on TB on 26 September 2018. The data in this report are updated annually. Global TB reports from previous years are available from the WHO Institutional Repository for Information Sharing (IRIS).

Eradication of yaws: a guide for programme managers. Geneva: World Health Organization. 2018, 52 p. ISBN 978 92 415 1269 5 Yaws mainly affects children living in poor communities in 14 countries of the World Health Organization (WHO) African, South-East Asia and Western Pacific regions. The disease is targeted for eradication by 2020. This document provides guidance for countries on how to implement activities to achieve the interruption of yaws transmission. It is intended for use by national yaws eradication programmes, partners involved in the implementation of yaws eradication activities and WHO technical staff who provide technical support to countries in the eradication of yaws. This guide should be used together with *Eradication of yaws: procedures for verification and certification of interruption of transmission* and *Summary report of a consultation on the eradication of yaws, 5-7 March 2012, Morges, Switzerland.*

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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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