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Viale Regina Elena 299, 00161 Rome, Italy
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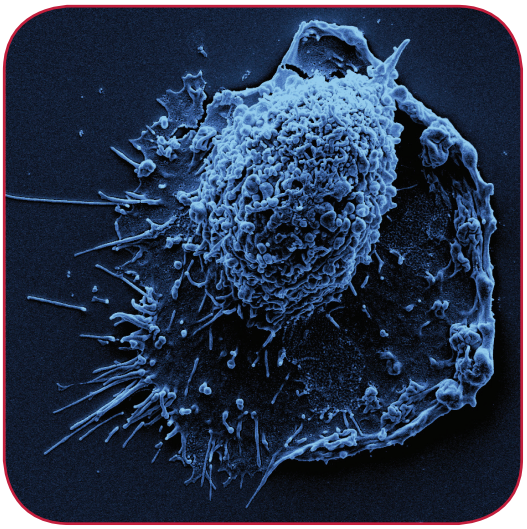

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Criteria for allocation of life-saving resources during the SARS-COV-2 pandemic: ethical implications and aspects of legal liability

Francesco Gambino[1], Carlo Petrini[2] and Luciana Riva[2]

[1]*Dipartimento di Giurisprudenza, Università degli Studi di Macerata, Macerata, Italy*
[2]*Unità di Bioetica, Istituto Superiore di Sanità, Rome, Italy*

Abstract
The issue of political, institutional and professional liability in the context of the SARS-COV-2 pandemic is currently widely debated and involves several levels of investigation. One crucial aspect relates to the allocation of life-saving resources in situations where there is an imbalance between need and availability and the associated questions of ethical and legal liability. This work looks at the implications of the criteria applied to rationing under extraordinary conditions and the issue of their legitimacy. Considering the European scenario, we describe the approach taken by Italy in proposing criteria for pandemic triage of intensive treatment and highlight certain problems and critical issues. We emphasise that the decision, based on a comparative assessment, to deny treatment to a patient in critical condition, compromising that patient's right to care, exceeds the scope of decision-making autonomy of the professional concerned and requires a theoretical and procedural definition shared at multiple levels of society.

Key words
- allocation of resources
- COVID-19 pandemic
- medical liability
- selection criteria

INTRODUCTION

A public health emergency with a major impact on people's health, such as the SARS-COV-2 pandemic, represents an extraordinary event that requires the timely implementation of appropriate response actions and strategies. From the initial months of 2020, the resilience of the economic and social systems in many countries around the world has been severely tested by the effects of an unknown virus. Healthcare systems have been required to adapt, in some cases revealing pre-existing organisational and structural problems. This unprecedented situation has created the inevitable conflict between protecting individuals and achieving collective public health objectives (ensuring maximum benefit for the greatest number of patients) [1]. Indeed, in a context of medical emergency, the public healthcare perspective is forcibly shifted from the individual to the general population, which is made up of all "statistical lives".

The issue of political and institutional liability during the SARS-COV-2 epidemic has been widely debated, both in relation to the role of preparedness before the event and in terms of the appropriateness of the actions implemented to address the specific situation. One crucial aspect of the discourse on liability, which soon emerged within the collective debate, relates to the conduct of physicians: there has been no shortage of legal suits brought in respect of alleged cases of negligence in relation to COVID-19. Doctors, like all healthcare workers, are those on the front line who have had to deal with the organisational and resource-related shortcomings of healthcare systems, who have had to work at a frantic pace and under stressful conditions, sometimes even without appropriate protective equipment. They have also had to take action in a situation characterised by significant scientific uncertainty due to the substantial novelty of the virus: as highlighted by the Italian National Bioethics Committee: "in fighting the COVID-19 infection, we are operating without consolidated guidelines or good clinical practices, recognised by the scientific community, therapeutic evidence" [1].

In addition, it is a fact that some medical professionals have had to make extremely difficult decisions about the allocation of life-saving resources for patients requiring intensive care treatment, in situations where there is an imbalance between need and availability [2].

Address for correspondence: Luciana Riva, Unità di Bioetica, Istituto Superiore di Sanità, Via Giano della Bella 34, 00162 Rome, Italy.
E-mail: luciana.riva@iss.it.

In such a scenario, the "irreducible core of the right to health" is inevitably compromised by the emergency situation and it can become difficult to ensure equal treatment for everyone. A catastrophic event can stress health systems to varying degrees: it may allow the system to continue providing healthcare in the normal way or it may be excessive in relation to the organisational and resource capacities and cause changes to the level of care considered to be standard. In this latter case, there can be a "substantial change in normal healthcare operations and in the level of care that it is possible to deliver (…) justified by specific circumstances and (…) formally declared by a national government in recognition of the fact that crisis operations will be in force for a prolonged period" [3]. To avoid situations where such a change occurs at the mercy of chance, it is essential to have specific preparedness plans in place, based on shared ethical values. The document "Guidance for Establishing Crisis Standards of Care for Use in Disaster Situations" drafted in the United States by the Institute of Medicine (IOM) lists certain key elements that should underpin action plans modifying the normal standard in crisis situations, including i) a strong ethical grounding that enables a process deemed equitable based on its transparency, consistency, proportionality, and accountability; ii) significant integrated and ongoing involvement by all stakeholders (such as, the public, at-risk populations, healthcare providers), where appropriate to promote trust in and transparency of the process and demarcate roles and responsibilities; and iii) careful consideration and possibly resolution of legal issues identified as emerging, including possible liability considerations [3].

This work will analyse, with reference to the Italian legal system, the issue of decisions made by healthcare workers required to choose those individuals who will get treatment in the exceptional case that there are not sufficient resources for everyone. We will analyse the implications of these decision-making criteria in an extraordinary context and will describe the approach applied by Italy to propose criteria for triaging intensive care treatment. We will discuss certain problems in the light of the legal implications of a decision that, in a case such as this, may result in a patient being excluded from access to intensive care treatment.

ETHICAL PRINCIPLES AND CRITERIA FOR SELECTING BETWEEN *ORDINARY* AND *EXTRAORDINARY*

The allocation of limited resources such as organs, drugs or technologies represents a persistent challenge for healthcare systems from both a regulatory and an ethical standpoint. The distribution choices are made in terms of "macro-allocation" – the specific area of competence of health policy – and "micro-allocation" – the scope of action of healthcare facilities and individual healthcare professionals. These choices always imply consideration of economic, political and ethical variables. The issue, which raises the central question of how to allocate the good in question fairly [4], has prompted discussions on both theoretical and operational levels. The general debate on models for allocation of resources – which involves the relationship between principles and the statement of empirical criteria – is complex and multifaceted and is beyond the scope of this work, which will focus on allocation criteria in the *extraordinary* healthcare context represented by the COVID-19 epidemic.

In this scenario, we have been confronted with an important ethical dilemma in terms of the triage of intensive care treatment. As was immediately apparent, there was no internationally shared ethical thinking or useful tools to deal with a complex decision on rationing of life-saving resources. In the debate that has developed, frequent reference has been made to shared ethical values and principles, but that reference alone is not sufficient: principles such as distributive justice (fair allocation of resources), equality or self-determination need to be reflected in operational criteria that are justified and verified, such as practical tools to guide decision-making. Over the course of the COVID-19 pandemic, numerous guides for professionals intended to regulate intensive care triage have been disseminated. However, subsequently, the criteria proposed have proven to be inconsistent, vague or even contrary to shared international principles or local legislative systems [5].

At the European level, the debate has developed not only on to general ethical criteria underlying choices [6] or on the organization of health systems [7, 8] but also, in individual states, in relation to the implications arising from their specific regulatory frameworks [9, 10].

Controversies and contrasts are reported in the absence of national guidelines or coordination [11]. It is interesting to note that the lack of an authoritative guide has been widely experienced despite the proliferation of documents and recommendations disseminated by authoritative sources [12]. Procedural queries about who should be involved in making decisions or what a fair or equitable allocation of scarce resources would look like are still ongoing [13]. On the basis of the existing literature and proposals developed during other pandemics, certain authors have noted that many approaches agree on four key values: i) maximising benefits; ii) treating people equally; iii) promoting and rewarding those with intrinsic value; and iv) giving priority to those who are worst off. However, as has been pointed out, these values in themselves do not constitute sufficient tool for directing the actions of doctors and guidelines should be provided at a higher level of authority. The authors have also analysed these guiding values in terms of the specific situation of the Sars-Cov-2 pandemic, providing recommendations to adjust their application. For example, they have noted that although the criterion of 'causal selection' should not be used, it could be permitted in the case of two patients with the same prognosis [14].

To the general question as to whether, during an *extraordinary* public health event, medical ethics are suspended and values and principles different from the *ordinary* apply, the response is that, under extraordinary conditions, there is no change to the reference ethical criteria of the medical profession or to the principles of a State or to fundamental human rights as these are recognised by international documents, such as the Eu-

ropean Convention on Human Rights (ECHR) [15]. The ethical principles to which healthcare professionals are required to adhere and that are laid down in the codes of ethics remain the same: respect for autonomy, beneficence, non maleficence ("first do not harm") and the principle of justice continue to guide the activities of medical professionals.

The issue of the legitimacy of allocation decisions also represents a question of primary importance in relation to the risks to which doctors are exposed. The legitimacy of interrupting mechanical ventilation treatment where it is clinically indicated will in fact also depend on the details of the triage procedure applied and who it was applied by. As has been clearly noted, there is an important legal difference between: (1) a procedure adopted by a government, and (2) a procedure suggested by a scientific society or committee of medical ethics experts. This is not because the information provided in the second case is intrinsically inaccurate, but rather because there is an issue of authoritativeness to be considered [5].

THE COVID-19 EPIDEMIC AND INTENSIVE CARE TRIAGE

When we refer to *triage*, we mean "a healthcare practice aimed at identifying care priorities by assessing the clinical condition of patients and the risk that they might get worse, so as to ensure that users are treated and to determine the order for access to treatment". It is important to note that this definition, provided in the "National guidelines on *intra-hospital triage"* from the Italian Ministry for Health [16] indicates that the goal of triage is exclusively to ensure the best possible management of the order for access to treatment and not to make a decision as to who can and cannot access such treatment, assuming that all patients requiring care will be treated. Other common triage contexts in contemporary medical practice are those relating to access to intensive care and to waiting lists for organ transplants. In these latter cases, considering the limited quantities of specific resources, whether intensive care beds or organs, it cannot be ruled out that some patients may not be able to access treatment. The fundamental issue in triage is therefore the following: not all those who need a particular form of healthcare will be able to access it immediately and unconditionally.

During the initial months of the SARS-COV-2 epidemic, doctors found themselves alone in having to make difficult decisions about "who to admit and who not to admit", so much so that in Europe, some scientific societies took urgent action through ad hoc recommendations for professionals [17]. Among the first was, in Italy, the Italian Society of Anaesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI), which published "Clinical ethics recommendations for admission to and suspension of intensive care, under exceptional conditions of imbalance between needs and available resources" on 6 March 2020 [18]. This document has generated fierce debate because of the problematic nature of some of its content, in particular the indication of the non-clinical, advance criterion of age for triage selection. Against this background, for example, the *European Alzheimer's Association* has highlighted the need for decisions about access to or denial of intensive care services to be based solely on an assessment of the individual prognosis of the patient and not "on the fact that the patient has a specific diagnosis (such as dementia)" or on non-medical criteria or characteristics "such as age, place of residence, gender, gender identity, ethnic affiliation or marital or parental status" or value judgements "such as probable life expectancy, presumed quality of life, potential future contribution to society, etc." [19].

There has been almost unanimous agreement that decisions on the allocation of resources must be transparent: the public must be able to understand the purpose of any triage protocol and how it will be applied and to trust that it will be applied consistently [20].

It is also valuable to consider how the conduct required of professionals has been codified: the question arises as to whether the appropriate instrument to regulate a problem of allocation of scarce resources can be scientific in nature, for example taking the form of a guideline for professionals, or whether it should be political and institutional, for example falling within the scope of a national pandemic preparedness plan. The latter would seem to be the most appropriate way of guaranteeing better assurance about the chosen allocation criteria, given that it involves political institutions (e.g., Ministry, regions) that are authorised to impose organisational rules in relation to healthcare.

During the second wave of the pandemic, and specifically on 30 October 2020, the SIAARTI and the National Federation of Associations of Surgeons and Dentists (FNOMCeO) made public a new document that made a strong appeal to professional ethics [21], which stated that: "If the imbalance between needs and available resources persists, precedence for access to intensive care will be given to those who will be able to obtain a concrete, acceptable and lasting benefit from that care. For this purpose, strict, explicit, consistent and integrated criteria must be applied, assessed on a case-by-case basis, such as: severity of the clinical symptoms, comorbidities, previous functional status, impact of the potential side effects of intensive treatment on the individual, knowledge of dispositions for advance care planning and biological age, which latter criterion may never take precedence". At the same time, those societies called for an addition to the code of ethics for doctors on the issue of tragic choices in the case of extraordinary or exceptional episodes. The document states that the individual right to equal access to healthcare must remain the cornerstone of the protection that the State is required to provide and that, therefore, "the selective use of criteria that legitimise differentiated treatment modalities should be considered only where absolutely necessary". Indeed, the use of such criteria may not be understood as a denial of the non-negotiable principle of the equal value of every human being.

In December 2020, the National Centre for Clinical Excellence, Quality and Safety of Care (CNEC) within the Italian National Institute of Health opened a public consultation on a document entitled "Decisions for

intensive care in cases where there is a disproportion between care needs and available resources during the COVID-19 pandemic", drafted by the SIAARTI and the Italian Society of Legal and Insurance Medicine (SIMLA). The final version, following the consultation, was published on 7 January 2021 in a section of the National Guidelines System dedicated to the COVID-19 epidemic.

SIAARTI-SIMLA DOCUMENT: A COMPARATIVE ASSESSMENT

The objective of the document, which was published in the section "Good Practices in the National Guidelines System", produced by the SIAARTI and the SIMLA, is to offer healthcare professionals "a suitable tool to enable them to respond appropriately to the current emergency situation due to the COVID-19 pandemic, potentially affecting the health of all citizens, if there is an imbalance between demand for healthcare and available resources, with particular reference to intensive care" [22].

According to that document, in the case of a disproportion between patient needs and medical resources, *triage* must be carried out, namely "a comparative assessment of the overall condition of the patients, not to determine whose condition is more serious or who has greater need of care, but to establish who is more likely (or less likely) to overcome the current critical situation with the support of that intensive care with a reasonable life expectancy outside Intensive Care: and thus short-term survival (several months) following discharge from hospital". The document excludes any assessment criterion associated with chronology (the order of arrival of patients), random choice (drawing of lots) or simple personal data, which would not be "in itself a criterion for establishing which patients may benefit most from intensive care". In a scenario where the "*saturation of healthcare resources making it impossible to guarantee that all sick people can receive the treatment indicated*" the following parameters are indicated for the overall assessment of the individual, to determine whether that individual is likely to overcome the critical condition with intensive care support: number and type of comorbidities; previous functional status and degree of fragility; severity of current clinical symptoms; and presumable impact of intensive treatments, especially considering the age of the patient.

Although the document was produced according to the specific procedure laid down in the "guideline recommendations" published in accordance with Article 5(3) of Law No 24 of 8 March 2017 – and drafted by scientific societies entered on the list created and regulated by a decree from the Ministry for Health in accordance with Article 5(1) of that law –, it has been included in the section on "Good Practices in the National Guidelines System".

It should be noted on this point that the good practices mentioned in Article 5 of the abovementioned law are the good clinical and care practices with which healthcare professionals – subject to the specific aspects of the case concerned – must comply "in the absence of the abovementioned recommendations" (Article 5(1)).

This first ambiguity requires a clarification – for the purposes of the legal framework of the document – of the general distinction between "guidelines" and "good practices". It is in fact because the specific case falls within the regulatory framework that there is any legal significance to the document, considering also the scope of decision-making autonomy of the healthcare professional concerned in terms of permitting, excluding or interrupting intensive care treatment.

In the Italian legal system – which is the reference framework for this work –, guidelines, unlike protocols, do not indicate an analytical succession of obligations, but, rather, express general directives, instructions or guidance [23]. Those recommendations (Article 5(1) of Law No 24 of 8 March 2017), created following a systematic review of the scientific literature, offer healthcare professionals an important support tool in clinical diagnostic, prognostic and therapeutic processes [24]. In this situation, dominated by informative contributions, there is scope for decision-making autonomy for doctors, on the basis of the words in the law "subject to the specific aspects of the case concerned" (Article 5(1) of Law No 24 of 8 March 2017). It is the professional operator who selects the behaviour that is appropriate on each occasion, and in the case of a court dispute, that behaviour will be evaluated by the technical experts and the judge. It can thus happen that "although the guidelines indicate a given strategy in relation to the condition being treated", the unique aspects of the clinical case suggest a need "to deviate from the ordinary course of action" [25].

The legal doctrine makes a distinction between these guidelines – which refer to clinical activity – and guidelines of a predominantly organisational nature, drafted not by scientific societies but, rather, by public institutions that sometimes report these in the Official Gazette or in official regional gazettes [24]. Examples we can cite here include the guidelines on the medical emergency No 1/1996, published in the Official Gazette, which are the result of an agreement between the Government and the regions.

In terms of "good practices" – to which the SIAARTI-SIMLA document also relates –Law No 24 of 8 March 2017 makes a distinction between *good safety practices* and *good clinical and care practices*.

The former relate to the safety of care and have stricter content and are more binding (for example, this covers the rule about pre-operative hand washing) [24]. The others, although not being subject to the drafting and publication procedure envisaged by the law for guidelines, are relevant in the absence of the latter, and have the same preventive, diagnostic, therapeutic, palliative, rehabilitative and forensic purposes (Article 5(1) of the Law of 8 March 2017). It can be said that such good practices, which have the same purpose as guidelines, are of the same type as guidelines. They are alike in that they both stem from scientific evidence [24].

In the light of the reconstructed and general findings, we can see the elements of ambiguity in the SIIARTI-SIMLA document which expose its somewhat hybrid nature.

In principle, it is a "guidelines" in accordance with Article 5 of Law No 24 of 8 March 2017, in terms of form and method of legal enacting. In terms of resource distribution, it is also organisational, although it does not involve the public institutions with jurisdiction in this area. Lastly, it is introduced as "good practice" with reference to the *nomen iuris* of the public web section in which it is published; it also could act as good safety practices that could further reduce the decision-making autonomy of healthcare professionals.

Hence the question as to whether the "good practices" for triage activities in the emergency situations described, produced in line with the requirements laid down in Law No 24 of 8 March 2017, can be classified as "guideline recommendations" or in any case as "good clinical and care practices" in accordance with Article 5 of Law No 24 of 8 March 2017.

It is well known that due compliance – by health professionals – with both assumes considerable importance in civil and criminal law, as a result of legislative reform.

In terms of the former, the guidelines or, in their absence, the good clinical and care practices – which are binding subject to the specific of the case – offer a parameter for assessment of the conduct of health professionals, including in the judicial determination of compensation for damages (Article 7(3) of Law No 24 of 8 March 2017) and in general of the extent to which the action performed is not in conformity with the expected action.

The conduct of the medical practitioner is at the heart of civil law discussion on medical services. It is on that behaviour that the specific discipline of medical liability can be based. For reasons of qualified social contact, this does not rise to the level of contractual liability, but neither can it be viewed in the same terms as an act of non-contractual negligence [26].

In relation to the scenario of possible disputes caused by COVID-19, the various foreseeable initiatives envisaged by the doctrine include cases brought against health professionals for imprudent, negligent or inexpert conduct and, with regard to the issue of the limited number of intensive care beds, cases brought against healthcare facilities called to account for organisational and management problems and deficiencies [27].

In terms of criminal law – as we know – the Italian law provides for a limitation on punishability due to compliance with guidelines or, if no such guidelines exist, good clinical and care practices.

THE CASE IN POINT, THE CRITERION OF GREATEST LIKELIHOOD OF SURVIVAL

The possibility of tying the "good practices" in question back to one or other "source" – and in particular to the guidelines or good practices mentioned in Article 5 of Law No 24 of 8 March 2017 – requires a preliminary clarification of the specific aspects of the case.

Let us imagine the case of two patients who both require intensive care treatment on the basis of the guidelines in use on the general conditions for access to such treatment but where, in an exceptional context where available resources are scarce, only one intensive care bed is available. A comparative evaluation of the overall condition of the two patients would be initiated, and priority would be given to the patient who is more likely to be able to overcome the critical condition and has a reasonable life expectancy outside the intensive care unit (short-term survival following discharge from hospital) [22]. However, this would disadvantage the patient less likely to survive and with shorter reasonable life expectancy.

This is a gradually developing case where the final segment is – dramatically – devastating.

To clarify the scope of the criterion being reviewed – greater likelihood of survival – we need to start with the general criteria for admission of patients to resuscitation and intensive care widely applicable in the period prior to the release of the document being analysed here [28].

Particular focus should be given to the criterion of clinical appropriateness, based on three elements: a) reversibility of the acute pathological condition; b) reasonable likelihood of benefits expected from intensive treatment, including in relation to the cost borne by the patient for that treatment; c) reasonable expectation that the critical condition can be overcome [28]. An order of priority is established according to a scale starting with maximum expected benefit (priority 1) and running to minimum or nil expected benefit (priority 4). With regard to geriatric patients, it should be noted that "chronological age in itself is not a criterion to decide appropriateness of intensive care, because it is not always correlated with biological age", and that "evaluation of the clinical appropriateness of intensive care must not in any case be influenced by the negative image that society has of old age" [28].

In the light of these indications, dating from 2003, we can state that, in an exceptional situation involving scarcity of resources, the criterion of the greatest likelihood of survival, viewed in terms of resource allocation, can be considered a logical consequence and development of the criterion – applied under normal resource conditions – of the reasonable likelihood of an expected benefit from intensive care treatment.

The SIAARTI-SIMLA document from 13 January 2021 states that triage represents an independent, subsequent process in relation to the evaluation of the appropriateness and proportionality of intensive care treatment, with appropriateness and proportionality of treatment being the ethical and professional prerequisite for any treatment. The Italian document is not a closed decision-making system: the authors explicitly exclude the possibility that "the outcome of triage for intensive care treatment could be dependent on the score resulting from the use of any instrument or algorithm, even if proposed or used in other countries" [22]. The only tool indicated as appropriate for guiding the triage process is the overall clinical evaluation, performed by the medical/healthcare team on the basis of recognised prognostic indicators. But the dilemma that can arise in cases where short-term survival estimated in several individuals is equivalent or in any situations where prognosis is uncertain – namely in those phases defined by some authors as "bottlenecks"

– seems to remain vague. It constitutes an element of incompleteness, perhaps to be resolved in subsequent documents, which has also been highlighted in relation to similar international guidelines [17].

The SIIARTI-SIMLA document states: "the increase in demand for healthcare (for three admission levels: standard, semi-intensive, intensive) induced by situations such as those caused by the pandemic, does not compromise the necessary adherence, in protecting health, to the constitutional and founding principles of the Italian National Health Service, or to ethical principles and in particular those of universality and equality (non-discrimination), solidarity and self-determination" [22].

A selection criterion based on these principles has been identified: priority is given to the patient who is more likely "to overcome the current critical situation with the support of that intensive care with a reasonable life expectancy outside Intensive Care: and thus short-term survival (several months) following discharge from hospital" [22]. The doctor must therefore carry out a clinical evaluation and determine an order of priority on the basis of the criterion stated, informing the sick person and any legal representatives and family members of the outcome of triage and an estimate of the likelihood of recovery in the case of admission to intensive care.

The document does not indicate practical decision-making criteria in cases where the prognosis is the same and does not provide any information about how to interrupt or reassign mechanical ventilation treatment if this is required.

The comparative assessment – referred to in the document discussed in these pages – to exclude a patient in critical condition from intensive care treatment is destined to create a conflict between perspectives, cultural discourse, scientific knowledge and social systems. It is in this scenario that ethics, economy and law may contend for the power – each from its own sovereign and unconditional point of view – to establish principles and parameters for evaluation that provide decisive guidance for decision-making by healthcare professionals.

It is only natural that each system, being operationally closed, releases *from within* independent criteria for judging the actual facts, using its specific language and operations.

This is not a question of determining a chronological order of priority, a "before" and an "after", but rather – in the emergency situation described – a *criterion*, in the final analysis, for *exclusion*. This is an "after" that can be fatal for the patient to the point of a tragic "never".

Thus, in economic terms, the clinical determination as to greater or lesser likelihood of survival leads to the conclusion, from that perspective, that the intensive care assigned to one or other patient is a more usefully employed resource. This is a manifestation of the criterion of distributive justice [29]. In other words, in terms of resource allocation, the criterion of greater likelihood of survival is translated into and reflected in the criterion – given certain specific clinical conditions – of the most efficient use of intensive care.

It is worth noting that in some legal systems (such as in Australia, New Zealand and South Africa) [17], for the situation described, emphasis is placed on the category of health professions who, especially in this historical period of pandemic, are a resource that is clearly considered indispensable for the system.

From another perspective, we should note that the criterion of greater likelihood of survival may imply a statistical fact, namely a tendency to exclude the most vulnerable patients (elderly and disabled) from access to intensive care treatment.

In Germany it has been asserted by the President of the German Patient Protection Foundation (Deutsche Stiftung Patientenschutz) that this is a reversal of ethical principles, which ultimately penalises the patients most at risk [30].

In this situation, dominated by contrasts and differences, positions in favour of a political and legislative solution to the problem are emerging. Issues have arisen that, on the one hand, because they involve fundamental human rights, call for political intervention, and that, on the other, trespass into the operational realm of the physicians" code of ethics [31].

GUIDING CRITERIA AND LEGAL ASSESSMENT

The legal assessment of the question requires discussion on the final segment of the case described. It could be said – by way of an explanatory observation – that this patient, excluded following the comparative assessment under extraordinary conditions, would have had access to intensive care treatment in a normal situation where there is a balance of available resources. This is because that patient is the holder of a right – the right to intensive care treatment – that the health professional would have effectively provided, on the basis of the criterion of clinical appropriateness.

If that right to intensive care is restricted or even denied for a person in critical condition – and assuming that patient dies – this scenario could potentially be grounds for civil and criminal legal action.

It is necessary – as a general criterion – to assume the alleged proper conduct (in this case, the assignment of the intensive care unit) and then to determine, according to the counterfactual principle, whether that conduct would have had a positive effect on the survival of the patient [32].

A new comparative assessment can then be carried out by a technical expert comparing the clinical condition of the patient excluded and the patient admitted, and referring where appropriate to similar cases where another patient with similar critical aspects survived and then recovered from the illness due to intensive care treatment.

In that context, with its many uncertainties, the most pressing problem now is to find a guiding criterion that is *legally useful*, a criterion that enables the medical professionals involved in *triage* to calculate the legal consequences of their actions. In other words the risk-reducing behaviour of the professional must also be, in the eyes of *third parties* (interpreter and decision-maker), the behaviour that is legally appropriate.

In the absence of a law, the right – as in so many other

cases – remains uncertain and is destined to manifested *ex post*. It will be the judge who interprets Law No 24 of 8 March 2017 and examines the legal relevance of the document, in this case the SIAARTI-SIMLA document, applying his or her own decision-making criterion to what happens in reality.

We cannot exclude the possibility that a judge, not being convinced of the binding nature of the "good practices" in question, might review the legal framework in order to extract *the value content beyond the law* [33] as values that underpin and drive the legal system, giving precedence in such emergency situations, for example, to the principle of equality that could point, in cases where critical condition and severity of danger to life are the same, towards the different, albeit relativised, criterion [31] of "first come, first served".

This is a perspective – the most rigid – that ties in with a line of argument that can be articulated in these terms.

The "good practices" outlined in the SIAARTI-SIMLA document, do not share the same purpose as guidelines and good clinical and care practices in the technical sense, because they are not intended for preventive, diagnostic, therapeutic, palliative, rehabilitative and forensic purposes. In other words, the behaviours referred to or implied in Article 5(1) of Law No 24 of 8 March 2017 do not have the weight – human, ethical or legal – to exclude a patient in critical condition from access to intensive care treatment.

It could therefore be said that the decision, based on a comparative assessment, to deny intensive care treatment to a patient in critical condition – and thus compromise that patient's right to treatment – is conduct that does not fall within the regulatory framework laid down in Article 5(1) of Law No 24 of 8 March 2017.

From that point of view, the document, which does not fall under a regulatory paradigm, would be irrelevant and ineffective in legal terms [34]. Substantial encroachment into matters of political and deontological autonomy would reduce the "good practices" in question to "pseudo-guidelines" [31].

However, it should be noted that this is still a matter of criteria intended to guide the actions of physicians – the only guidelines existing in Italy in this sphere, which have been developed using more streamlined procedures and published in line with the legal provisions – which, because of their form and the formal nature of their presentation, are undoubtedly blamelessly relied on by the people for whom they are intended. In this context, because of the varying interpretative options, two paths can be envisaged here, suggested also by common sense.

a) In questioning the legal framework, the judge will apply the same criteria indicated by the "good practices" in question, either because he or she considers them binding on the basis of Article 1 (which also refers to "the appropriate use of resources") and Article 5 of Law No 24 of 8 March 2017, following logically from the general criteria for admission of patients to resuscitation and intensive care contained in those guidelines, or because he or she infers these criteria from the legal system by some other means (analogy, general principles, the Constitution); b) In questioning the legal framework, the judge will apply criteria different from those indicated in the "good practices" in question. In this case anyway, in any potential claim for damages that suggests a case for damages for loss of opportunity, the judge will take into consideration behaviour based on observance of those "good practices" and resulting from blameless reliance on them (Article 7(3) of Law No 24 of 8 March 2017).

CONCLUSIONS

As noted above, exceptional decisions on the allocation of life-saving resources, affecting the right of access to care, involving various areas of competence and potentially implying non-conventional actions (such as non-application or suspension of mechanical ventilation treatment), exceed the scope of autonomous decision-making of professionals and require a shared theoretical and procedural definition at multiple levels of society.

It is important to emphasise that the decision to exclude a patient in critical condition from access to intensive care treatment should be made as a last resort as part of a logic imposed out of necessity by external events. It could also be a condition of necessity generated by a situation where such access to care is impossible, because of political and economic responsibilities in the local and national management of resources intended for public health. These facts are a matter of political and institutional responsibility in adopting all strategies intended to prevent problems and serious deficiencies in available health resources.

We can discuss the clinical or non-clinical nature of the selection criterion for intensive care in a situation of imbalance between demand for healthcare and available resources, but we cannot doubt the fact that *the reasons for an – uncomfortable – need for a criterion* fall outside the purview of medicine and originate from afar.

We can grasp the underlying sense of the initiatives of the scientific societies in Italy and elsewhere intended to indicate solutions to the problem. This is to put pressure on institutions, to promote a sort of communication with other systems, to reclaim the value of legal certainty under the banner of the law, which is manifested not *ex post* but, rather, *ex ante*.

It is not surprising that the debate that has opened up on the issue is part of a conflict of discourses representing different areas of society, each with an underlying communication strategy, intended to persuade, impact, shake up the many sensitivities of the audience ignited by the pandemic.

Author's contribution statement

FG, CP, LR: conceptualization and argumentation of the paper. FG: legal assessment. FG, LR: drafting the original article.

Conflict of interest statement

The Authors declare no conflicts of interest.

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How can we manage the COVID-19 infodemics? A case study targeted to health workers in Italy

Luigi Bertinato[1], Gianfranco Brambilla[1], Paola De Castro[2], Antonella Rosi[3], Roberto Nisini[4], Annarita Barbaro[5], Donatella Gentili[5], Franco Toni[5], Antonio Mistretta[2], Raffaella Bucciardini[6], Duilio Carusi[1], Aurora Angelozzi[6], Luca Busani[8], Ernesto Costabile[7], Patrizia Mochi[2], Susanna Caminada[6], Fabio Magurano[4] and Silvio Brusaferro[9]

[1]*Segreteria Scientifica del Presidente, Istituto Superiore di Sanità, Rome, Italy*
[2]*Servizio Comunicazione Scientifica, Istituto Superiore di Sanità, Rome, Italy*
[3]*Centro Nazionale Tecnologie Innovative in Salute Pubblica, Istituto Superiore di Sanità, Rome, Italy*
[4]*Dipartimento di Malattie Infettive, Istituto Superiore di Sanità, Rome, Italy*
[5]*Servizio Conoscenza (Documentazione, Biblioteca), Istituto Superiore di Sanità, Rome, Italy*
[6]*Facoltà Medicina e Odontoiatria, Sapienza Università di Roma, Rome, Italy*
[7]*Centro Nazionale Salute Globale, Istituto Superiore di Sanità, Rome, Italy*
[8]*Epidemiologia, Biostatistica e Modelli Matematici, Istituto Superiore di Sanità, Rome, Italy*
[9]*President, Istituto Superiore di Sanità, Rome, Italy*

Abstract

Introduction. The Istituto Superiore di Sanità (ISS) has been asked for rapid technical and scientific advice to the State and Regions during Sars-CoV-2 pandemic preparedness.
Methods. An *ad hoc* Working Group on Scientific Literature updates (WG SL) was set up at ISS (March-May 2020) to screen pre-prints and peer reviewed papers from arXiv, medRxiv, bioRxiv, and Pubmed to provide a real time knowledge and empirical evidence addressed to health-workers.
Results. The WG SL screened a total of 4,568 pre-prints and 15,590 peer reviewed papers, delivered as daily summary report of pre-print selection for ISS President activity in the National Scientific Technical Committee framework and a weekly open access publication (COVID Contents) on peer-reviewed papers of interest for health professionals, monitored by a satisfaction questionnaire.
Conclusions. Promoting heath literacy, with a cross-cutting approach is a powerful heritage of Public Health Institutes and a proven effective non pharmacological intervention.

Key words
- COVID-19
- Public Health
- infodemics
- health literacy

INTRODUCTION

On January 7, 2020 a novel coronavirus, originally abbreviated as 2019-nCoV by WHO, was identified from the throat swab sample of a patient in Wuhan, PRC. This pathogen was later renamed as Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) and the disease was named COronaVIrus Disease 2019 (COVID-19) by the WHO [1].

Countries all over the world have not been prompt enough to adequately fight such an aggressive pandemic and needed to implement different approaches: the clinical and laboratory diagnosis, the management of symptomatic people (home assistance, hospitalization and ICU, therapy strategy), and the so called non-pharmaceutical interventions based on social distancing, hygiene, and mask wearing [2]. Italy was the first European country to be affected by COVID-19 [3-5], and, like the majority of Western countries, was not adequately prepared for the rapid spread of the pandemic [6].

The COVID-19 pandemic is producing an unprecedented 360° explosive impact of "health on all policies", (i.e., socio-economy, environment, education), creating serious problems but also giving rise to opportunities for a tighter co-operation among different institutional levels towards a resilient approach, mainly on the backs of the workers of the National Health Systems, and on those of citizens, asked to follow the so-called Non Pharmaceuticals Interventions.

The COVID-19 spread triggered an avalanche of scientific research, both inside and outside the medical domain, to provide communities with tools to overcome

Address for correspondence: Gianfranco Brambilla, Segreteria Scientifica del Presidente, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: gianfranco.brambilla@iss.it.

this pandemic by minimising its adverse impacts. This resulted in the production of an unprecedented number of preprints and peer reviewed papers at a such high speed to pose in serious difficulty all people involved. In fact, it became difficult to stay abreast of the research explosion by continuously monitoring real time knowledge, identifying gaps and overlooking areas in order to better guide and mobilise the expertise of scientists towards effective solutions [7, 8]. This rapid accumulation of empirical evidences obliged policymakers and emergency managers to provide their indications and decisions by taking into account these rapidly changing scientific evidences [9]. Committed institutions were, as first, charged to develop recommendation addressed to citizens as well as to health workers [10], under a strong demand of real time information, and a huge mass media coverage of all the pandemic aspects, with a diversity of experts asked to give their opinion at any prompted claim [10, 11].

The Istituto Superiore di Sanità (ISS), as leading technical and scientific body of the Italian National Health Service and public advisory body for the Ministry of Health, has been appointed to give technical and scientific advices to the Government and Regions on aspects related to public health. So, as COVID-19 pandemics started in Italy, ISS has been involved in the Scientific Technical Committee (CTS) to manage the phase 1 of emergency. It has been asked to give advices and by setting up rules at national and local level to fight COVID-19 pandemic. In this period, a Working Group on Scientific Literature updating (SL WG, a 10 people team) has been set up at ISS and received the mandate to manage such huge mass of manuscripts to provide a real-time updating on "emerging issues" and "scientific claims" for the ISS President within the preparedness frame of the CTS activities (*Figure 1*). In this paper, we wish to report such experience, to propose it as a readiness tool for future global health emergencies.

MATERIALS AND METHODS

The activity design and workflow of the SL WG is illustrated in *Figure 2*. Briefly, the ISS Library staff searched from PubMed to report the links to peer reviewed papers on COVID-19 twice a day (7/7 day a week). The following search strategy was used: (coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR COVID[All Fields] OR "covid-19"[All Fields] OR "covid19"[All Fields] OR "novel coronavirus"[All Fields] OR nCoV[All Fields] OR "SARS-CoV2"[All Fields]. Similarly, the links to pre-prints from medRxiv.org, bioRxiv.org, and arxiv.org were downloaded. The titles, authors, journals (for peer

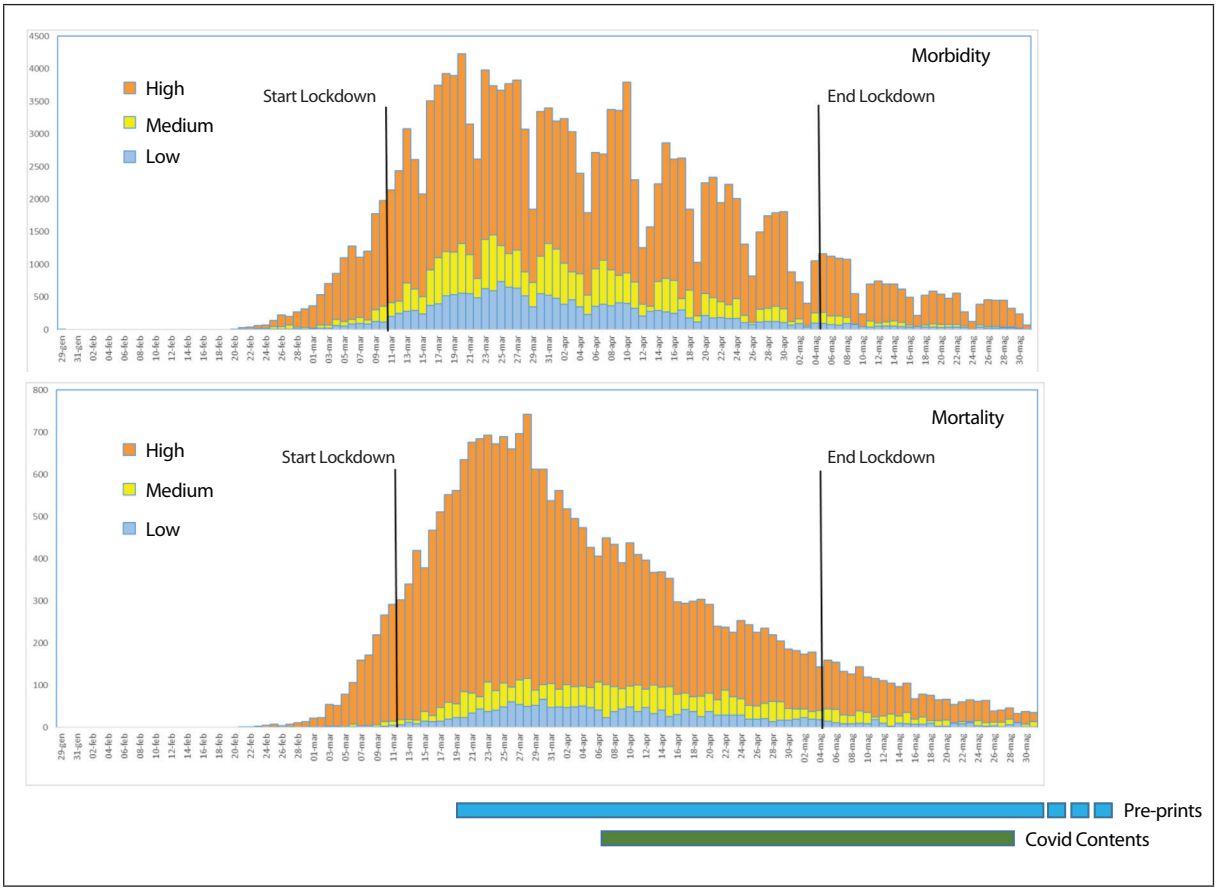

Figure 1
Distribution curves of COVID-19 A) morbidity and B) mortality in Italy until May 30 with the peaks reached in the second half of March. Bars under graphics report on COVID Content and Preprint ISS activity.

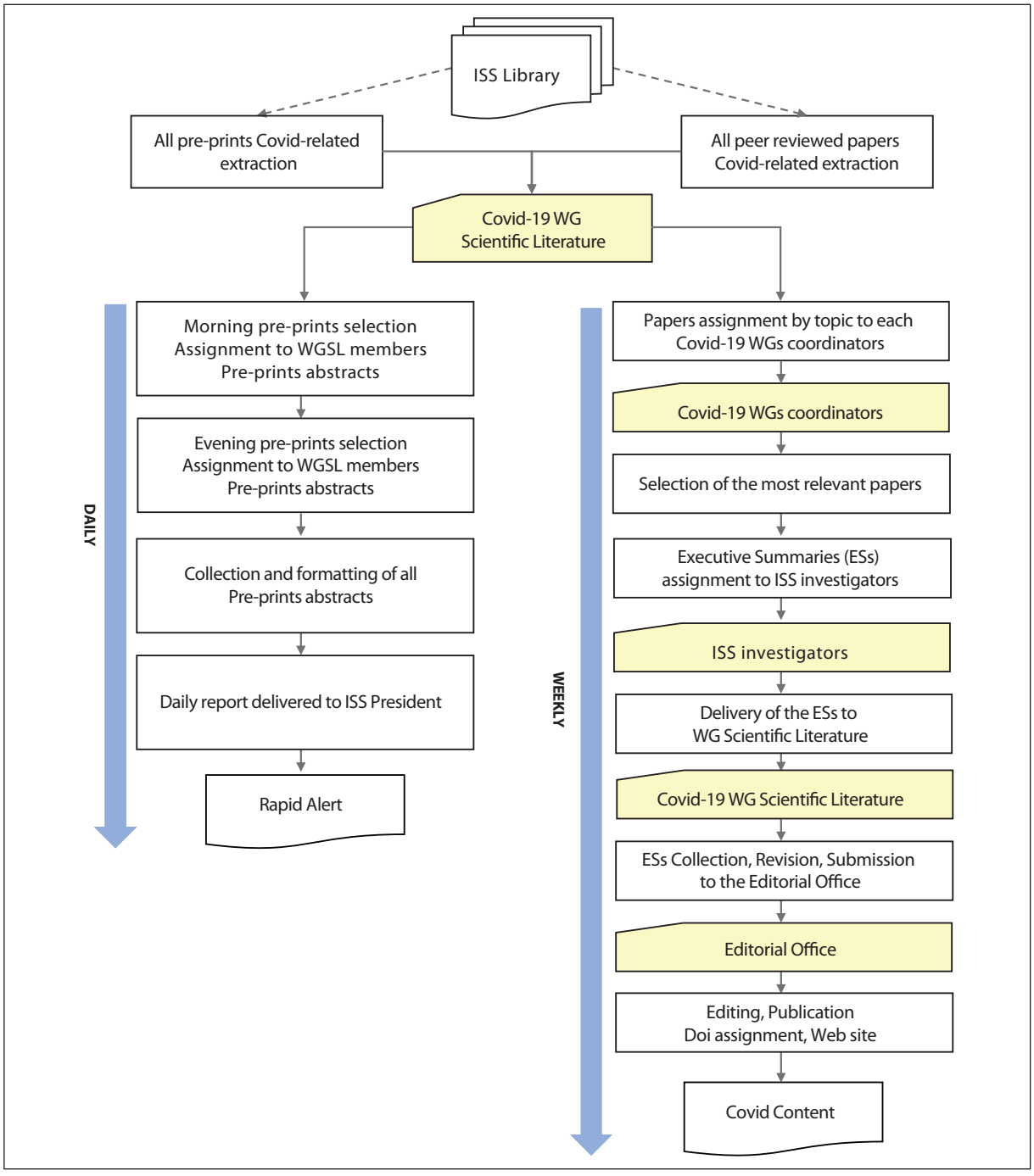

Figure 2
The activity design and workflow of the WG SL activity at ISS.

reviewed papers only) and the associated hyperlinks were listed into two separate PubMed and pre-prints .xls files and delivered to ISS researchers involved in COVID-19 activities and to the WG SL, twice a day. Pre-prints were downloaded, examined by the WG SL group, and those of higher relevance were chosen to produce a report including the most hot topics, tackled in selected pre-prints along with their executive summary and a selection of most representative figures and tables. Such report had to be delivered to ISS President within the next 24 h usually at 08:00-09:00 am timeframe, well in advance of the scheduled daily meeting of the National Scientific Committee for COVID-19, chaired by the Civil Protection framed in the Prime Minister Cabinet. This activity, started on March 18, 2020 and is still ongoing.

In parallel, twice a week, a list of freshly available peer reviewed papers was shared among other ISS COVID-19 WGs. Researchers from ISS WGs with consolidated expertise in the different fields were asked to select the most relevant papers and to provide within the next 48 h a summary of the manuscript. The final

goal was to provide health professionals a weekly online publication, called COVID Contents (CC), with an assigned DOI, based on an expert selection of peer rewieved papers covering the different aspects of the pandemic. Owing to the above, researchers were asked to explain in Italian, in an easy and rapid way (via a .pdf download on smartphones) those scientific evidences, most in the media focus, useful to orient and to motivate health workers during their hard and h 24 COVID-19 duties.

Within this context, from no. 3 to no. 6 of CC issues, the SL WG decided to propose to CC readers a picture illustrating a logical scientific frame, citizen/patient centered, of the most discussed topic of the week. To have a feed-back on the success of this COVID Contents initiative, a 7 Q open questionnaire, was delivered to the readers with CC issue no. 7 and main results are reported in *Table 1S,* available online as Supplementary Material. The 8 weekly COVID Contents issues covered the time frame from April 18 to May 28 and basically overlapped the peak of the Italian pandemic (*Figure 1*).

RESULTS

Within the selected time frame, the number of the main manuscripts selected from preprints and peer-reviewed papers quoted in the CCs and ranked according to the main topics of this pandemic (i.e., Epidemiology Infection Control, Preparedness, Immunology, Drugs and Vaccines) is reported in *Table 1*. The CC issue progressively enrolled up to 150 experts, on voluntary basis, aiming to contribute with their expertise and ability to explain in few and simple words the context, objectives, methods, results, and relevance for the NHS of rather complex topics. An example (in Italian) of a CC contribution is available online as Supplementary Material, *Figure 1S a and b*. The 8 CCs issues can be still consulted at www.iss.it/it/pubblicazioni-cessate.

Figure 3 reports the trend of the 30,723 access for CC download from ISS web site for the considered timeframe. The 6 figures accompanying the no.-3-no. 8 CC issues and illustrating the most relevant topics during the phase 1 of the pandemic are shown in *Figure 2S* (available online as Supplementary Material).

DISCUSSION

At national level, the demand of scientific evidences about the COVID-19 pandemic reached its peak just after the records of the first autochthonous cases in Codogno and Vo' on February 21, 2020, and kept a high level till the beginning of the first epidemic downslope [11] (*Figure 1*). To this respect, ISS was able to react faster to the challenges represented by the real-time mass media amplification of news from pre-prints, as matter of an easier organization of the workflow within the 10 person team of the WG on Scientific Literature. Nevertheless, the main goal was to have an open access publication mainly addressed to the personnel of the National Health System, rather than to investigators. Talking about the selection of pre-prints, the attention during the phase 1 was mainly focused on the topics about infection control: availability, proper use, and sanitization of PPE in the health settings, as well as viral shedding and contagiousness in health care and residential settings. Particularly, cleaning and decontamination procedures on surfaces were the most debated issues (18%) (*Table1*). Epidemiology accounted for the 13% of the pre-prints selected. The daily broadcasted

Table 1
Description of the topics most in the focus of the papers considered for the Covid Contents 8 week issues (above) and for the the pre-prints alert (below) during the considered 12-22 week period in 2020 (*see Figure 1*)

Covid Contents issue	no. 1	no. 2	no. 3	no. 4	no. 5	no. 6	no. 7	no. 8	Total	%
Topics										
Miscellaneous	1	0	3	7	4	2	3	1	**21**	2.4
Environment	0	0	1	0	10	2	1	2	**16**	1.9
Communication	1	7	4	5	5	5	7	4	**38**	4.4
Diagnosis	17	10	10	8	7	8	15	12	**87**	10.1
Epidemiology	6	9	8	11	4	11	5	5	**59**	6.9
Infection control	7	7	3	3	1	8	0	6	**35**	4.1
Pathology and Clinic	13	8	22	30	27	31	22	27	**180**	20.9
Preparedness	12	15	8	5	11	10	16	8	**85**	9.9
Mental Health	6	5	6	7	13	10	9	10	**66**	7.7
Veterinary Public Health	1	2	1	2	0	0	4	0	**10**	1.2
Support Technology	9	7	6	13	13	6	5	8	**67**	7.8
Telemedicine	1	6	10	10	8	9	11	6	**61**	7.1
Therapy	14	4	5	7	14	17	12	22	**95**	11.0
Vaccines	0	0	3	10	7	7	7	6	**40**	4.7
Total	**88**	**80**	**90**	**118**	**124**	**126**	**117**	**117**	**860**	**100**

Continues

Table 1
Continued

Rapid Alerts													
Week	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**Total**	**%**
Topics													
Environment	6	5	6	4	7	4	5	4	2	4	2	**49**	2.8
Communication	2	5	4	10	3	4	7	5	4	12	6	**62**	3.6
Diagnosis	9	13	5	16	11	14	19	18	5	12	11	**133**	7.7
Epidemiology	31	38	27	31	18	17	15	10	13	13	7	**220**	12.7
Infection control	12	22	30	42	33	37	24	30	26	27	24	**307**	17.7
Pathology and Clinic	3	15	10	10	2	17	7	7	16	11	11	**109**	6.3
Preparedness	18	23	14	7	6	17	12	12	16	8	12	**145**	8.4
Mental Health	3	4	1	2	1	3	3	5	2	1	2	**27**	1.6
Veterinary Public Health	3	2	6	2	2	4	3	7	3	2	2	**36**	2.1
Support Technology	7	15	17	24	17	7	11	2	9	9	14	**132**	7.6
Telemedicine	0	2	0	0	1	0	0	0	0	2	0	**5**	0.3
Drugs and therapy	8	8	25	19	17	11	7	6	3	6	18	**128**	7.4
Immunology	5	12	9	14	17	14	7	11	11	19	14	**133**	7.7
Biocides	1	0	0	0	0	0	0	0	0	0	0	**1**	0.1
Bioethics	0	0	1	0	0	0	0	0	0	0	0	**1**	0.1
Causes of death	3	6	12	7	12	12	8	5	8	6	14	**93**	5.4
Economics	0	1	3	3	2	3	1	1	0	0	1	**15**	0.9
Training	0	2	0	1	0	0	1	0	2	1	0	**7**	0.4
Genomics	3	8	16	21	8	16	14	14	9	1	4	**114**	6.6
Rare diseases	0	0	0	0	0	0	0	0	0	0	0	**0**	0.0
Traslational research	0	3	9	2	0	0	3	0	0	0	0	**17**	1.0
Total	114	184	195	215	157	180	147	137	129	134	142	**1734**	100

reports of the number of cases and deaths requested a continuous check of any manuscript claiming SEIR models and previsions of the national pandemic curve, and the comparison with data coming from Popular Republic of China, and South Korea, mostly, as countries more impacted by the first wave in the same timeframe. To this respect, also the efficacy of the NPI and the lasting and/or recovery of lockdown periods was attentioned. Other less frequent issues in the focus were embedded in the Preparedness and Supporting Technology categories, i.e., the availability of beds in COVID-19 units in hospitals and ICU, the best technologies available for contact tracing and their impact on the General Data Protection Regulation (GDPR). The publication of the first issue of the COVID Contents requested about three weeks, because the different target of the readers – Health Workers –, the delivery in open access, and the need to train the collaborators towards contribution in line with the editorial aim. The challenge was to explain in a plain and immediate way the relevance of a selected peer reviewed paper for the routine experience in fighting against the pandemic. Owing to the above, the manuscripts talking about the pathology, symptoms associated to the disease progressions due to the citokines storm, the multi-organ damage due to an induced micro-coagulopaty, up to the Kawasaki disease and Multi Inflammatory Syndrome in Children were the most represented (20%) (*Table 1*). Following, the repurposing of already registered drugs, the potential use of plasmatherapy and monoclonal antibodies, and the vaccines pipelines in place accounted for 11% + 4.7%. The support to the clinical diagnosis accounted for the 11% of the selected papers: the use of artificial intelligence for the examination of CT findings in the lung, a machine learning approach to rank the evolution of the disease based on blood and immunological parameters of the patient (the so called "coronascore"), as well longitudinal studies about the genomic identification of the COVID-19 by RT-PCRs, and the sero-conversion. Last but not least, in term of preparedness, the ability to cope with the induced mental stress in health care workers, pregnancy, jailed persons, refugees, and all the other fragile groups/communities. The level of interest from Health professional and public has been monitored through, highlighting a very good consensus of the initiative among ISS and NHS readers. The peaks of the COVID Contents access following the weekly ISS President's webinars addressed to NHS operators (*Figure 3*) indicate the effectiveness in reaching such target audience, even if a traceability of the access was hampered by data protection rules.

Finally two additional aspects emerged during this

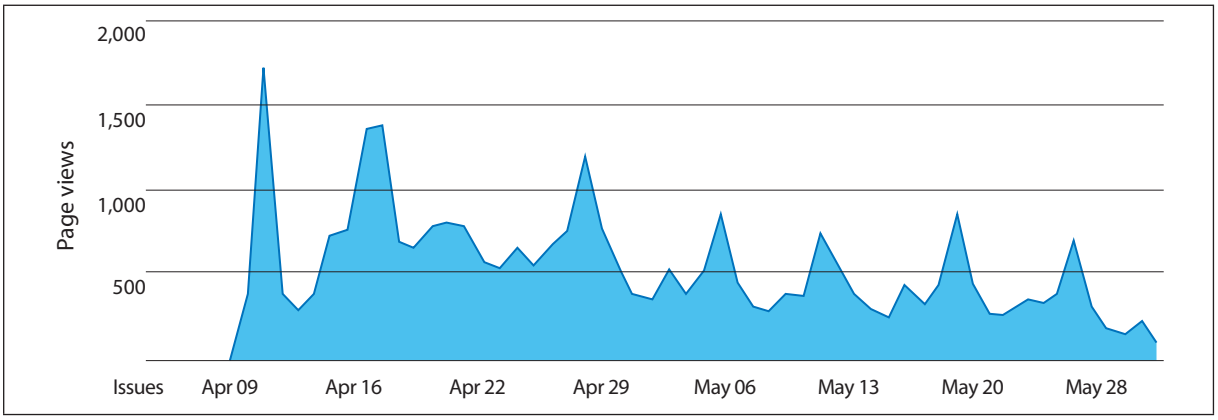

Figure 2
Trend of the 30,723 access for CC download from ISS web site for the considered timeframe.

WG activity: a) the new culture of open access literature; and b) the women role in the COVID-19 pandemic. The COVID-19 open access approach to medical literature is a unique opportunity to raise awareness among researchers and stakeholders about the importance of open science for human health. Demanding initiatives are emerging, especially in developing countries, addressed to sharing of post-prints at individual, group and multi stakeholder partnership level, but to make this plan effective, a more widespread culture of cooperation is fundamental. As the women role in COVID-19 pandemic is concerned, our limited experience shows that women represent the most responsive percentage to the questionnaire, and the most supporting contributions to the COVID Contents activity. Finally, literature reports that female-led countries acted quickly, implementing measures of lockdown early on as recommended by national health experts. Women are more likely to take up positions of leadership in societies that value equity, nurturing, solidarity, and collaboration, which are usually associated with healthier communities, more resilient to external shocks.

To conclude, while the pre-prints screening by is still in place, the COVID Contents experience ended on May 28. This decision was taken because of the increasing availability of systematic reviews and metanalysis about first evidences, accounting for the new "phase 2" scenario, mostly addressed to post lock-down policies, quite far from the pressures of emergencies determined by the phase 1 overwhelming of the Health Care Services in Northern Italy. The interdisciplinary activity described in this paper proved that quick sharing of the scientific knowledge with health workers during the pandemic can be eligible among readiness tasks for the future pandemic challenges. Furthermore, such information sharing could represent a benchmarch for effective communication among first responders to natural and human-made large-scale catastrophes and can be included among the necessary efforts to achieve a higher degree of effectiveness in synergy with environment and technology involved to support first responders operations.

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Screening for celiac disease among the personnel in active service of an Italian Armed Force

Mariateresa Panici[1], Olimpia Vincentini[2], Sara Ciardi[1], Italo De Vitis[3], Serafino Ricci[4], Elena Bartoccioni[1] and Marco Silano[2]

[1]*Comando Generale dell'Arma dei Carabinieri, Servizio Sanitario, Rome, Italy*
[2]*Dipartimento di Sicurezza Alimentare, Nutrizione e Sanità Pubblica Veterinaria, Istituto Superiore di Sanità, Rome, Italy*
[3]*Unità Operativa Complessa di Medicina Interna e Gastroenterologia 2, Fondazione Policlinico Gemelli - Università Cattolica del Sacro Cuore, Rome, Italy*
[4]*Dipartimento di Scienze Anatomiche, Istologiche, Medico Legali e dell'Apparato Locomotore, Sapienza Università di Roma, Rome, Italy*

Abstract

Introduction and objective. Celiac disease (CD) affects the 1% of the general population worldwide. Because of its clinical variability, roughly the 70% of CD patients are not correctly diagnosed and not adequately treated. Active military personnel represent an interesting cohort for a CD screening. Upon the enrollment in the Armed Forces, a complete health check is carried out to exclude any diseases. Aim of the present work is to assess the CD prevalence among the personnel of Carabinieri Corps, an Italian armed force, through a serological screening.

Results and discussion. Out of 291 militaries (281 M, 10 F age range: 18.2-61.5) enrolled, 2 resulted affected by CD (prevalence: 0.7%); 1 to have high serological anti-TG and EMA level without duodenal mucosal lesions and 1 to have high serological anti-TG, but not EMA.

Conclusion. These results show that the CD prevalence among a cohort of Italian militaries is similar to that of the general population.

Key words
- celiac disease
- screening
- military personnel
- gluten-free diet

INTRODUCTION

Celiac disease (CD) is a permanent inflammatory enteropathy, triggered in genetically predisposed individuals, by dietary gluten. Gluten is the alcohol protein fraction of some cereals, such as wheat, barley and rye. CD is the most frequent food intolerance worldwide, with a globally estimated prevalence of 1% [1].

CD is usually defined as a clinical chameleon. In fact, this condition might show up with a wide range of signs and symptoms, involving different organs and systems: anemia, hypertransaminasemia, oral aftosis, recurrent miscarriages, osteoporosis, and chronic fatigue are just some of these. In addition, the CD-associated symptoms can range for very mild to severe [1]. These forms of CD are diagnosed casually during a screening program in the healthy population or among the first-grade relatives of CD patients, that are known to have a 10-fold risk to develop these conditions, respect to the general population [2]. Because of its clinical variability, CD is very under-diagnosed. The data from the Italian Ministry of Health report that in our Country roughly 200,000 patients are diagnosed with CD, out of 600,000 estimated to be affected. Therefore, the 70% of CD patients are not diagnosed and consequently are consuming gluten in their diet [3]. The long-lasting exposure to dietary gluten maintains the symptoms and signs related to CD and, most of all, increases the risk to develop the life-treating complications of CD, such as intestinal adeno-carcinoma and T-cell lymphoma [4].

At the moment, the only effective treatment for CD is a strict a life-long withdrawal of gluten from the diet. A gluten-free diet (GFD) determines the remission of the CD-related symptoms and histological lesions in the duodenal mucosa and prevents the onset of the neoplastic complications [1].

Military personnel represent an interesting cohort for a screening of CD prevalence. At the moment of the enrollment in the Italian Armed Forces, a complete health check is carried out to exclude any diseases, including CD.

Address for correspondence: Marco Silano, Dipartimento Sicurezza Alimentare, Nutrizione e Sanità Pubblica Veterinaria, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: marco.silano@iss.it.

Several epidemiological studies on CD have been performed among the military personnel, in active service or retired. A first paper, in 1999, described retrospectively, the clinical features of 458 individuals, dismissed with the diagnosis of CD from the US military hospitals in the period 1986-1995 [5]. In 2011, Langreden *et al.* reported the risk of developing a cancer in a cohort of 4,5 millions of US Veterans. Although this study did not investigate the CD prevalence in the cohort, it concluded that CD is a risk factor for intestinal and esophagus cancer [6]. More recently, a case-control analysis including 13,7 millions of US militaries in active service reported an increasing prevalence of CD over the years, ranging from 1.3/100,000 in 1999 to 6.5/100,000 in 2008 [7]. While it is out of doubt that the prevalence of CD is raising worldwide, this paper is likely to over-estimate the dimension of CD prevalence. It did not take in account several confounding factors, such as the ascertainment bias and the different access to health services that the US militaries have in the different Region of service [8].

It is clear that, despite the body of evidence available on the CD epidemiology among military personnel, data on the real prevalence of CD lack.

So, the aim of the present work is to assess the CD prevalence among the personnel of Carabinieri Corps, an Italian armed force, through a serological mass-screening program.

MATERIALS AND METHODS

The study has been approved by the Ethical Committee of the Istituto Superiore di Sanità (protocol n. 568/16) and the diagnosis of CD is made according to the National Guidelines of the Italian Ministry of Health – revision 2015 [9]. All the Carabinieri admitted in the period February 2017-August 2018 to the Carabinieri Health Service (Infermeria Presidiaria della Legione Carabinieri Lazio) in Rome, Italy, were asked to enroll in the study. After signing the informed consent, a 5 ml blood sample was withdrawn form a peripheral vein and collected in a vacutainer blood-tube containing a serum separating gel, centrifuged at 1900 rpm for 15 minutes without brake to separate plasma from cells. The plasma was tested for the anti-transglutaminase (tG) IgA levels by a commercially available ELISA kit (Eurospital, Trieste, Italy; normal level <9 UI/ml) at the laboratory of the Unit of Human Nutrition and Health of Istituto Superiore di Sanità. Those patients resulted to have an anti-tG plasma titre above the positivity cut-off, are investigated for plasma EMA and eventually, undergo to duodenal biopsy. These two examinations were performed at the Department of Gastroenterology, Columbus Hospital – Catholic University, Rome.

RESULTS

In the study, 291 militaries (281 M, 10 F; age range: 18.2-61.5) were enrolled. Out of them, 3 patients resulted to have the anti-TG plasma titre above the cut-off (*Table 1*).

Patient 1 was a 39.8-years old, male military, that at the moment of the enrollment in the study did not report any symptom or disease. When interviewed more in depth after the result of the anti-TG determination, he reported to suffer from frequent oral aphthosis and mild dyspepsia. After the CD diagnosis, he was put on a GFD with a complete remission of the above-mentioned symptomatology.

Patient 2 resulted positive to both anti-TG and EMA, but he did not show the diagnostic alteration of celiac duodenal mucosa. He was diagnosed with potential CD and according with the guidelines, he is still consuming gluten in the diet and undergoes periodically to clinical and serological examination.

Patient 3 showed an anti-TG titre slightly positive. He did not perform the duodenal biopsy since the EMA negativity and the anamnestic record that he was affected by an autoimmune chronic kidney disease. So, the serum presence of the anti-TG is likely to be related to the concomitant auto-immune nephropathy.

Finally, we included in the series a military already diagnosed with CD, treated with a GFD. His serum anti-TG levels resulted below the cut-off, showing a clinical remission of the condition.

The overall prevalence of overt CD in our cohort resulted to be 0.7% (2/291).

DISCUSSION

The main result of this study is that the prevalence of CD among the military personnel in service is quite similar to that of the general population [10]. This result is surprising, at the light of the fact that all the militaries undergo a complete health check-up upon the enrollment, that excludes, among the other conditions, the present of overt CD and CD autoimmunity. So, the 2 celiac militaries developed the CD after the enrolment in the Arma of Carabinieri, that occurred when they were 19 and 21 years old, respectively.

Table 1
Clinical features of patients with overt celiac disease (CD) or CD-autoimmunity

Patient (n)	Sex	Age (years/months)	anti-tG (UI/ml)	EMA	Mucosal histology (Marsh classification)
1	M	39.8	53	+++	IIIa
2	M	45.4	50	+	I
3	M	41.9	20	-	Not performed
4*	M	45.1	<9	-	Not performed

*Patient diagnosed with CD out of this study, already on a gluten free diet at the moment of enrolment in the study.

Our study also confirms that CD may present with very mild signs and symptoms, that very often lead to misdiagnosis CD. The Patient 1 in our series did not report any symptoms or signs when interviewed before the anti-TG determination. Then, when checked with the patient more accurately his medical history after the positive result of the anti-TG, he reported some mild but frequent gastro-intestinal symptoms. When these symptoms remitted after 6 months on a GFD, the patient recognized how much these affected his well-being.

It is still controversial whether the most suitable diagnostic strategy for CD is the mass screening or the case finding [11]. The case finding as it is performed at the moment, misses most of the cases of overt CD [12], on the other hand mass screening is expensive, lack of a validated non-invasive blood test and we do not still have ultimate evidences to set an age which CD certainly develops within. Our study shows that the best strategy to make the hidden part of the celiac iceberg emerged is a way between the mass screening and the case finding and it might be a screening in the high-risk group. High-risk groups are to be identified on the basis of a careful evaluation of clinical symptoms and signs, associated autoimmune diseases, consanguinity for CD and CD-autoimmunity.

We diagnosed a military with potential CD. This form of CD is characterized by the serological positivity for EMA and/or anti-TG in absence of significant mucosal lesions (Marsh 0 and 1, according to the Marsh-Oberuhuber classification). At the current stage of the knowledge, this form of CD is more frequent in children and quite rare in adults. The current guidelines suggest keeping these individuals on a free diet and follow them periodically, since most of the cases solves spontaneously, with the disappearance of the serum CD-specific antibodies [13].

Individuals with CD properly treated with a strict and long-life GFD has a normal quality of life and physical performances [14]. As proof of the fact, a treated CD individual can serve unconditionally as military in Arma the Carabinieri as well as in the other Italian Armed Forces. The Directive IGESAN/PS-15 of the General Inspectorate of the Military Health Service – Italian Armed Forces dated in 2015, verbatim states that: *"for those diagnosed with CD after the enrolment into the Armed Force, this diagnosis does not imply any leave provision"*. This normative offers a high protection for celiac militaries, that can receive a diagnosis of CD and the life-saving treatment, without being forced to leave their job and their position in the Armed Force. So, further and larger screening program for CD could be performed among the Armed Force personnel to increase the number of CD diagnosis.

The CD prevalence found in this study is similar to that found in previous screening program in adults, in Europe and worldwide. Mustalahti *et al.* have reported a CD prevalence among adults ranging from 0.3% in German, 0.7% in Italy to 2.4% in Finland [15]. An anti-TG IgA-based screening performed in Wyoming, United States, has described a prevalence of overt CD of 0.80% among healthy individuals [16]. In Brazil, the serum anti-TG IgA have been found in 1.5% of blood donors and the 66.7% of them have presented also the mucosal histological lesions, pathognomonic of CD [17]. Finally, in Australia, the screening for CD in blood donors has brought to the CD diagnosis the 0.96% of the screened population [18].

This study has two limitations. The first is the M/F ratio of the cohort, that is very unbalanced towards the male sex. The M/F ratio in this study reflects that of the militaries of the Arma dei Carabinieri, where only the 5% are females. On the contrary, CD is a condition much more frequent in women than men with a ratio 2.5/1. Nevertheless, we have found in our population a CD prevalence similar to that of general population, where the women are predominant [3]. This finding might suggest that the higher CD prevalence among women respect to the men should be due to some referral bias, such as the more severe symptoms at onset of the disease in the women.

The other limitation consists in the relatively small number of militaries included in our series. The main problem in a mass screening for CD in an adult population is to make acceptable to people that do not feel complaining any health problem, the possibility that they have a condition, whose treatment will limit their dietary choices and consequently, their social life.

In conclusion, our study reports that the prevalence of CD among militaries in service is equivalent to that in the general population. This finding supports the hypothesis that it is worth identifying the misdiagnosed CD cases among the Armed Forces, with a program based firstly on a careful clinical identification of mild symptoms, signs, associated diseases and consanguinity and then on serological testing for at risk individuals.

Authors' contribution

MP conceived the experimental design, enrolled the patients and drafted of the paper. OV performed the ELISA kit and drafted the paper. SC and SR maintained the study database and drafted the paper. IDV performed the clinical analysis in patients found positive at the screening. EB conceived the experimental design, enrolled the patients and drafted the paper. MS supervised the study, gave critical advices and drafted the study. All the Authors contributed to the final version of the paper and approved it.

Conflict of interest statement

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A far-reaching Regulation for the Italian National Registry of Implantable Prostheses: a possible model for other health registries

Virgilia Toccaceli[1] and Marina Torre[2]

[1]*Centro di Riferimento per le Scienze Comportamentali e la Salute Mentale, Istituto Superiore di Sanità, Rome, Italy*
[2]*Segreteria Scientifica della Presidenza, Istituto Superiore di Sanità, Rome, Italy*

Abstract
Medical device registries are major tools for public health, able to provide early warning systems for increasing the patient safety. We are now at the forefront of a final legal and procedural step to design the Regulation of the Italian Implantable Prostheses Registry (RIPI) and to make data collection mandatory. This can ensure prostheses traceability, recall of patients and fuel biomedical and epidemiological research. Data completeness will be greatly improved when the Regulation is issued. At that time, rules for accessing data and subjects/entities allowed to access the Registry will be clearly defined. Therefore, the Regulation content is crucial, with no chance to fail in its design. The thorough expertise gained at the Italian National Institute of Health (Istituto Superiore di Sanità) by the Italian Arthroplasty Registry in terms of scientific, technical and privacy management may represent a prototypical model for other registries. Our aim is to identify a few key issues to shape a far-reaching Regulation that might permit the flexible and dynamic functioning of RIPI providing suggestions for other registries at national and international level.

Key words
- registries
- government regulation
- medical device legislation
- prostheses and implants
- patient safety

INTRODUCTION

The important role of the medical registries has been widely recognized from a public health perspective [1]. Medical device registries are major tools for decision-makers and managers as they potentially provide an early warning system for identifying patients at risk, shortening the time before health hazards can be widely perceived. Furthermore, they are recognised as useful tools for collecting post-market surveillance data and, in case of implanted devices, they may allow to understand if a complication is related to the surgical procedure or to the implant type [2, 3]. Therefore, they allow to improve the quality of medical treatments and procedures, as devices failure can be rapidly detected, and potentially dangerous implants averted [4]. Such registries are also able to provide data for research, to test epidemiological and biomedical hypotheses and to avoid useless and costly surgical procedures for national health services. All these roles are well recognised in the European Medical Device Regulation issued in 2017 (*Table 1*, n. 9).

In Italy, as well internationally, the number of implants is increasing together with the potential revision procedures, therefore, the limitation of the number of revisions is a prior objective to be pursued. To provide an example, if only the number of revisions of hip and knee arthroplasties in Italy might be reduced even by 1% (in 2019, 15,043 hip and knee revisions were performed), the total cost saving would be more than 1.8 million euros per year, taking into account the only surgical DRGs. There is no doubt that thanks to a good working registry, the burden of revision procedures can decrease dramatically [5]. More importantly, to achieve this result and have the best impact on public health, an efficient registry needs to be based on a standardized high-quality data collection [3, 6]. In this regard, we have now a unique opportunity to make a final step from a legal and procedural point of view towards the best realization of the Italian Implantable Prostheses Registry (RIPI). The aim of this paper is to identify a few key issues to shape a far-reaching Regulation for the RIPI dynamic functioning at national and international

Address for correspondence: Marina Torre, Segreteria Scientifica della Presidenza, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: marina.torre@iss.it.

level that might serve as a reference for the implementation of other registries in Italy as well as in other European countries with similar governing structures.

THE NATIONAL REGISTRY OF IMPLANTABLE PROSTHESES IN ITALY: THE STATE OF THE ART

RIPI is in the provision of a Governmental Decree issued in 2017 (hereinafter "DPCM") (*Table 1*, n. 6) that addresses 38 national surveillance systems and 28 national health registries. Most of them are operating on the basis of already existing legal norms or research initiatives of the Italian National Institute of Health (Istituto Superiore di Sanità, hereinafter ISS) jointly with the Ministry of Health [7]. Actually, the DPCM lays the basis for an unprecedented functional framework for these registries and surveillance systems, taking into account the European personal data protection regulation (EU GDPR/2016) (*Table 1*, n. 2] and domestic privacy provisions (*Table 1*, n. 1, 3).

RIPI is conceived as an umbrella structure of specific registries of high risk- and high health-impact implantable prostheses. Following specific agreements between the Ministry of Health and the ISS, a few studies started at the beginning of 2019 [8] to empower the already existing registry of joint prostheses, the Italian Arthroplasty Registry (RIAP), and to launch the new registries of spinal implants, of pacemakers and defibrillators, and of heart valves.

ISS can provide an effective contribution to the achievement of this goal, thanks to the multi-faceted expertise, practice and procedures already operating at national level for RIAP, whose effectiveness has rapidly improved over the past decade [9]. Accordingly, the pioneering activities of RIAP will be able to speed up the implementation of the forthcoming RIPI, structured as a federation of regional registries under the coordination of ISS. In fact, RIAP has already established a strong and successful collaboration with several Italian Regions that were able to develop or improve their own data collection, launch registries at regional level and, in some cases, elaborate specific safety indicators (e.g. prosthesis revision rate). Moreover, RIPI will adopt the same architecture of data collection process of RIAP, based on electronic Hospital Discharge Records (e-HDR) routinely collected in all Italian hospitals. Associated with a minimum dataset of additional variables (MDS), these provide crucial data that make it possible to perform outcome studies, assess device safety and assure its traceability [10]. Therefore, the conceptual and organizational heritage of RIAP will be transferred into a comprehensive system of several registries (one for each implantable prosthesis). It will involve the following actors (*Figure 1*):

- hospitals that record MDS in the Platform;
- Regional Centres that access the Platform, link MDS to HDR and send the linked data to RIPI Surgical procedures database;
- manufacturers that upload in the RIPI Medical Device Database all the information needed for device identification and characterisation.

Currently, this model seems to be the most cost-effective way to easily integrate the registry data collection into the regional/national health information systems. Indeed, it allows to re-use the already existing information technology infrastructure and, therefore, requires only minimal investments by both regional and national governments. In the meantime, it makes it possible to assure patient and implanted device traceability. Finally, it is designed to be easily integrated, in the near future, into the data flows of the National Health Service (SSN) and to allow for benchmarking with data collected by other similar registries in Europe and for interconnections with international databases, to associate more detailed technical information to each device.

THE IMPACT OF A STREAMLINED AND EFFECTIVE REGULATION

The establishment of a registry has to cope with administrative and practical challenges, in particular in Italy. In other international contexts, such initiatives have followed simpler paths [11-13]. For what concerns RIPI, the final step of a legal production, that has lasted 14 years (*Table 1*), is the establishment of an operating Regulation (hereinafter, "Regulation"). Focussing on the impact of a clear, comprehensive and prompt Regulation, a few key issues are at stake. The first is the *completeness* of data. Everyone knows there is a continuous threat to completeness when a registry is based exclusively on patients' consent, as it currently is for many Italian registries and surveillances according to the provision of personal data protection legislation (*Table 1*, n. 1, 2). Completeness, therefore, will be greatly favoured by the issuing of the Regulation, because its coming into force will make the individuals' consent not necessary any longer. Consequently, we can foresee that the lack of data might be eventually overcome in the medium term. The second key question is "governmental support". Following the positive experience of the German Registry [14], the participation of all the hospitals might be achieved through a joint effort between the central government and other stakeholders including, as in our setting, the regional governments. Finally, following the example of well developed registries in other European countries [4, 12] the Regulation should consider the adoption of a unique "national patient identifier" (i.e. an alphanumerical code able to trace the patient, without infringing the privacy rules, throughout the health records collected by SSN). In the meantime, to achieve this purpose the pseudonymization procedures designed by ISS experts and successfully applied to RIAP, will be extended to RIPI.

In Italy, we are now on the threshold of the final important step to design the regulations for all the epidemiological surveillances and registries listed in the DPCM. This is, actually, the most important provision currently pending. In this enterprise, it would be advisable to involve all the stakeholders: patients' representatives, policy makers, health managers, clinicians, researchers, and manufacturers when necessary, being all of them a real asset for this purpose.

As for RIPI, the Regulation approval will mainly give rules for accessing the data, establish the subjects/entities allowed to access them, as well as the data that can

Table 1
Summary of the legal provisions impacting on the establishment and regulation of the Italian Implantable Prostheses Registry

Relevant to	n.	Provision	Title	Relevant issues
Personal data protection	1	Italian Law Decree 30 June 2003, n. 196	*Codice in materia di protezione dei dati personali. GU, Serie Generale n. 174 del 29 luglio 2003 - Suppl. Ord. n. 123*	Regulation (EU) 2016/679 (GDPR), together with the provisions of the Italian Legislative Decree 196/2003 (as modified by the Legislative Decree 101/2018), defines the framework for personal data protection procedures
	2	Regulation (UE) 2016/679 of the European Parliament and of the Council, 27 April 2016	*Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation, GDPR). Official Journal of the European Union L119/1, 4.5.2016*	
	3	Italian Law Decree 10 August 2018, n. 101	*Disposizioni per l'adeguamento della normativa nazionale alle disposizioni del regolamento (UE) 2016/679 del Parlamento europeo e del Consiglio, del 27 aprile 2016, relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati e che abroga la direttiva 95/46/CE (regolamento generale sulla protezione dei dati). GU Serie Generale n. 205 del 4 settembre 2018*	
Registries establishment and implementation	4	Italian Law 27 December 2006, n. 296	*Disposizioni per la formazione del bilancio annuale e pluriennale dello Stato (legge finanziaria 2007). GU Serie Generale n. 299 del 27 dicembre 2006 - Suppl. Ord. n. 244*	It foresees funding to establish disease registries requiring the use of medical devices (Paragraph 825)
	5	Italian Law Decree 18 October 2012, n. 179 Converted with amendments by the Law 17 December 2012, n. 221	*Ulteriori misure urgenti per la crescita del Paese. GU Serie Generale n. 245 del 19 ottobre 2012 -Suppl. Ord. n. 194/L* *GU Serie Generale n. 294 del 18 dicembre 2012 - Suppl. Ord. n. 208*	It establishes surveillance and registry systems, among them the registries of prosthetic implants (Art. 12 paragraphs 10-14)
	6	Italian Decree of the President of the Council of the Ministers (DPCM), 3 March 2017	*Identificazione dei sistemi di sorveglianza e dei registri di mortalità, di tumori e di altre patologie. GU Serie Generale n. 109 del 12 maggio 2017*	Following the provisions of Law 221/2012, this Decree addresses 38 surveillance systems and 28 registries. It defines the national and regional institutions in charge for their management and maintenance and states that their final operativity will be achieved when their own Regulations are approved
	7	Italian Law 30 December 2018, n. 145	*Bilancio di previsione dello Stato per l'anno finanziario 2019 e bilancio pluriennale per il triennio 2019-2021. GU Serie Generale n. 302 del 31 dicembre 2018 - Suppl. Ord. n. 62/L*	Data collection is mandatory for regions and health operators. "Implantable medical devices" registries are introduced for the first time besides the "prosthetic implants" registries (Paragraph 558 modifies paragraph 11 of Law 221/2012 and introduces paragraph 11-bis)
	8	Italian Law 22 March 2019, n. 29	*Istituzione e disciplina della Rete nazionale dei registri dei tumori e dei sistemi di sorveglianza e del referto epidemiologico per il controllo sanitario della popolazione. GU Serie Generale n. 81 del 5 aprile 2019*	The transmission of data to the national registries by the regions is a prerequisite for the distribution of funds to the regional health services (Art. 5)
EU Regulation for Medical devices	9	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017	*Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. Official Journal of the European Union L117/1, 5.5.2017*	This Regulation is centered on the improvement of patient safety. In particular, it recognizes the medical device registries as important tools to achieve this aim (Art. 108 Device registers and databanks)

be accessed. Moreover, it will allow the registry to work as a mandatory system of national and regional registries. From the juridical perspective, in fact, there will be an important shift from individual patient's consent to a mandatory collection of data for the following specific recognised purposes: traceability of the implanted prostheses, recall of patients by the competent authority when a high number of adverse events are reported, and epidemiological and biomedical research. It is important to underline that, according to personal data

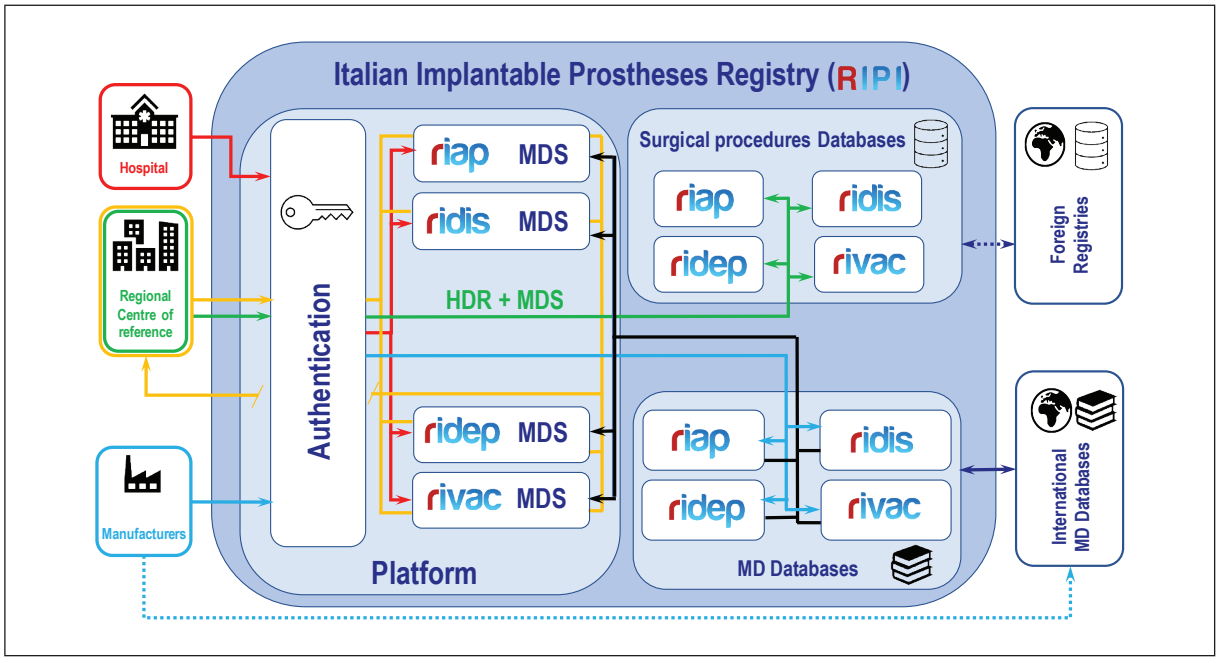

Figure 1
Italian National Registry of Implantable Prostheses (RIPI): data collection flow.
MDS: Minimum Data Set; HDR: Hospital Discharge Record; RIPI: Registro Italiano delle Protesi Impiantabili; RIAP: Registro Italiano ArtroProtesi (Italian Arthroplasty Registry); RIDIS: Registro Italiano Dispositivi Impiantabili per Chirurgia Spinale (Italian Spinal Implants Registry); RIDEP: Registro Italiano Defibrillatori e Pacemaker (Italian Implantable Cardioverter-Defibrillator and Pacemaker Registry); RIVAC: Registro Italiano Valvole Cardiache (Italian Heart Valves Registry); MD: Medical Device.

protection legislation, information regarding RIPI procedures and aims shall be always given to the patients, in spite of the fact that their informed consent will be no longer necessary.

Actually, there is still a long way to go before the Regulation is officially adopted. In fact, it will require a proposal by the Ministry of Health, an agreement by the Permanent Conference of the Regions and Autonomous Provinces, the approval of the National Authority for Personal Data Treatment and, eventually, of the Council of State, after a deliberation of the Council of Ministers. Lastly, it will be adopted by means of a Decree of the President of the Italian Republic.

TEN RECOMMENDATIONS FOR BETTER FUNCTIONING OF A HEALTH REGISTRY

Registries and surveillance systems at national and European level are based on directives and regulations common to all the Member States. In this framework, the thorough experience in RIAP scientific, technical and privacy issues allowed to identify the following 10 key points that a Registry Regulation, particularly for medical devices, might consider:

1. To define the specific aims and objectives of the Registry, at national and regional levels [3].
2. To settle the whole Regulation on general principles that can maintain their universal validity over time and over different scenarios. For example, prostheses are subject to rapid technical and technological development. Likewise, the Regulation should not restrict the Registry's functionality when new tasks emerge from epidemiological and public health perspectives. There might be the need for international benchmarking requiring the availability of individual records or for eventual inclusion of other "items"[3].
3. To introduce specific terms clearly addressing the data needed for the medical devices traceability (i.e. Unique Device Identifier – UDI; manufacturer; product catalogue code; serial number; lot) and to provide a set of key words to which the Regulation will make reference. These key words will be used to describe the Registry's objects, tools and pathways. They will prevent anyone, among different stakeholders, from misinterpreting and making ambiguous the meaning of the rules. For example: i) the terms addressing the subjects/entities in charge of the data collection and of the data flow implementation like "National Registry" and "Regional Registry"; ii) the specific objects to be dealt with by the specific Registry, for example "implantable prosthesis" which is different from "implantable device"; iii) the terms related to the main purpose of the Registry.
4. To establish a Registry's governing body, like a scientific board. Its composition, in terms of expertise and tasks, should be clearly addressed. The role of this board is to take necessary measures for updating the Registry, easily placeable within the framework provided by the Regulation. The Regulation, in fact, to be fully applied, has to rely on the judgment of this specific governing body whose choices are of highly technical and scientific value and may assure a dynamic and evolutionary functioning of the Registry in step with the times [3].

5. To define the type of data to be collected and processed. Data should not be restricted or fixed in a non-reversible way. It is advisable to make a list of data which is as much as possible all-encompassing (e.g. the data collected by PROMs, i.e. questionnaires measuring the quality of life of patients, should be included). The list can be updated on the basis of the indications given by the Scientific Board [3].
6. To adopt updates, when needed, on different issues like "sources" and "type" of data and "subjects admitted" to access the data, following the Scientific Board advice.
7. To delimit the procedural steps for accessing the data and to outline access in relation to the hierarchical levels established for specific subjects. This means to discriminate "individual pseudonymized data", subjected to restricted access, from "aggregated data" that is possible to share upon request by each recognized subject, and, finally, from data defined as "open data".
8. To update the list of Institutions, at national and international level, that can be included as partners for data sharing and/or data analyses, with the clear definition of each data controllers' roles and of the specific data to be treated, under the general provision of the Regulation.
9. To outline the specific tasks that national and regional data have to accomplish and which data they govern in their specific context. According to GDPR, in fact, the data controller is "the legal person, public authority, agency or other body which, alone or jointly with others, determines the purposes and means of the processing of personal data".
10. To clearly address the deontological rules that medical, biomedical and epidemiological research activities – to be performed on data realeased by the Registry – have to refer to, on the basis of specific objectives and protocols and according to national rules for data protection, when available.

THE CRUCIAL GOAL: TO IMPROVE PATIENT SAFETY

According to the European perspective (EU Regulation 2017/745) (*Table 1*, n. 9], in the future RIPI should be encompassed within the widest Registry of the "Implantable medical devices" – for the first time mentioned in Italy by the law 145/2018 (*Table 1*, n. 7) – expanding, indeed, the monitoring to all kinds of implanted devices. Therefore, the work to be done immediately, for a prompt issuing of an effective Regulation, will perfectly fit in the new defined legal European framework which will come into force in a very short time (the initial May 26th 2020 deadline was postponed to May 26th 2021, due to the COVID-19 pandemic challenge). As a matter of fact, Europe underlines the importance of establishing these registries as their role is central to improve patient safety. Hence, we have to take into account this urge that commits several important stakeholders as well, like Competent Authorities on Medical Devices, implantable devices Manufacturers and Notified Bodies. The boost given by the EU is consistent and demands smooth functioning registries as strategic tools for further post-marketing surveillance as well as for implantable devices safety monitoring improvements [15]. As a matter of fact, medical device registries should be considered a structured piece of the whole national health service that might be empowered when different data collection flows are interconnected.

The recent, unprecedented COVID-19 pandemic has strongly underlined that Public Health needs rapid interventions, high quality data, as well as the most efficient working of networks operating for health-related activities and data flows: Health Registries - and RIPI can be a good reference - are, in fact, valuable health networks for epidemiological monitoring. To speed up RIPI implementation, it is unavoidable to put in practice the surveillance on prostheses and provide sound data to epidemiological monitoring; it will then be possible to translate the new knowledge, continuously gathered, into effective public health actions. It is a virtuous circle for which the legal norms are to be a driving force not a hindrance. If there is indeed room for maneuver in defining the rules, it is necessary to proceed rapidly, and adopt them. We have to reflect on the fact that the first attempt to rule health registries in Italy was made in 2006, a long and complex path requiring more than 14 years. On the contrary, in 2019, the German government, on the basis of huge experience of the National Orthopaedic Registry [14], in less than six months proposed and approved the law establishing and ruling the German Registry of Implantable Devices (Implantateregister Deutschland) as mandatory [16]. As stated by Steven Graves, Director of the Australian Joint Replacement Registry: «Change occurs most effectively when all relevant stakeholders have ownership of data. This is why it is so important that Italy has its own registry. Italian data is necessary to improve Italian outcomes» [17]. The time has come for Italy to make fully operational its own national registry to further improve the safety of implanted patients. Hopefully, the ten key points of the Italian experience we describe might be a model for the establishment of national registries in those countries with similar governing structures.

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Authors' contributions

VT pictured the study conception and drafted the

manuscript. MT contributed to the study conception, provided data, revised the manuscript for important intellectual content.

Conflict of interest statement

Virgilia Toccaceli is a member of the Italian Arthroplasty Registry (RIAP) Steering Committee as the expert of personal data protection. Marina Torre is the Scientific Director of the Italian Arthroplasty Registry (RIAP) and of the Italian Implantable Prostheses Registry (RIPI).

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Attitude of potential biobank donors screened for depression towards disclosure of individual health results

Virgilia Toccaceli, Corrado Fagnani, Antonella Gigantesco, Angelo Picardi and Maria Antonietta Stazi

Centro di Riferimento per le Scienze Comportamentali e la Salute Mentale, Istituto Superiore di Sanità, Rome, Italy

Abstract

Background. Research based on biological material with linked health and clinical data may produce new strategies for disease prevention, diagnosis and treatment. A survey was conducted among individuals previously screened for major depressive disorder (MDD) to explore participants' attitude towards research biobanking.

Methods. The survey used self-report questionnaires about donation for research biobanks, self-perceived health and life satisfaction. Means and percentages were compared across groups by using t test, ANOVA and chi-square test.

Results. Of 416 subjects who underwent the MDD screening, 51 (12.2%) responded to the survey, with the majority of them (42) agreeing to the use of their biological samples only in absence of feedbacks about health or diseases. Agreement towards biobanking was not affected by life satisfaction or self-perceived health.

Conclusions. Our findings show a prevailing preference against health results disclosure among MDD-screened subjects, suggesting a role of personal – particularly psychosocial – factors in research biobanking individuals' contribution.

Key words

- research biobanks
- donors
- individual health results
- depression
- mental health

INTRODUCTION

The importance and value of biobanking in health research has been growing during the last decades mostly due to genetic knowledge advancements and technology innovation. It is undeniable that, until now, biological materials have mostly been collected in the context of specific single scientific studies; however, recent outbreaks such as that of COVID-19, which can take tremendous advantage from appropriate biobanking, pose an urgent challenge to these activities: to increase potential donors trust towards large – rather than single study driven – collections of biomaterials for synergetic biomedical research. Actually, potential donors for both disease oriented and population biobanks, deserve particular attention, being a bit overlooked under the great pressure and major concerns regarding the collaboration of stakeholders such as Academia, research institutions and industry [1].

In the context of mental health, research based on the use of biological material with linked health information and clinical data may produce new strategies for prevention, early detection, accurate diagnoses, and tailored treatments [2]. In particular, among psychiatric disorders, major depressive disorder (MDD) is the most frequent, persistent and debilitating disorder occurring in the general population, with an estimated lifetime prevalence of approximately 12.8% in Europe [3]. Moreover, MDD has major public health implications. In fact, it is the fourth leading cause of worldwide disease burden accounting for 12% of all years lived with disability, and has severe consequences in terms of economic costs [4]. In a high proportion of patients, neither is MDD recognized nor treated adequately [5].

Together with a "moral duty" to participate in research biobanks [6], it is important to highlight the emerging importance of psychosocial wellbeing of potential donors for the success of research biobanks. Psychosocial wellbeing is, in fact, one of the core "welfare interests" at stake in the process of establishing an organized collection of biological samples and associated data for health research. Therefore, coping with psychosocial wellbeing represents a central duty that the biobanking endeavour has to accomplish. In some respects, this "core" interest enlarges the concept of individual's welfare in research upon which the ethical debate has been focusing for a long time [7], placing it in the highest

Address for correspondence: Virgilia Toccaceli, Centro di Riferimento per le Scienze Comportamentali e la Salute Mentale, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: virgilia.toccaceli@iss.it.

ranking of the issues to be addressed by both researchers and Internal Review Boards.

The present study is part of the SET-DEP project (Screening and Enhanced Treatment for DEPression in Primary care, in Rome, Italy) funded by the Italian Ministry of Health [8], whose main objective was to test the feasibility and effectiveness of a program for early detection and treatment of depression in primary care. One secondary objective of the SET-DEP project was the donation and biobanking of saliva from the participants for future research purposes. We report the results obtained with a mail survey that explored, beforehand, the attitude of the SET-DEP participants towards biological material donation for research purposes. In particular, the focus of the survey was on the importance these potential donors attributed to the future disclosure of individual health results in relation to donors' decision about the use of their biomaterials.

MATERIALS AND METHODS

This study aims at exploring the attitude of the SET-DEP participants towards the potential future disclosure of individual health results when participating in research biobanking, with the underlying hypothesis that the agreement towards the use of the biomaterials for research purposes might be influenced by perceived health and/or by life satisfaction of the potential donors.

Study population

Participants were healthy individuals recruited from 13 urban general internal medicine practices, located in central Rome, Italy, from January 2009 to June 2010. They were previously asked to undergo a screening for MDD by means of specific questionnaires. The study inclusion criteria were age 18-65 and absence of psychosis or severe cognitive impairment as clinically determined by the primary care physicians according to anamnesis, prescription medicines, and medical history. The physicians or their assistants informed the eligible participants about the SET-DEP project, its aims and objectives including the collection of saliva for research purposes in a second phase of the project; fliers describing project aim and objectives were available in the waiting room.

Depression screening was performed by administering the Primary Care Screener for Affective Disorders (PC-SAD) [9], which is a 37-item self-administered questionnaire designed to screen for Major Depressive Disorder (MDD) and Dysthymic Disorder (Dys) in primary care. It consists of a 3-item pre-screener, a 26-item Major Depressive Disorder (MDD) section, and an 8-item Dysthymic Disorder section. The pre-screener consists of two depression questions and one dysthymia question, which are part of the screener score, but reduce respondent burden by terminating the questionnaire if all are negative. It has a sophisticated scoring algorithm that confers several advantages, such as the possibility to yield valid results even if many items are left unanswered. Its validity was first tested against other established screening questionnaires in health plan members, primary care outpatients, and psychiatric patients (Rogers et al 2002), and then was tested against a standardised psychiatric interview in dermatological inpatients [10] and in primary care patients [11].

After the screening for MDD, at the same time of the follow-up interviews or shortly later, a cross-sectional survey was launched. Both MDD positive and negative SET-DEP participants were administered a postal questionnaire to investigate preferences and concerns about biological material donation for research purposes.

Measures and questionnaires

The survey was conducted with a form for the collection of socio-demographic information, and with a validated questionnaire on the knowledge, attitude and willingness to donate biological material for research purposes used in previous research by our group [12]. In particular, the present study explored the agreement of respondents on the potential use of their biological samples for research purposes. Participants acceptance was operationalized as different levels of agreement with the following statement: "Would you agree with the potential use of your biological samples for research purposes?" Response statements were: a) "Yes, I would definitely agree"; b) "Yes, but only if results regarding my health or predisposition to diseases will be given to me"; c) "Yes, but only if results regarding my health or predisposition to diseases will not be given to me"; d) "No, I would not agree"; e) "I don't know". Furthermore, self-perceived health was measured on a four-point Likert scale (categories: "Bad", "Neither Bad nor Good", "Good", "Excellent") and the well-known and widely validated "Satisfaction With Life Scale" (SWLS) [13] was administered. Life satisfaction is a subjective, cognitive evaluation of an individual's life as a whole based on the fit between personal goals and achievements [14]. It is an indicator of subjective well-being, one of the main dimensions of mental health.

Statistical analyses

Descriptive analysis was performed by reporting means (with standard deviations) for continuous variables and percentages for categorical variables. To explore the association between variables, means and percentages were compared across groups by using t test or ANOVA and chi-square test respectively, with *alpha* set at 5%.

The Ethics Board of the Istituto Superiore di Sanità approved the SET- DEP project and an informed consent procedure was adopted to conduct the survey.

RESULTS

Out of the 416 SET-DEP participants who underwent the screening for MDD, 402 individuals received the mail questionnaire, and 51 subjects responded (12.2%). Respondents showed a similar distribution by sex, age, marital status and education level compared to the reference SET-DEP cohort, with only a slight over-representation of subjects with a university degree in our sample. The 51 respondents (12 males, 39 females) represented ages 19 to 66 years (mean age 49 years, median age 51 years). More than half were married and about 90% of them had at least a high school diploma. Of all respondents, 21 (41%) screened positive for

MDD (similar positivity rate compared to the reference SET-DEP cohort, 37%), with no difference in the positivity rate between genders [5 out of 12 males (41.67%) and 16 out of 39 females (41.03%) screened positive; chi-square test: p=0.97]. Positive subjects tended to be older (mean age 53 years) than negative ones (mean age 46 years; t test: p=0.06) *(Table 1)*.

As expected, MDD negative subjects reported a better self-perceived health (chi-square test: p=0.013) and a higher level of life satisfaction (t test: p<0.001) compared to positive ones *(Table 2)*.

Seven respondents (14%) declared they had already donated biological material (blood, saliva, urine, or other tissues) for research purposes in other research settings. Noteworthy, the large majority of respondents (42 subjects, >82%) declared they would agree to the potential collection and use of their biological samples for biomedical research purposes only if no feedback results regarding health or predisposition to any diseases would be given to them. This proportion was even higher in negative compared to positive subjects at the screening for MDD (90% *vs* 71% respectively; chi-square test: p=0.025) *(Table 2)*. The percentages of other response categories were negligible ["No, I do not agree" (5.9%), "Yes, but only if results regarding my health or predisposition to diseases will be given to me" (3.9%), "Yes, I definitely agree" (2%), "I don't know" (5.9%)].

Finally, the agreement towards research biobanking was not associated with self-perceived health (chi-square test: p=0.98) or life satisfaction (ANOVA: p=0.82).

Table 1
Socio-demographic characteristics and MDD screening for the study sample

Variables	N (%)	Mean (SD)
Age (years)		48.7 (12.3)
Gender		
Male	12 (23.5)	
Female	39 (76.5)	
Education		
Primary school	0 (0)	
Secondary school	2 (3.9)	
Vocational school	3 (5.9)	
High school	24 (47.1)	
3-year degree	2 (3.9)	
5-year degree	20 (39.2)	
Marital status		
Single	14 (27.4)	
Married or living with a partner	30 (58.8)	
Separated, divorced or widowed	6 (11.8)	
Missing	1 (2.0)	
Screening for depression		Mean age (SD)
Positive	21 (41.2)	52.5* (9.2)
Negative	30 (58.8)	46.1* (13.6)

* p=0.06 (t test)

DISCUSSION

Some lack of knowledge regarding study participants' perspectives and opinions on biobanks is well known among main stakeholders such as scientists, researchers and biobanks' sponsors [15]. It is our opinion that, especially for conditions of high public health relevance such as psychiatric illnesses, this gap has to be promptly filled in order to favour biobanking, and most of all, individuals' aware participation to these activities.

So far, many authors have focused on the effect of "non-welfare" interests on willingness to donate to a biobank [16-18]. It is widely recognized, in fact, that the willingness diminishes when the research scenario raises moral, religious or political concerns. Nevertheless, it is worth considering that other emerging concerns, more deeply linked to an individual psychosocial sphere, may also affect the compliance.

In our study, we found that a high percentage of subjects, though within a small sample, expressed concern about the potential disclosure of individual results, no matter whether these results were study results or incidental findings; they stated that such a disclosure would negatively affect their willingness to allow the use of their biomaterial and, consequently, to donate for research purposes.

This finding is quite odd in the landscape of studies on the same topic. In fact, regardless of the settings and type of participants surveyed, e.g. general population [19, 20], general population *vs* research participants [21], patients [22, 23], biobank effective participants *vs* potential participants [24, 25], a great majority of studies found that the disclosure of individual results is well accepted and can be even positively influential in the decision to donate. However, a few studies have already highlighted certain specific signals of the difficulties in disclosing individual health information. In this trend, for instance, Janssen and colleagues reported that patients are interested in receiving information when the disclosure regards very low risk events [26]. In the same line, Meulenkamp and colleagues [27] found that, even if only low percentages of individuals (both patients and healthy subjects) do not want to receive aggregate or individual results, the type of results in terms of severity of the conditions in question really matters for decision. Moreover, they also found that anxiousness, as perceived by respondents, is associated with lower preference for results information. Similar effects of anxiousness are detectable in other studies [28]. Among the SET-DEP respondents to our survey, we found a prevailing preference opposing the disclosure of individual results, not only among those who screened positive for depression but also – and even more – among those who screened negative. This suggests that there may be relevant personal factors influencing people's preferences with respect to the feedback of individual results, at least when psychiatric disorders such as anxiety or depression are at stake. Moreover, these preferences do not seem to depend on the health status or subjective wellbeing as perceived by respondents. A first straightforward hypothesis may be formulated, that interest in knowing the results of biosample testing could be markedly affected by fears

Table 2
Description of survey items by MDD screening test results

Variables	MDD Negative		MDD Positive		Total	
	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)
Agreement on the use of a biological sample for research purposes§						
I don't agree	0 (0%)		3 (14.3%)		3 (5.9%)	
Only if no results will be given to me	27 (90%)		15 (71.4%)		42 (82.4%)	
Only if results will be given to me	2 (6.7%)		0 (0%)		2 (3.9%)	
I definitely agree	1 (3.3%)		0 (0%)		1 (2%)	
I don't know	0 (0%)	#	3 (14.3%)	#	3 (5.9%)	
Previous donation of a biological sample for research purposes						
No	27 (90%)		15 (71.4%)		42 (82.4%)	
Yes	3 (10%)		4 (19.1%)		7 (13.7%)	
I don't know	0 (0%)		2 (9.5%)		2 (3.9%)	
Self-perceived health						
Bad	2 (6.7%)		4 (19.1%)		6 (11.8%)	
Neither bad nor good	12 (40%)		15 (71.4%)		27 (52.9%)	
Good	14 (46.7%)		2 (9.5%)		16 (31.4%)	
Excellent	2 (6.7%)	*	0 (0%)	*	2 (3.9%)	
SWL score		**25.6^ (4.4)**		**18.6^ (8.2)**		**22.7 (7.1)**

§ For complete answer categories, see text; MDD, Major Depressive Disorder; SWL, Satisfaction with life.
#p=0.025 (chi-square test)
*p=0.013 (chi-square test)
^p=0.0003 (t test)

of negative consequences such as labelling, social stigma or discrimination [29] or risk to become more prone to depression and to compromise the successful management of symptoms. Considering that respondents voluntarily participated in the screening for MDD, a certain degree of concern for depression and mental disorders can be envisaged in all the respondents, irrespective of the results of the screening itself and, of note, irrespective of the fact that these results had already been communicated to the participants at the time the present survey started. Taking this latter aspect into account, the hypothesis may be enriched by a further consideration about the strength of a generalized concern not only for ascertained mental illnesses but also for a threat of mental illnesses.

Further factors, such as family history or social and cultural features of the individuals might also contribute to explain the results. Clearly, a pure selection bias may have occurred: our study sample represents subjects coming from the general population who voluntarily joined a screening programme, whose decision may have been highly influenced by fear of being at high risk for anxiety or depression on the basis, for example, of a specific personal or family history of the disease. Although the selection bias is possible, at the same time we have observed that the preference for not disclosing individual results is not driven by the perceived health status of respondents or by the level of subjective well-being that can be considered as a proximal measure of anxiety and depression, and this finding would deserve further and deeper investigations. Furthermore, our sample shows a high education level that in itself has often been associated with a major selectiveness regarding the type of "information" individuals wish to receive when participating in research [30].

The survey has two main methodological limitations. First, a low response rate has produced a small sample size that makes the results prone to random variability; in this respect, the SET-DEP project may have strained the potential participants as the request to participate in this survey partly overlapped with other requests and the follow-up interviews planned in the project. A second limitation is that the questionnaire item regarding the disclosure of individual health results did not specify any "diseases" or "syndromes", and consequently, no information was provided to respondents about different therapeutic scenarios. Therefore, we cannot exclude that the knowledge of specific treatments or cures regarding the potential health results to be disclosed might have produced different findings in a similar survey.

Nevertheless, this study also has a few strengths, such as the use of a validated questionnaire and the fact that our sample, though small, closely reflects the main socio-demographic characteristics and the MDD positivity rate of the reference SET-DEP cohort.

CONCLUSIONS

The survey provides cues for reflection on the importance of welfare interests in biobanking, particularly psychosocial wellbeing of individuals, and their potential impact on research that makes use of biological sample collections. The rate of disagreement towards potential health information disclosure among study

respondents is too high to be ignored, and therefore, we consider these results as clues of several factors that would be worth being further investigated, such as psycho-social, cultural and communication-related factors. Moreover, the fact that a small proportion of the SET-DEP participants replied to this survey make it possible to hypothesize that non-respondents were even less "interested" in or less sensitive to biobank participation, and this, in general, might represent a pitfall for the biomedical research biobank enterprises, which urgently calls for improvement.

Given the important role that biobanking activities currently play in the field of mental disorders and other diseases that challenge medical actionability, we consider these results worth of further testing in larger samples, taking into account explanatory factors not necessarily related to mental health. It will be of note to disentangle the complex interplay of personal, psychological and social factors shaping the contribution of study participants and potential biobank donors, as well as to assess the "psychological burden" that both healthy and diseased individuals variously have to withstand to contribute effectively to research biobanking.

Authors' contributions

VT contributed to the study conception and design, supervised data collection and drafted the manuscript. CF contributed to the study design, performed statistical analysis and revised the manuscript for important intellectual content. AG contributed to the study conception and revised the manuscript for important intellectual content. AP contributed to the supervision of data collection and revised the manuscript for important intellectual content. MAS contributed to the study conception and revised the manuscript for important intellectual content.

Availability of supporting data

The minimum dataset analyzed during the current study is available from the Corresponding Author on reasonable request.

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Conflict of interest statement

The Authors declare that they have no competing interests.

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The complex and constantly evolving public health threat of new psychoactive substances in Italy: addressing the main functions of a national observatory of drugs

Silvia Graziano[1], Simona Zaami[2], Roberta Tittarelli[2], Simona Pichini[1], Michele Sciotti[1], Paolo Berretta[1], Francesco Paolo Busardò[3], Enrico Marinelli[2], Anastasio Tini[2], Giulia Scaravaggi[4], Eleonora Buscaglia[4], Elena Brambilla[4], Marco Cavallo[5], Carlo Alessandro Locatelli[4], Roberta Pacifici[1] and Maria Rosaria Varì[1]

[1]*Centro Nazionale Dipendenze e Doping, Istituto Superiore di Sanità, Rome, Italy*
[2]*Scienze Anatomiche, Istologiche, Medico Legali e dell'Apparato Locomotore, Sapienza Università di Roma, Rome, Italy*
[3]*Dipartimento di Scienze Biomediche e Sanità Pubblica, Università Politecnica delle Marche, Ancona, Italy*
[4]*Centro Antiveleni, Centro Nazionale di Informazione Tossicologica, IRCCS Maugeri, Pavia, Italy*
[5]*Direzione Centrale per i Servizi Antidroga, Dipartimento della Pubblica Sicurezza, Rome, Italy*

Abstract

At the end of the 90s in Europe, the new psychoactive substances (NPS) phenomenon was limited to a small number of molecules created to mimic the actions and psychoactive effects of licensed medicines and existing drugs that are controlled by the United Nations drug conventions and therefore traded as their "legal" replacements. NPS were mostly circulating in rave parties and electronic music festivals. The globalization, the evolution of e-commerce and the growing popularity of NPS, facilitated the development of a wide illegal market in constant expansion. The dynamic nature of this phenomenon has led to an evolution in the prevention and monitoring of NPS trafficking within the European Union. The European legislative system has been amended with the aim of creating a faster and more effective regulatory system to tackle NPS diffusion and ban their sale and circulation. At the end of 2008, in compliance with the European Council Decision 2005/387/JHA, the Anti-Drug Policies Department of the Presidency of the Council of Ministers activated the National Early Warning System to promote a rapid exchange of information on NPS between Italy and the EU.

Key words
- NPS
- early warning system
- Italy
- psychoactive drug

INTRODUCTION

New psychoactive substances (NPS) are drugs that are not controlled by the United Nations international drug control conventions of 1961 and 1971 but may pose similar threats to public health [1]. At the end of the 90s in Europe, the NPS phenomenon was limited to a small number of molecules traded as "legal" replacements for the controlled drugs (such as cannabis, heroin, benzodiazepines, cocaine, amphetamines, and 3,4-methylenedioxymethamphetamine – MDMA), and were mostly circulating in rave parties and electronic music festivals.

The globalization, the evolution of e-commerce and the growing popularity of NPS, which were not expressly prohibited at the time, facilitated the development of a wide illegal market in constant expansion. In less than twenty years, NPS production and sale increased exponentially: at the end of 2019, the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) had reported approximately 790 NPSs circulating throughout Europe, 53 of which were identified for the first time that year [2].

Many NPS were originally developed as therapeutic drug candidates and/or as pharmacological tools to investigate endogenous systems of the body, although none of them were clinically tested [3]. For example,

Address for correspondence: Silvia Graziano, Centro Nazionale Dipendenze e Doping, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: silvia.graziano@iss.it.

the synthetic cannabinoids were originally developed to provide insights into the endocannabinoid system and help develop new medicines [4, 5]. The majority of NPS, however, were specifically synthesized for recreational use. Due to the absence of experimental and clinical data of NPS, pharmacological and toxicological data are rarely available [6-9]. Therefore, NPS use may induce unknown and unexpected effects, including acute and chronic toxic effects, as reported in numerous cases of intoxication and deaths in Europe and abroad [10].

Clinical similarities exist between NPS classes and the more established illicit substances they are intended to mimic. These similarities are assumed on the basis of their similar chemical structure and pharmacological actions. However, their harms can be qualitatively more serious, and sometimes different from those produced by controlled drugs. Moreover, some NPS such as fentanyl derivates and synthetic cannabinoids, show high potency that make easier to unintentionally overdose.

Little is currently known about the chronic harms of NPS use. There is emerging evidence that synthetic cannabinoids might be associated with more rapid onset of dependence and a more complex withdrawal syndrome than is cannabis [11]. Risk of dependence and withdrawal has also been noted with some stimulant NPS [12].

Despite the recent efforts towards NPS control, most of these substances are still legal in many countries, hindering the combat against drug trafficking and exposing oblivious consumers to potential health risks [13, 14]. At any times, new molecules are ready to be introduced onto the market, both to satisfy the consumer demands and to evade international ban. The NPS phenomenon therefore represents a serious, complex, and constantly evolving public health threat [15-17]. New challenges related to the growing number of highly potent substances, like synthetic cannabinoids, new synthetic opioids and fentanyl analogues, which have been responsible for explosive outbreaks, have emerged [18-21].

Over the years, the dynamic nature of the NPS phenomenon has led to an evolution in the prevention and monitoring of NPS trafficking within the European Union (EU). The European legislative system has been amended with the aim of creating a faster and more effective regulatory system to tackle NPS diffusion and ban their sale and circulation [22].

THE EUROPEAN EARLY WARNING SYSTEM (EU EWS)

In 1997, on a proposal from the EU Council, an early warning system (EWS) was implemented in Europe for the rapid exchange of information on NPS between EU Member States, to rapidly detect, assess, and respond to health and social threats (97/396/DJHA). The EWS was characterized by a regulatory structure organized in three phases: 1) the early warning of Member States upon the identification of new NPS in Europe, 2) the assessment of the risk associated with their consumption, and 3) the rapid implementation of control measures. The EMCDDA was responsible for the application of the first two phases.

However, this strategy needed to evolve to keep up with the spread of NPS. With the Framework Decision of May 10, 2005 (2005/387/JHA), the European Council established the current European EWS, coordinated by the EMCDDA in close collaboration with Europol and its law enforcement networks, the European Medicines Agency (EMA), the European Commission, the European Center for Disease Prevention and Control (ECDC), the European Chemicals Agency (ECHA), and the European Authority for Food Safety (EFSA). The European Commission is responsible for proposing control measures. The European Council also instructed all EU Member States to implement similar EWS to build a solid network for collecting, analyzing, assessing, and communicating the data on NPS throughout Europe. To date, the EWS includes 30 national EWS (28 EU Member States, Turkey, and Norway). The organization and functioning of the national early warning systems is a national responsibility. While these systems have developed to meet national needs, they draw on a common format and guidelines to report information to the EMCDDA. EWS guidelines and Risk Assessment Guidelines have been developed in 2007 and 2010 respectively, to provide the rationale, steps, procedures, roles, and responsibilities for the operation of the EU EWS. In January 2020 EWS guidelines have been updated to reflect the requirements of the new legislative package with respect to information exchange and the early warning system [23]. New Risk Assessment guidelines have been updated and published in December 2020 [24].

THE ITALIAN EARLY WARNING SYSTEM

At the end of 2008, in compliance with the European Council Decision 2005/387/JHA, the Anti-Drug Policies Department (Dipartimento per le Politiche Antidroga, DPA) of the Presidency of the Council of Ministers (PCM) activated the National EWS (Sistema Nazionale di Allerta Precoce, SNAP) to promote a rapid exchange of information on NPS between Italy and the EU.

In June 2016, the DPA designated the National Center for Addiction and Doping (CNDD) of the Istituto Superiore di Sanità (ISS) to organize and manage SNAP. The CNDD-ISS is supported by the Poison Center of the Maugeri Scientific Clinical Institutes of Pavia (CAV-PV) to manage NPS clinical and toxicological aspects, the Research Unit of Forensic Toxicology of the Sapienza University of Rome (FT-UNIROME1) to manage biotoxicological and analytical/technical aspects, and the Central Antidrug Service (Direzione Centrale per i Servizi Antidroga, DCSA) to ensure law enforcement. SNAP also involves Collaborative Centers across the country, such as law enforcement agencies and their laboratory networks, analytical toxicology laboratories, forensic toxicology laboratories, poison centers, health and care systems, universities and research institutes, medicines regulatory authorities.

SNAP follows and integrates the three regulatory phases of the EU EWS. When a NPS is first identified in Europe, SNAP is informed through a detailed report from EMCDDA and relays the information to the

national network. Conversely, all the reports on NPS circulating in Italy, which are collected by the national network of Collaborative Centers, are conveyed to the CNDD-ISS, the three support units, and the DPA, which relays the information to the EMCDDA. This system allows the EU and national EWS networks to detect and assess any potential threats, and identify and implement any response measures that might be required.

Phase 1 – Early warning

The early warning phase involves an input information flow and an output information flow managed by the CNDD-ISS and its three support units. The input flow includes the reports on the identification of NPS in Europe, from the EMCDDA, and in Italy, from the Collaborative Centers, based on seizures and/or acute intoxication and/or deaths.

These reports are supported by laboratory and analytical data (e.g., chromatograms and mass spectra) of the NPSs identified in seizures (e.g., powders, tablets, tablets, herbal preparations) or biological samples (e.g., blood, serum, urine, hair) and by other any available information.

The CNDD-ISS developed a new online platform to facilitate the contribution to the network by individual collaborative centers [snap.iss.it]. This system simplifies and harmonizes the collection of NPS data in Italy, optimizing the reporting activity. Moreover, it collects all the reports concerning NPS identified in Europe from the EMCDDA. An internal database archives chemical and analytical data of more than 600 NPS.

The data from the input flow are verified and supervised by the CNDD-ISS, in collaboration with CAV-PV and of the FT-UNIROME1

Specific informative documents are thereafter produced about NPS reported in the EU from the EMCDDA and in Italy from the Collaborative Centers. These documents represent the output information flow, supervised and approved by the DPA, and are sent to all the Collaborative Centers and to specific departments of the Ministry of Health to keep them constantly updated on the NPS circulating in the EU and on the national territory.

From June 2016 to June 2020, the SNAP received almost 590 reports from the EMCDDA and the network of Collaborative Centers. About 62% of these reports concerned 169 NPS circulating in Italy and reported by the Collaborative Centers network during the considered period *(Figure 1)*. The number of new substances reported has increased each year reflecting the growth in the NPS market. It may also reflect the increasing contribution by individual Collaborative Centers, especially law enforcement agencies, toxicology laboratories and poison centers, in reporting NPS detection to the SNAP. The drop in 2020 may reflect the impact of the response measures, such as the closure of public spaces and "stay-at-home" measures, related to the coronavirus disease (COVID-19) pandemic [15, 16]. These 169 NPS belong to different classes of compounds such as synthetic cannabinoids, synthetic cathinones, phenethylamines, synthetic opioids, tryptamines, arylalkylamines, benzodiazepines, piperazines, and plants. During the considered period, the most representative classes were synthetic cathinones (28%), synthetic cannabinoids (14%), and synthetic opioids (12%) *(Figure 2)*. These findings are concordant with NPS data from the EU EWS network and reported annually from the EMCDDA. From 2007 to the end of 2018, the EMCDDA was monitoring 190 synthetic cannabinoids, 138 synthetic cathinones and 49 synthetic opioids [25].

Synthetic cathinones are typically sold as legal replacements for controlled stimulants such as amphetamine, cocaine, and MDMA [26, 27]. They act on the central nervous system with sympathomimetic effects

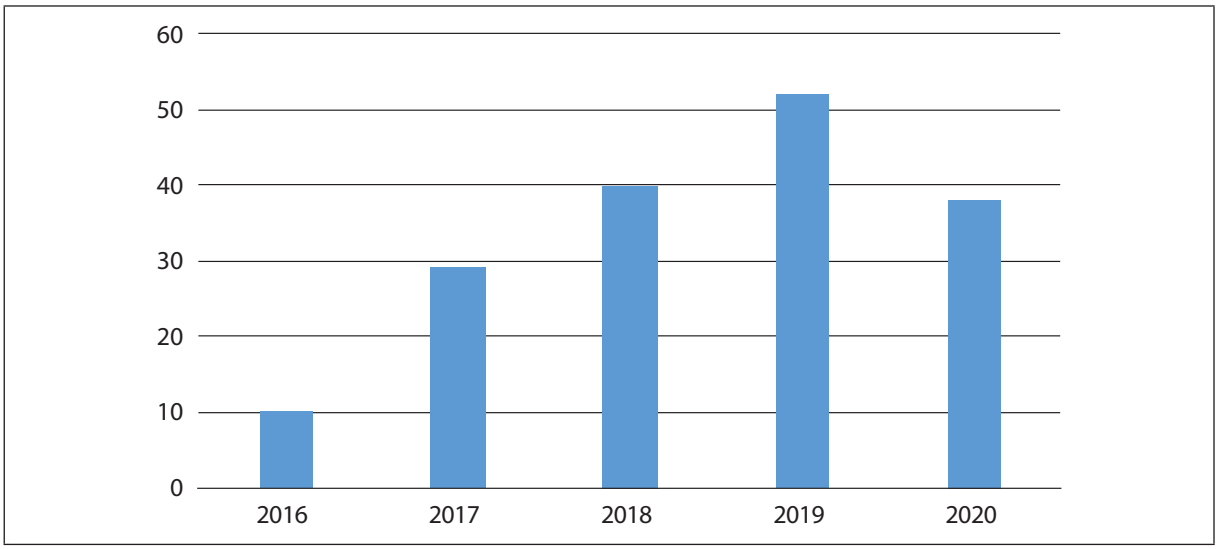

Figure 1
Number of NPS (new psychoactive substances) identified in Italy by the Collaborative Centers network by year (June 2016 – June 2020).

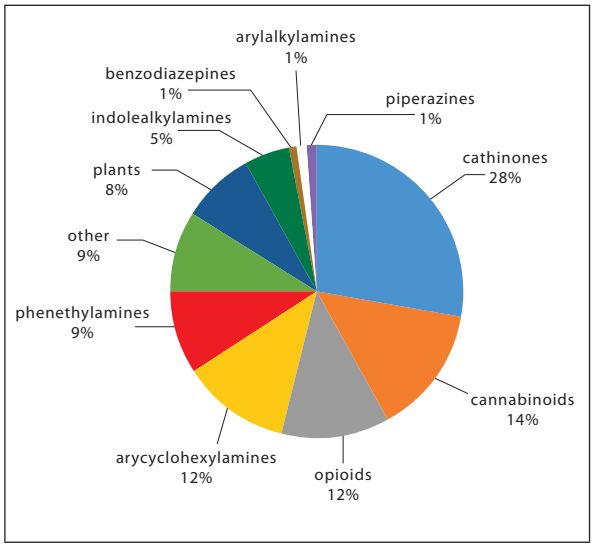

Figure 2
Chemical classes of the 169 NPS (new psychoactive substances) identified in Italy by reporting activity of the Collaborative Centers network.

(i.e., allucinations, overstimulation) similar to those occurring after cocaine or amphetamine overdose. Generally the cathinones are used recreationally; however they are also used by high-risk drug users, including people using stimulants and/or heroin and other opioids [28]. In Italy, synthetic cathinones were identify both in sized sample from law enforcement and in biological samples of intoxicated users, mephedrone, MDPHP, α-PVP, α-PHP, 3-MMC, and eutylone being the most frequently reported. Increased availability and harms associated with synthetic cathinones have been reported by several EU countries (i.e., Belgium. Netherland, Latvia) [29]. Synthetic cannabinoids are sold also as legal replacement for cannabis. Generally, they are sprayed on herbal plant material and smoked [30, 31]. They act on the same brain cell receptors as tetrahydrocannabinol (THC). However, synthetic cannabinoids may affect the brain in different and unpredictable ways: people who smoke these products can react with rapid heart rate, vomiting, agitation, confusion, and hallucinations. Their high potency can pose a high risk of severe poisoning that can also be fatal. In Italy, synthetic cannabinoids were identify mostly in samples seized by law enforcement, and to a lesser extent, in biological samples of intoxicated users. Over the last year France, Germany, Swiss and the Netherlands reported samples of cannabis contain low level of THC and synthetic cannabinoids. In France these detections have been associated with "light intoxications" [29]. Synthetic opioids, and in particular fentanyl and fentanyl derivatives, are sold as legal replacement for controlled opioids, such as heroin [21, 32]. They are also used as adulterants in street heroin, cocaine, and methamphetamine, or as heroin substitutes sold to unaware users with a high risk of overdoses. Fentanyl and its derivatives have also been identified throughout Europe in counterfeit medicinal products, such as oxycodone, hydrocodone, and alprazolam tablets, or as components of speedball mixtures together with cocaine or other stimulants. Synthetic opioids have high abuse potential and pose a severe risk of life-threatening poisoning, as they can cause severe respiratory depression leading to coma and death [33]. Due to their high potency, few grams are sufficient to make many thousands of doses for the drug market [34]. This makes them easier to import undetected into the Schengen Area, as small letters and packages can easily be disguised. In Italy, synthetic opioids were identified mostly in seizures, tramadol, fentanyl, isobutyrfentanyl (iBF) and 4-fluoro-isobutyrfentanyl (4F-iBF) being the most frequently reported. Tramadol was also involved in few acute intoxications. Three deaths associated with the consumption of two fentanyl derivatives (ocfentanil and furanylfentanyl) and of U-47700, another synthetic opioid, were reported during 2017-2018.

From June 2016 to June 2020, 49 NPS were identified for the first time in Italy in seizures and/or cases of acute intoxication and/or deaths reported by the Collaborative Centers network. These NPS belong mainly to the chemical class of synthetic cathinones (34.7%), synthetic cannabinoids (18.4%), arylcyclohexylamines (12.2%), and synthetic opioids (10.2%). Similarly, synthetic cathinones and synthetic cannabinoids account for the majority of the total number of NPS notified to the EU EWS for the first time in the considered period [25]. The larger number of synthetic cannabinoids identified for the first time at EU and national level reflects their use as "legal" replacements to cannabis, which is the mostly commonly used drug in Europe. The larger number of synthetic cathinones reported for the first time at EU and national level reflects their use as "legal" replacements for large markets in cocaine, amphetamines, MDMA, and other controlled stimulants.

When a NPS is identified for the first time in Italy, a document called "Reporting form" is issued by the SNAP under the supervision of the DPA, and then sent to the EMCDDA to quickly update the EU EWS network. The Reporting form includes information about the circumstances of the event (i.e., seizure, intoxication), chemical and analytical data, and any other relevant information. Analytical data facilitate NPS identification by laboratories across Europe, especially when a NPS is identified for the first time. Isobutyrfentanyl and 4F-furanylfentanyl and the 2F-QMPSB, a synthetic cannabinoid, were detected for the first time in the EU in Italy during 2019-2020.

Reporting by Member States allows the EMCDDA to constantly monitor NPS throughout Europe. The acquired informations allow to detect and assess any potential threats in a timely manner, and to improve any response measures that might be needed at a national or EU level.

Phase 2 – Risk assessment

The risk assessment concerns health and social risks embedded in NPS manufacture, trafficking, and use. Based on the information reported by the EU EWS and the national Collaborative Centers network, the three SNAP operating units generate a number of outputs to provide timely awareness to the national network.

The most relevant warnings are the "Alerts", providing vital, time-sensitive information for a specific event or situation associated with a NPS that may pose a serious public health or social risk in Italy. Alerts are classified according to the seriousness of the event and its consequences on health (I, II, and III degrees). Grade I alerts refer to a phenomenon with a risk of social unease (worry, anxiety, conditions of social alarm). Grade II alerts are associated with a risk of minor damage to health (temporary non-lethal disorders) and spreading onto the illicit market. Grade III alerts involve a concrete risk of serious damage to health (disabling diseases, deaths).

From June 2016 to June 2020, the SNAP issued 52 alerts (14 grade I, 14 grade II, and 24 grade III alerts), the majority of which involved cases of NPS acute intoxications in Italy that were reported by the Collaborative Centers network. Other alerts concerned NPS that had been involved in severe public health and social risk at the European level, such as the use of NPS as adulterants (i.e. Cannabis adulterated with synthetic cannabinoids) or as fake medicines (i.e. benzodiazepines).

Almost 20 alerts involved fentanyl and derivatives. Fentanyl derivatives are a group of synthetic opioids with a long history of illicit use as substitutes for heroin and other controlled opioids [35]. From their first appearance in 2012 on the European drug market, 34 fentanyl derivatives were identified in Europe, and were involved in more than 250 deaths in Europe at the end of 2018, as reported by the EMCDDA [36].

The rapid growth in the number and identification of fentanyl derivatives in Europe is reflected at the Italian national level. Ocfentanil and furanylfentanyl were responsible for two deaths in 2017 and 2018. Moreover, it was the first time that these molecules were detected in Italy. Afterwards, carfentanil, butyrylfentanyl, tetrahydrofuranylfentanyl (THF-F), acetylfentanyl, and methoxyacetylfentanyl were identified for the first time in Italy; isobutyrfentanyl and 4F-furanylfentanyl were identified for the first time in Europe in seizures by law enforcement on the national territory.

Phase 3 – Control measures

At the Italian national level, the reference text for the cultivation, production, trade and use of narcotics and other psychoactive substances in Italy is the "Testo unico delle leggi in materia di disciplina degli stupefacenti e sostanze psicotrope, prevenzione, cura e riabilitazione dei relativi stati di tossicodipendenza (Consolidation of the laws governing drugs and psychotropic substances, the prevention, treatment, and rehabilitation of drug addicts)", referred as Presidential Decree 309/90. All narcotic drugs and psychoactive substances are listed in four Tables (I, II, III, and IV), indexing the substances with strong addictive liability and potential for abuse; these Tables are amended whenever a substance should be introduced, reclassified, or removed. Updating the Tables involves a complex process of discussion and coordination between the Central Narcotics Office of the Ministry of Health, the ISS, and the Superior Health Council [37].

SNAP information on the NPS circulating in Europe and Italy allows prompt legislation. NPS inclusion in the Tables of the Presidential Decree 309/90 thus allows the police to combat trafficking and user exposure to potential health risks.

From June 2016 to June 2020, 139 NPS were included in Table I of the Presidential Decree 309/90. These substances are classified based on their chemical structure, opioids (25.2%), synthetic cannabinoids (19.4%), and phenethylamines (15.1%) being the most represented.

CONCLUSION

In the last years the operating national network on NPS has represented a point of integration and coordination between the various national and European actors involved in response activities to the spread of NPS. The future developments of these substances are difficult to predict, with possible growing health and social harms linked to the appearance of more potent molecules or new consumption patterns. To respond to such a dynamic and complex scenery, the coordination of local, national, and European efforts needs to be consolidated and the development of new tools for collecting, analysing and reporting on all aspects of the NPS phenomenon is highly recommendable.

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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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Smoking prevalence among healthcare workers in Italy, PASSI surveillance system data, 2014-2018

Valentina Minardi[1], Paolo D'Argenio[2], Rosaria Gallo[3], Valentina Possenti[1], Benedetta Contoli[1], Giuliano Carrozzi[4], Maria Sofia Cattaruzza[5], Maria Masocco[1] and Giuseppe Gorini[6]

[1]*Centro Nazionale per la Prevenzione delle Malattie e la Promozione della Salute, Istituto Superiore di Sanità, Rome, Italy*
[2]*Tobacco Endgame Italia*
[3]*Azienda Sanitaria Locale "Città di Torino", Turin, Italy*
[4]*Dipartimento di Sanità Pubblica, AUSL Modena, Italy*
[5]*Dipartimento di Sanità Pubblica e Malattie Infettive, Sapienza Università di Roma, Rome, Italy*
[6]*Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO), Florence, Italy*

Abstract

Introduction. Data on smoking among Italian Health Personnel (HP) from PASSI surveillance system from 2014-2018 were analysed.

Materials and methods. Among 169,678 working-age respondents, smoking prevalence was estimated among 1,253 Medical Doctors (MDs), 4,840 Non-Medical HP (NMHP), 87,749 Non-HP (NHP) and multivariate analysis was conducted.

Results. Current smokers were 23.0% among HP. Smoking prevalence in MDs (16.0%) was significantly lower than those observed in NMHP (25.3%) and NHP (28.6%). A declining trend was detected in all three groups and was more evident among MDs: from 20.8% in 2014 to 11.5% in 2018. Amongst MDs, smoking was significantly associated with male gender (Adjusted Odds Ratio, AdjOR=1.61), younger age (AdjOR=2.00), residing in South (AdjOR=1.71). Among NMHP, smoking prevalence was associated with low economic condition (AdjOR=1.54) and non-university education.

Discussion and conclusions. To further reduce smoking in HP, it is necessary to develop specific training courses in educational curricula.

Key words

- smoking
- health personnel
- health care worker
- smoking cessation training
- educational curricula

INTRODUCTION

In Italy, tobacco smoking is a major threat to health: it has been found to be the third cause of death and the leading cause of years life lost [1]. Healthcare professionals – physicians included – represent a behavioural model to their patients and have an enormous potential to play a key role in battling the tobacco epidemic, both in terms of spreading and tackling this habit [2]. Within their care function in supporting smokers who want to quit, health personnel indicate and/or offer effective treatments [3-7], and abundant literature shows that medical doctors and nurses who currently smoke are less likely to deal with smoking issues and cessation methods than their non-smoking peers [8-12]. Health professionals can also be a powerful support group to tobacco control policies: they have a role clearly known to tobacco companies which, within their marketing strategies, have been looking after the relationship with physicians in a privileged way [13]. According to the Michael Kunze two-phase model, the maturity of the smoking epidemic in a country could be evaluated by the ratio between doctor and general population smoking prevalence: during the ascendant phase of the smoking epidemic, the prevalence of smokers is higher among medical doctors rather than in other social groups, likely due to the better availability of economic resources (phase 1). Conversely, when the smoking epidemic curve starts to decline, probably for the better access to information on health damage provoked by smoking, the medical category seems to anticipate cessation behaviours and abstinence from tobacco (phase 2) [14]. While in some countries this second phase has already been underway for some time, in Italy it may be in its early stages.

Given that there are few recent studies on this highly relevant issue, we analysed data from the Italian Be-

Address for correspondence: Valentina Minardi, Centro Nazionale per la Prevenzione delle Malattie e la Promozione della Salute, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: valentina.minardi@iss.it.

havioural Risk Factor Surveillance System (Progressi delle Aziende Sanitarie per la Salute in Italia – PASSI), with the aim to estimate cigarette smoking prevalence among healthcare workers in the timeframe 2014-2018. Moreover, we compared these results with those published in scientific literature on smoking prevalence among Italian health professionals.

MATERIALS AND METHODS

PASSI is the surveillance system that monitors the main health-realted behaviors among adult population, aged 18-69, residing in Italy. PASSI study design is cross-sectional with continouos data collection; the units of data collection are the Local Health Units (LHUs), where public health departments' personnel conduct phone interviews using a standardised questionnaire [15]. In the temporal interval 2014-2018, the response rate was 81%; in 2018, 110 out of 121 LHUs from all Regions and Autonomous Provinces except one, participated in the surveillance, covering more than 90% of the adult popultaion living in Italy.

As shown in *Figure 1*, records gathered in the years 2014-2018 on working-age adults (n=169,678) were considered. We selected 107,468 interviews of participants who reported to be working at that time; from this total number we removed 11% of records because of missing information on the "type of work" (employees/in layoffs/with solidarity contract, self-employment, on non-standard employment contracts) or to the question "What is your work?". Aggregating and recoding data from two variables ("work sector" and "type of job"), 7,805 individuals working in the health sector and 87,749 in other sectors have been identified. Among people reporting to work in the health sector, 1,253 were Medical Doctors (MDs), 4,840 Non-Medical Health Personnel (NMHP) and 1,712 did not practice health professions and were not considered in the analysis. An amount of 296 individuals were excluded

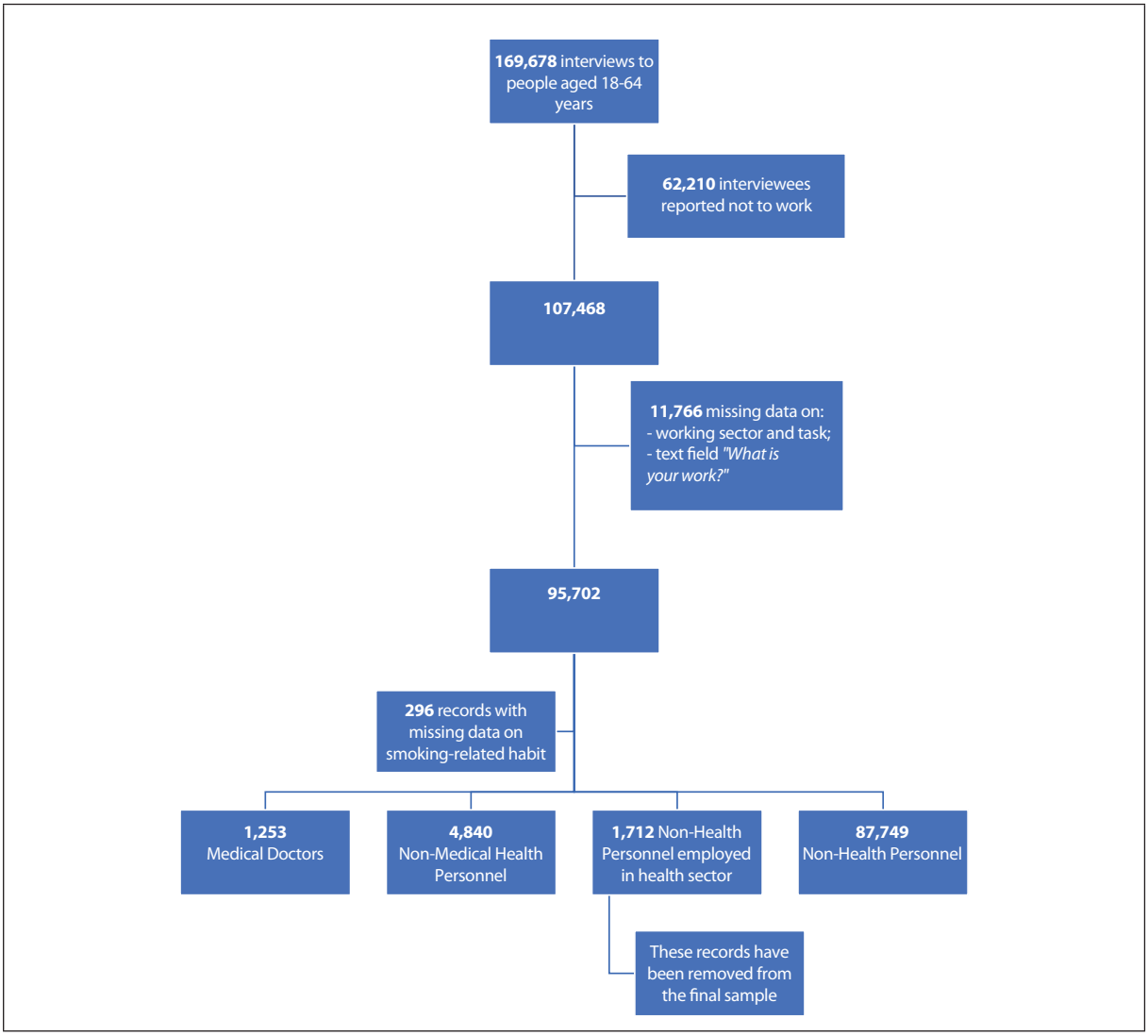

Figure 1
Flow chart describing the selection procedure of individuals belonging to the three professional categories: Medical Doctors (MDs), Non-Medical Health Personnel (NMHP), Non-Health Personnel (NHP) among the working-age respondents to the surveillance system PASSI interview, 2014-2018 (n=169,678).

because additional information on the smoking habit were not available (*Figure 1*). PASSI adopts the definition of current smoker from the World Health Organization, that is "people who declare to have smoked at least 100 cigarettes in their entire life and to be smoking currently or to have quit smoking since less than one year".

Moreover, we conducted a review on articles published from 1985 to 2020 in peer-reviewed journals on smoking prevalence among Italian health care workers.

Statistical analysis

Three categories were considered: MDs, NMHP and workers employed in different sectors from healthcare (Non-Health Personnel; NHP). Prevalence rates with 95% Confidence Intervals (CI 95%) were calculated for these three groups. Prevalences were then stratified by the following socio-demographic variables: age groups, gender, education levels, geographic areas and economic difficulties. This last variable was assessed by asking: "With your monthly household income, how do you manage until the end of the month?" Answers were categorized into two categories: "very easily or easily" = None; "with some/many difficulties" = Some or many economic difficulties. A multivariate logistic regression model was applied to each working category under consideration (MDs, NMHP, NHP) that generated Adjusted Odds Ratio (AdjOR) estimates for interactions and confounding factors. Statistical analysis was performed using Statistical package Stata 16 software (StataCorp LP).

RESULTS

Among NMHP, women were mostly represented (73.6%) than in the other two groups: MDs (44.8%) and NHP (41.9%; *Table 1*). Medical doctors were older, had less economic difficulties and, holding a university degree, had higher education levels than the other two groups. A higher education level was reported among NMHP: 49.2% of them had university degree *vs* 20.0% of NHP (*Table 1*).

In Italy, in the time period 2014-2018, smoking prevalence among healthcare workers (MDs and NMHP) was 23.0%, a percentage which is not statistically lower than that observed among workers employed in other sectors (NHP) (28.6%) (*Table 2*). In MDs, smoking prevalence (16.0%) was significantly lower than that observed among NMHP (25.3%) who, in turn, reached a significantly lower prevalence than that recorded in NHP. From 2014 to 2018, we detected a decrease of smoking prevalence in the three groups, that is even more evident among medical doctors (from 20.8% in 2014 to 11.5% in 2018), with a drop of over 40% in five years, although it does not reach statistical significance due to small sample size. The reduction is less evident but significant in the NHP group (*Figure 2*).

Table 1
Socio-demographic characteristics of the three professional category samples: Medical Doctors (MDs), Non-Medical Health Personnel (NMHP), Non-Health Personnel (NHP). PASSI 2014-2018 (N=93,842)

	Healthcare Personnel (HP)				NHP (n=87,749)	
	MDs (n=1,253)		NMHP (n=4,840)			
	%	*(IC 95%)*	%	*IC 95%*	%	*IC 95%*
Total	1.3	-	5.2	-	93.5	-
Gender						
Men	55.2	(52.5-58.0)	26.4	(25.2-27.7)	58.1	(57.8-58.5)
Women	44.8	(42.0-47.5)	73.6	(72.3-74.8)	41.9	(41.5-42.2)
Age group						
18-34	16.6	(14.6-18.8)	21.3	(20.2-22.5)	23.6	(23.3-23.8)
35-49	29.3	(26.8-31.9)	44.7	(43.3-46.1)	44.3	(43.9-44.6)
50-69	54.1	(51.3-56.9)	34.0	(32.6-35.3)	32.2	(31.9-32.5)
Economic difficulties						
Some or many	10.3	(8.3-12.7)	42.1	(40.3-43.9)	48.7	(48.3-49.1)
None	89.7	(87.3-91.7)	57.9	(56.1-59.7)	51.3	(50.9-51.7)
Educational level						
Up to junior high school	-	(-)	10.0	(9.0-11.1)	28.4	(28.0-28.8)
High school diploma	-	(-)	40.8	(39.0-42.5)	51.6	(51.2-52.1)
University degree	100.0	(-)	49.2	(47.5-51.0)	20.0	(19.6-20.3)
Geografic area						
North	39.0	(35.6-42.4)	43.3	(41.6-45.0)	40.2	(40.0-40.4)
Centre	22.8	(20.3-25.4)	21.7	(20.4-23.0)	25.1	(25.0-25.3)
South and Isles	38.3	(34.6-42.1)	35.0	(33.2-36.9)	34.7	(34.5-34.9)

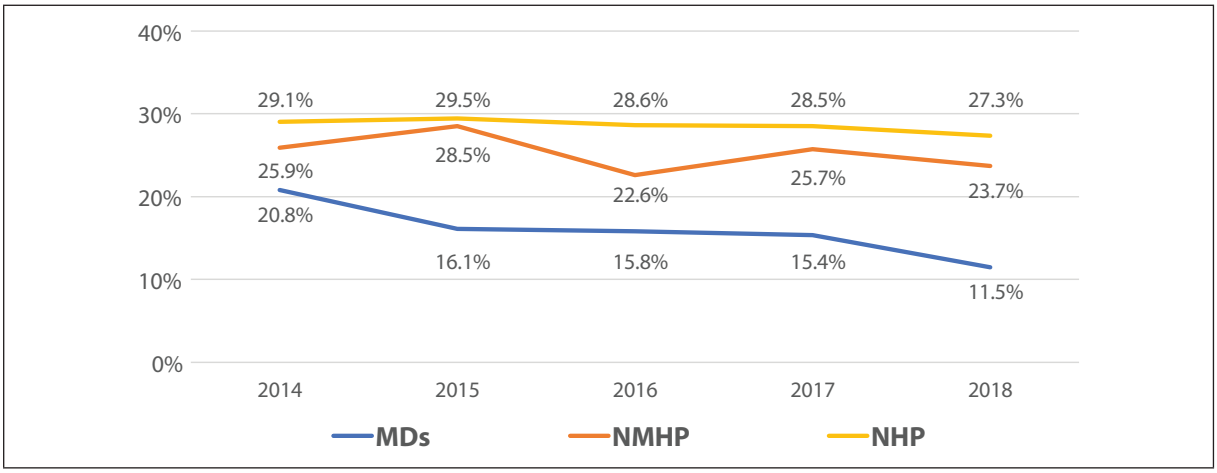

Figure 2
Temporal trend of smoking prevalence among Medical Doctors (MDs), Non-Medical Health Personnel (NMHP), Non-Health Personnel (NHP). PASSI 2014-2018.

Smoking prevalence was lower in women in comparison to men: 13.9% *vs* 18.4% among MDs and 23.7% *vs* 31.9% among NHP, respectively. On the contrary, no differences by gender were found in the NMHP group (*Table 2*). Smoking prevalence was higher among younger MDs, aged 18-34 years (24.4%), that is ten points higher than that recorded in older physicians aged >35 years. In NMHP, there were small and not statistically significant differences by age group. Instead, the older the NHP, the less they tended to smoke, from 35.2% to 24.6%. In all three groups, differences were observed in smoking prevalence according to the perceived economic difficulties (many *vs* none): MDs 22.4% *vs* 15.3%; NMHP 31.0% *vs* 21.0%; NHP 33.4% *vs* 24.1%. Amongst NMHP and NHP, the education gradient was relevant: smoking prevalence was higher among those with lower education levels: 37.4% and 36.4%, respectively. Additionally, we observed a geographic gradient; subjects living in the South reported higher smoking prevalence both among MDs (19.8% South *vs* 12.0% North) and NHP (30.5% South *vs* 26.8% North). This geographical trend was less evident for NMHP (26.4% South *vs* 24.2% North). Smoking prevalence in MDs group was significantly lower, about six percentage points lower than that recorded among graduated NMHP (16.0% *vs* 21.9%). Even though smaller and not statistically significant, a gap in favour of MDs was also found in the comparison with graduated NHP (16.0% *vs* 19.5%).

In the multivariate analysis (*Table 2*), MDs showed a smoking prevalence that was significantly associated with gender (AdjOR=1.61 in men *vs* women), age (AdjOR=2.00 in 18-34 *vs* over 50 years) and geographic area (AdjOR=1.71 Southern *vs* Northern Italy). Amongst NMHP, smoking prevalence was instead associated with economic condition (AdjOR=1.54 in NMHP with some or many difficulties *vs* no difficulties) and education level (AdjOR=1.96 in people with the lowest education level; AdjOR=1.24 in high school graduates *vs* people with university degree). Among NHP, smoking prevalence was associated with male gender, younger age, experiencing economic difficulties, lower education level and living in Central Italy (AdjOR=1.12 compared to North; *Table 2*).

Few and outdated studies on smoking prevalence among health professionals are available (*Table 3*) [16-39]: since 1985, 24 studies have been published, and only eight were carried out in the period 2011-2020 [32-39]. Furthermore, several analyses provided prevalence data referring to few hospitals, and thus were not representative of the Italian health professionals. Another limitation of most of these studies is a response rate lower than 60% of the sample, actually causing a possible bias related to a selection of respondents according to their own smoking habit.

A recent systematic review on prevalence of tobacco use in healthcare workers in each country, reported for Italy a prevalence of 30.6% among men and of 23.7% in women. Anyway, the reference year was outdated (2006; range 2000-2013). Moreover, studies in this review were heterogeneous and mostly of low quality [40]. In order to compare PASSI data here presented with studies carried out on smoking prevalence among healthcare workers in Italy since 1985, we considered papers published after 2000, with a response rate >60% and with a sample size of health professionals coming from at least four hospitals. The following studies were then excluded: four studies since they were published before year 2000 [16-19], six out of 12 referring to the time period 2000-2010 [20-31] because of samples <3 hospitals, and two due to a response rate lower than 60%. Moreover, none of the eight studies carried out in 2011-2020 [32-39] reported a response rate >60% and a greater than three-hospital sample. Considering the remaining studies available for comparison with results from the present study, in 2000, 28% was the smoking prevalence in a sample of General Practitioners (GPs) in Piedmont and Basilicata Regions [24]. In 2000-2002, another sample of GPs in Lombardy Region reported a 22.3% smoking prevalence [25]. Between 2006 and 2008, according to Ficarra *et al.* [32], in seven Italian hospitals located in the three main country areas (North, Centre and South), 33.9% of doctors were

Table 2
Prevalence of smokers and Adjusted Odds Ratio (AdjOR) by socio-demographic characteristics among Medical Doctors (MDs), Non-Medical Health Personnel (NMHP), Non-Health Personnel (NHP). PASSI 2014-2018 (N=93,842)

	Healthcare Personnel (HP)					
	MDs (n=1,253)		NMHP (n=4,840)		NHP (n=87,749)	
	% (IC 95%)	AdjOR (IC 95%)	% (IC 95%)	AdjOR (IC 95%)	% (IC 95%)	AdjOR (IC 95%)
Total	16.0 (13.3-19.1)	-	25.3 (23.7-26.9)	-	28.6 (28.2-29.0)	-
Gender						
Men	18.4 (14.3-23.3)	1.61[a] (1.05-2.46)	24.7 (21.7-28.0)	0.98 (0.80-1.20)	31.9 (31.4-32.5)	1.44[a] (1.38-1.49)
Women	13.9 (9.9-16.7)	1.00[c]	25.5 (23.7-27.3)	1.00[c]	23.7 (23.2-24.3)	1.00[c]
Age group						
18-34	24.4 (14.7-34.2)	2.00[a] (1.10-3.61)	25.3 (22.0-28.5)	1.21 (0.941- 1.56)	35.2 (34.3-36.0)	1.93[a] (1.83-2.03)
35-49	13.7 (9.4-17.9)	1.10 (0.68-1.76)	25.0 (22.6-27.3)	1.02 (0.83-1.25)	27.9 (27.4-28.5)	1.28[a] (1.22-1.46)
50-65	14.7 (11.0-18.4)	1.00[c]	25.6 (22.9-28.4)	1.00[c]	24.6 (24.0-25.3)	1.00[c]
Economic difficulties						
Some or many	22.4 (11.8-33.0)	1.49 (0.81-2.74)	31.0 (28.3-33.7)	1.54[a] (1.28-1.85)	33.4 (32.8-34.0)	1.42[a] (1.36-1.47)
None	15.3 (12.2-18.3)	1.00 [c]	21.0 (19.2-22.9)	1.00[c]	24.1 (23.6-24.6)	1.00[c]
Educational level[b]						
Up to junior high school	-	-	37.4 (32.1-42.8)	1.96[a] (1.47-2.60)	36.4 (35.6-37.1)	2.17[a] (2.04-2.31)
High school diploma	-	-	26.3 (23.8-28.8)	1.24[a] (1.01-1.52)	27.8 (27.3-28.4)	1.46[a] (1.38 – 1.54)
University degree	16.0 (13.3-19.1)	-	21.9 (19.7-24.1)	1.00[c]	19.5 (18.8-20.3)	1.00[c]
Geografic area						
North	12.0 (8.9-15.0)	1.00[c]	24.2 (22.1-26.3)	1.00[c]	26.8 (26.3-27.3)	1.00[c]
Centre	16.4 (12.1-20.7)	1.39 (0.90 - 2.14)	25.5 (22.7-28.3)	1.12 (0.92 - 1.36)	28.9 (28.2-29.6)	1.12[a] (1.07 - 1.17)
South and Isles	19.8 (13.5-26.2)	1.71[a] (1.06 - 2.78)	26.4 (23.1-29.6)	1.06 (0.86 - 1.31)	30.5 (29.7-31.3)	1.05 (1.00 - 1.10)

[a] Significant (p<0.05).
[b] The logistic model for the medical doctors' group does not include the educational level in the covariates.
[c] Reference category.

current smokers, that is much higher than what was documented previously [24, 25]. Such a difference may suppose a greater smoking prevalence among hospital doctors rather than in GPs: even if not ubiquitously, this finding is described elsewhere [41].

DISCUSSION

Among healthcare staff, the lowest smoking prevalence was observed among MDs (16.0%), whereas in NMHP it was 25.3%. Looking at the whole period, even if the trend is not statistically significant, smoking prevalence among physicians has decreased by 45%, from 20.8% in 2014 to 11.5% in 2018. A similar percentage was found by the Italian Federation of General Practitioners (Federazione Italiana Medici di Medicina Generale – FIMMG). Indeed, in 2018, FIMMG conducted a survey on the "Management of smoking in general practice" and interviewing 563 physicians, reported that only 10% were current smokers, whereas 40% declared to have quit and 50% to be never smokers [42].

These findings are encouraging, since smoking status of physicians can impact their professional practice. When physicians smoke themselves, they are in no position to advise or help their patients to stop and they are more likely to believe that they have other priori-

Table 3
Study on smoking prevalence among health care workers in Italy, 1985-2020

Reference	Survey year	Setting/Reference population	Sampling strategy or type of survey	Sample (N)	Type of health care workers (HCWs)	Response rate	Smoking prevalence*
16 Franceschi *et al.*	1985	Pordenone, Friuli Venezia-Giulia	Postal questionnaire	824	Physicians	86%	31%
17 Nardini *et al.*	1995	Attendees at the National Meeting of the Italian National Thoracic Society (AIPO)	Anonymous questionnaire	983	Pneumologists	61.5%	25%
18 Zanetti *et al.*	1996	Three hospitals in Emilia Romagna Region	Anonymous questionnaire	2,453	All	68%	Doctors (31%); nurses (41%); other HCWs (48%)
19 Nardini *et al.*	1996	Sondalo Hospital in Lombardy	Questionnaire sent to all health staff	959	All	57%	Doctors (39%); nursing students or other HCWs (47%)
20 La Vecchia *et al.*	1999	Physicians registered with the Italian Medical Federation (FNOMCeO)	Representative sample by age, gender, and area; phone survey	501	Physicians and dentists	Not reported	Overall (24%); men (24.5%); women (23.1%)
21 Principe	1998	58 Italian Hospitals, involved in the project AIPO – Smoke-free Hospitals	Paper questionnaire	14,348	All including administrative staff	67%	Overall (33.3%); doctors (24.7%); nurses (36.2%); other HCWs (38.4%); administrative staff (32.3%)
22 Invernizzi *et al.*	2000	General Practitioners registered with the Italian GP Society	Questionnaire	428	General Practitioners	100%	24%
23 Muzi *et al.*	2001	One general hospital in Perugia, Umbria	Interviews during occupational health surveillance	2,743	All including administrative hospital crew	100%	Overall (36.5%); doctors (26.3%); %); nurses (38.9%); other HCWs (45.2%)
24 Pizzo *et al.*	2000	General Practitioners in 6 Local Health Authorities: 2 in Turin, Piedmont, 4 in Basilicata	Representative sample; phone interview	729	General Practitioners	72%	28.3%
25 Pretti *et al.*	2000-2002	General Practitioners in Lombardy Region	Anonymous questionnaire	5,348	General Practitioners	67%	Overall (22.3%);
26 Proietti *et al.*	2004	Two general hospitals of Eastern Sicily	Interviews during occupational health surveillance	2,000	Hospital staff	100%	Doctors (27.7%); nurses (36.2%); other HCWs (36.4%)
27 Masia *et al.*	2004	The University Hospital in Sassari, Sardinia	Anonymous questionnaire	1,550	Hospital staff	Not reported	Doctors (21.4%); nurses (35.5%); service staff (40.4%)
28 Negro *et al.*	2007	Trieste Local Health Unit and hospital (Friuli Venezia-Giulia)	Interviews during occupational health surveillance	492	All	100%	37%
29 Copertaro *et al.*	2005	Marche Region	Interviews during occupational health surveillance	262	130 rotating shift nurses and 132 non-shifting nurses	100%	Men (32%); women (23.1%)
30 Incorvaia *et al.*	2008	One public hospital in Milan, Lombardy	Questionnaire	383	All including administrative staff	24%	HCWs (25.8%)
31 Copertaro *et al.*	2008	Marche Region	Interviews during occupational health surveillance	414	193 shift HCWs; 221 non-shifting HCWs	100%	Men (35%); women (23%); shift HCWs (31%); non-shifting HCWs (27%)

Continues

Table 3
Continued

Reference	Survey year	Setting/Reference population	Sampling strategy or type of survey	Sample (N)	Type of health care workers (HCWs)	Response rate	Smoking prevalence*
32 Ficarra *et al.*	2006-08	Seven hospitals in Italy	Questionnaire	1,082	All	98%	Doctors (33,9%); nurses (49.8 %); other HCWs (50.4%)
33 Faggiano *et al.*	2012	Three scientific societies of Italian cardiologists	Web-based survey	5,240	Cardiologists	33.7%	12.4%
34 Frisinghelli *et al.*	2013	Attendees at the 44° National Congress of the Italian Association of Hospital Cardiologists (ANMCO)	Anonymous questionnaire	1,200	Cardiologists	50%	9.5%
35 Nappini *et al.*	2014	Nurses of Pistoia Local Health Unit (Toscana)	Questionnaire	400	Nurses	64%	Men: (33.3%); women (26.3%)
36 Giorgi *et al.*	2015	One hospital in Rome, Lazio	Anonymous questionnaire	320	All	40%	Overall (47%); physicians (42%); nurses (43%); other HCWs and administrative staff (58%)
37 Lina *et al.*	2015	Hospital "National Institute of Cancer", Milan (Lombardy)	Web-based survey	285	Hospitalists	75%	14%
38 Pianori *et al.*	2006, 2011, 2015	Perugia Local Health Unit (Umbria)	Standardised questionnaire	163 (2006), 161 (2011), 151 (2015)	All	100%	33.7% (2006), 36.0% (2011), 33.8% (2015)
39 Provenzano *et al.*	2018	Nursing students at Palermo University, Sicily	Anonymous questionnaire	492	Nursing students	61%	32.9%

* Where not specified, the overall prevalence is reported.

ties than helping patients to quit smoking, given that tobacco and tobacco related diseases are considered as "minor issues" in comparison to other diseases [43]. Doctors should not only have an ethical obligation to act in the best interest of public and patient health but could also play a prominent role in tobacco control as social models, counsellors and the professional category able to lobby for the development of policies [2-12]. Thus, PASSI data provide a more encouraging and updated picture compared to the one outlined by previous studies which reported a higher smoking prevalence in the Italian medical doctors than that recorded in the general population [40, 42].

The present study on the smoking prevalence among healthcare workers in Italy, which is carried out within a population-based survey, is the only one available since 2000 with a large and nationwide sample. The 45% decline in smoking prevalence recorded among MDs in the present study (from 20.8% in 2014 to 11.5% in 2018) seems to belong to a decreasing trend that started earlier, looking at the smoking prevalence of 28% recorded in 2000 among GPs [23] (*Figure 3*). This declining trend is around two times higher than that observed in Italy among the general population in the same period: a 22% decrease from 2001 to 2019 among people aged >14 years, according to ISTAT data; a 16% reduction from 2008 to 2019 among Italian adults aged 18-69 year, according to the PASSI Surveillance System data (about 35,000 people each year) (*Figure 3*).

Consistently with the estimates from the PASSI surveillance system, in the last years in high-income countries, smoking prevalence among health professionals has been declining constantly, with a pooled prevalence, estimated by a meta-analysis of studies carried out in the period 2011-2015, of 19% (CI 95% 15-22%), that is little lower than the percentage of the present study (23%; CI 95%: 22%-29%) [40]. In some countries, smoking prevalence in healthcare workers was significantly much lower, such as in the USA, with 7.2% in 2013 [44], or in Belgium in 2011 reaching 10% in men and 5% in women [40]. Evidence from our study about a lower smoking prevalence among medical doctors compared to other healthcare professionals (16% *vs* 25%) is consistent with other Italian and international studies [18, 19, 40]. In

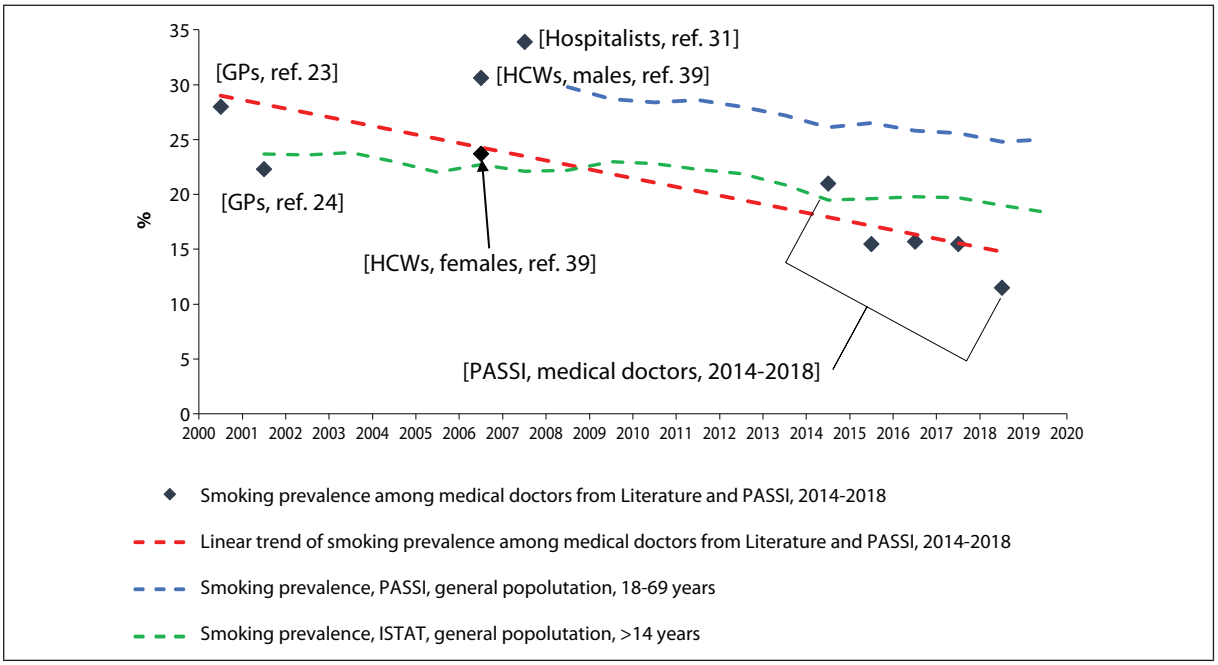

Figure 3
Data from literature, PASSI included, on temporal trend of smoking prevalence among medical doctors in Italy within the last two decades. Sources: ISTAT and PASSI. General Practitioners (GPs), Health care workers (HCWs).

the present analysis, the NMHP group is heterogeneous because it includes nurses, auxiliary personnel, technicians and health assistants, biologists and chemists. For this reason, within this group, important socioeconomic differences occur, both in terms of educational grade and perceived economic difficulties. Additionally, tobacco smoking among doctors is associated with demographic factors (gender, age), whereas in other healthcare workers it is mainly related to socioeconomic level, such as education and economic difficulties. This is likely due to the greater homogeneity of the medical category in socioeconomic characteristics. During the last 20 years, smokers with higher education levels were more likely to quit smoking and thus they recorded lower prevalences [45, 46]. In high-income countries, where tobacco control policies are well developed, medical doctors recorded significantly lower smoking prevalence in comparison to other university graduates [40]. In Italy, this declining trend has just started; as reported in the present study, in 2014-2018 smoking prevalence for MDs was 16%, while in graduated NMHP and NHP it was 21.9% and 19.5%, respectively.

Limitations and strengths

The PASSI surveillance system gathers self-reported data during phone interviews which are based on a standardised questionnaire that is administered by public health professionals to a representative sample of the adult population living in Italy. This kind of information may be affected by bias. In particular, on smoking, social desirability could occur because of the reticence to declare a behaviour that is prone to social disapproval, and healthcare professionals may feel this issue more strongly. However, in the PASSI questionnaire, questions regarding smoking habits are not asked immediately after those regarding socio-demographic and working characteristics, and this could be a strong protective factor from the social desirability bias.

Additionally, the NMHP is quite heterogeneous, since it includes several professional categories, by educational level or type of work.

A limitation to the national representativeness of the data sample is that Lombardy Region did not participate to PASSI Surveillance System, accounting for about 11% of PASSI reference population. However, it is worth to note that in the first years of PASSI Surveillance System, when five LHUs from Lombardy participated in the surveillance, the regional smoking prevalence was similar to those observed in other Northern Italy Regions.

A main strength in the PASSI, is its protocol that achieves a high response rate (81%) due to the standardized procedures of contacts and recall techniques which ensure minimisation of selection bias [40].

CONCLUSION

Smoking behaviour in healthcare workers is important because they represent a model to the general population. Over the last two decades in Italy, a downward trend can be observed in the medical profession, while only a small hint of a reduction has been observed among other health professionals. In order to achieve a further decrease in smoking prevalence among healthcare workers, especially among non-medical health care workers, specific training on the harms of tobacco smoke and on smoking cessation methods should be developed in health professions curricula, both undergraduate and postgraduate.

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Conflict of interest statement

All authors declare that they have no conflict of interest.

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Members of the PASSI coordinating group

Maria Masocco, Benedetta Contoli, Valentina Minardi, Centro Nazionale per la Prevenzione delle Malattie e la Promozione della Salute (Cnapps), Istituto Superiore di Sanità, Roma; Nicoletta Bertozzi, Dipartimento di Sanità Pubblica, Ausl Romagna, Cesena; Stefano Campostrini, Dipartimento di Economia, Università Ca' Foscari, Venezia; Giuliano Carrozzi, Dipartimento di Sanità Pubblica, Ausl Modena; Marco Cristofori, Unità Operativa Sorveglianza e Promozione della Salute, Ausl Umbria 2, Orvieto; Angelo D'Argenzio, Igiene, Sicurezza Luoghi di Lavoro e OER, Regione Campania, Napoli; Amalia Maria Carmela De Luca, UOSD Epidemiologia e Sorveglianza di Popolazione, ASP Cosenza; Pirous Fateh-Moghadam, Azienda Provinciale per i Servizi Sanitari, Trento; Mauro Ramigni, Dipartimento di Prevenzione, Aulss 2 Marca Trevigiana, Treviso; Massimo Oddone Trinito, Dipartimento di Prevenzione, Asl Roma 2, Roma; Stefania Vasselli, Ministero della Salute, Roma.

Authors' contributions

VM, GG, PDA, GC, MM conceptualized and designed the study. VM and RG analysed the data. PDA, VP, VM and GG drafted the manuscript. PDA, BC and MM contributed to the data interpretation and reviewed the manuscript. MSC and GG critically reviewed the manuscript approved the final version.

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Breastfeeding promotion and support: a quality improvement study

Daniela Menichini[1], Francesca Zambri[2], Laura Govoni[3], Alba Ricchi[3], Ramona Infante[3], Elisabetta Palmieri[3], Maria Cristina Galli[4], Maria Teresa Molinazzi[3], Marisa Patrizia Messina[5], Angela Putignano[4], Federico Banchelli[6], Sofia Colaceci[7], Isabella Neri[3] and Angela Giusti[2]

[1]*Dipartimento di Scienze Biomediche, Metaboliche e Neurali, Università degli Study di Modena e Reggio Emilia, Modena, Italy*
[2]*Centro Nazionale per la Prevenzione delle Malattie e la Promozione della Salute, Istituto Superiore di Sanità, Rome, Italy*
[3]*Dipartimento di Scienze Mediche e Chirurgiche, Università di Modena e Reggio Emilia, Modena, Italy*
[4]*Dipartimento Materno Infantile, Università degli Studi di Modena e Reggio Emilia, Modena, Italy*
[5]*Dipartimento di Scienze Ginecologiche e Ostetriche, Sapienza Università di Roma, Rome, Italy*
[6]*Dipartimento di Diagnostica, Medicina Clinica e Sanitaria, Unità di Statistica, Università degli Studi di Modena e Reggio Emilia, Modena, Italy*
[7]*Saint Camillus International University of Health and Medical Sciences (UniCamillus), Rome, Italy*

Abstract

Background. Breastfeeding success is determined by early skin to skin contact, early initiation of breastfeeding, rooming-in, baby-led breastfeeding, creation of a favorable environment, specific training of health professionals, and continuity of care.

Objective. To investigate the women's satisfaction regarding the care and support received in the first days after childbirth.

Material and Methods. A questionnaire of 24 items was administered to mothers before discharge, from May to September 2019 at the University Hospital of Modena.

Results. The predictive variables of exclusive breastfeeding were the delivery mode, age at birth and parity. The multivariate analysis showed that a high satisfaction score was associated with vaginal birth (OR=2.63, p=0.005), rooming-in during the hospitalization (OR=8.64, p<0.001), the skin to skin contact (OR=6.61, p=0.001) and the first latch-on within 1 hour after birth (OR=3.00, p=0.02).

Conclusions. Mothers' satisfaction is one of the important factors of positive experience during hospital stay and of better health outcomes.

Key words

- exclusive breastfeeding
- breastfeeding promotion
- breastfeeding support
- mother's satisfaction

INTRODUCTION

Breastfeeding is the physiological protraction of the relationship created between mother and child during pregnancy, and it is an investment for life [1]. Breastfeeding and breast milk are the biological norm, the expression of a sophisticated evolutionary mechanism that combined the need for neurobiological, microbial, psychological, affective and emotional imprinting and infant's nutritional needs [2]. Furthermore, it is always ready, at "zero kilometer" at the right temperature, highly digestible and protects the newborn from many diseases and infections that occur more frequently in formula fed babies [3, 4]. The Italian National Prevention Plan [5] and the international Agencies as World Health Organization (WHO) and UNICEF, states that "the breastfeeding promotion and support are a public health priority" [6]. According to the international [7] and national [8] indications, it is recommended to breastfeed exclusively during the first 6 months and continue breastfeeding for two years or more, while providing adequate and safe complementary foods. There is a consensus on the need for increasing the global prevalence of exclusive breastfeeding in the first 6 months of a child's life by 2025, with positive impact on the individuals, the health system and the society [9, 6].

In order to effectively start and continue breastfeeding, mothers need facilitating environments "to make healthy choices easy" [10], including active support from families, communities and healthcare services during pregnancy and after childbirth [7]. Since 1991, WHO and UNICEF launched the "Baby-Friendly Hospitals Initiative", providing the "ten steps to successful

Address for correspondence: Francesca Zambri, Centro Nazionale per la Prevenzione delle Malattie e la Promozione della Salute, Istituto Superiore di Sanità, Via Giano della Bella 34, 00162 Rome, Italy. E-mail: francesca.zambri@iss.it.

breastfeeding" as evidence-based strategy to support healthcare service in policy and procedures implementation. WHO has called upon all facilities providing maternity and newborn services worldwide to implement the "Ten Steps" [11].

Several studies highlighted the determinants of breastfeeding success, like early skin to skin contact [12, 13], early initiation of breastfeeding [14], rooming-in [15], baby-led breastfeeding [16], favourable environment [17], appropriate information at discharge [18] specific training of health professionals [19], continuity of care [20].

In order to guarantee the continuity of care, during mother and newborn's discharge, breastfeeding outpatient services are accessible and available in several Italian Regions. The Emilia-Romagna Region recognizes the importance of breastfeeding as a public health priority. Therefore, to protect and support breastfeeding practice, since 2005 a set of regional policies and programs have been provided to support the implementation at hospital and community healthcare level [21, 22]. According to the regional indications, a specific breastfeeding promotion and support outpatient service was introduced in 2011 at the University Hospital of Modena.

The study aims to investigate the women's satisfaction regarding the care and support received in the first days after childbirth at the University Hospital of Modena, in order to highlight aspects that can affect pre-discharge exclusive breastfeeding.

MATERIALS AND METHODS

From May to September 2019 an observational descriptive study was carried out at the Maternity Unit of the University Hospital of Modena, organized according to midwifery led-care model. We included all mothers during discharge, regardless the type of newborn feeding.

An *ad hoc* questionnaire was created by integrating two different tools: the first was the World Alliance for Breastfeeding Action (WABA) questionnaire, translated into Italian by the Italian Maternal Breastfeeding Movement (MAMI) [23]; the second was designed within the Emilia-Romagna breastfeeding promotion strategy [24] with the aim of improving the quality of healthcare practices.

The questionnaire consisted of 24 items; the first section was designed to collect socio-demographic data (age, nationality, level of education), obstetric anamnesis (attendance to antenatal classes, parity, mode of birth, gestational age, breastfeeding in the first 24-48 hours of life and neonatal feeding at discharge). The second section investigated the perceived quality as outcome of good practices implemented by healthcare personnel.

The study protocol has been approved by the Health Department of the University Hospital of Modena. The questionnaire was administered to pre-discharge mothers by the midwife dedicated to post-natal care. The exclusion criteria were the non comprehension of the Italian language, as the questionnaire was provided in Italian.

The aims of the statistical analysis were to estimate the association between the characteristics of mothers, the mode of delivery, hospitalization variables considering as outcomes 1) exclusive breastfeeding and 2) satisfaction score.

Categorical variables were described as absolute and percentage frequencies, quantitative variables as mean ± standard deviation (SD) and 95% confidence interval (95% CI).

A multivariable logistic regression model was performed to evaluate the likelihood of exclusive breastfeeding and the satisfaction score. For the satisfaction a 1-4 items scale was used, where 1 represented "highly inadequate" and 4 "highly adequate". For the multivariable logistic regression, the mean satisfaction score was dichotomized as high satisfaction (mean score ≥3) and low satisfaction (mean score <3) to evaluate the likelihood of high satisfaction expressed as Odds Ratio (OR) and 95% CI.

RESULTS

The questionnaire was administered to 176 women; all women accepted to be enrolled. Out of these, 165 (93.7%) answered to all the questions and were, therefore, included in the analysis.

The description of maternal characteristics, delivery and hospitalization are reported in *Table 1*.

Most of the women included in the study aged between 26-35 years. The 92.1% of women resulted to be of Italian nationality, with a high education level (50.3% had a master degree) and attended birthing classes for the 69.1% of the sample.

Seventy-four women had a spontaneous delivery (44.8%), while 75 had an induced and/or operative delivery receiving also epidural analgesia (45.5%). The caesarean section rate was 9.7% (16 women).

The vast majority of newborns weighted between 2.5-3.9 kg at birth (89.7%) and were delivered at term. Only 5 women delivered before 36 weeks of gestational age (3.0%) *(Table 1)*.

As far as the characteristics of hospital stay, in the University Hospital of Modena, the rooming-in is guaranteed for all mothers and babies unless there are medical conditions that do not allow it. Indeed, the 88.5% of newborns stayed with their mothers for all the hospitalization.

The use of breast-pumps was necessary in 59 women (35.8%), a similar percentage was also found for the use of the formula (35.8%) in addition to or in place of breast milk, where not available; while low percentages of use of nipple shields (7.3%) and glucose solution (1.2%) were found.

Exclusive breastfeeding during the hospital stay was 59.4% among the included women. The satisfaction of the quality of care received, calculated using a rage from 1 to 4, averaged from 3.24± 0.54, and the high satisfaction (expressed as mean score ≥3) was found in 129 women (78.2%).

The associations between maternal characteristics, delivery mode and the likelihood of exclusive breastfeeding are reported in *Table 2*. We found that mothers aged 18 and 25 compared to those aged over 35 years,

Table 1
Mother characteristics, birth mode and hospital stay

		n=165	%
Characteristics of mother at birth			
Age	18-25	26	15.8%
	26-35	94	57.0%
	>35	45	27.3%
Italian nationality	yes	152	92.1%
Master degree	yes	83	50.3%
Attended a birthing class	yes	114	69.1%
Previous births	yes	47	28.5%
Characteristics of childbirth			
Birth modality	spontaneous	74	44.8%
	induced/analgesia/ operative	75	45.5%
	caesarean	16	9.7%
Birth weight	<2.5 kg	9	5.5%
	2.5-3.9 kg	148	89.7%
	≥4.0 kg	8	4.8%
Gestational age	≤36 weeks	5	3.0%
	>36 weeks	160	97.0%
Characteristics of hospital stay			
Rooming-in	yes	146	88.5%
Breast-pump	yes	59	35.8%
Nipple shields	yes	12	7.3%
Formula	yes	59	35.8%
Glucose solution	yes	2	1.2%
Exclusive breastfeeding at discharge	yes	98	59.4%
Skin to skin	yes	149	90.3%
First latch-on after birth	none after more than 1 hour within 1 hour within 30 minutes	4 16 50 95	2.4% 9.7% 30.3% 57.6%
Mean satisfaction score	1-4	3.25 ± 0.54	
High satisfaction	≥3	129	78.2%

were more likely to breastfeed exclusively (OR=5.87, p<0.001). Furthermore, mothers who had already given birth were more likely to breastfeed exclusively (OR=4.23, p=0.005). Likewise, women delivering vaginally, when compared to those undergoing to operative or caesarean delivery were more likely to have an exclusive breastfeeding (OR=1.22, p=0.03). To worth noting that exclusive breastfeeding resulted strongly associated with the rooming-in, the skin to skin practice and a first latch-on within 1 hour after birth, as well as having received a practical support by midwives to breastfeed during the hospital stay.

The associations between maternal characteristics, delivery mode, hospital stay and satisfaction score are reported in *Table 3*.

Table 2
Association between maternal and childbirth characteristics and the likelihood of exclusive breastfeeding

		OR	95% CI	p-value
Maternal age	18-25 *vs* >35	5.87	2.43-14.16	**<0.001**
Master degree	yes *vs* no	0.66	0.37-1.20	0.18
Attended a birthing class	yes *vs* no	1.33	0.51-3.45	0.55
Previous births	yes *vs* no	4.23	1.56-11.51	**0.005**
Vaginal birth	yes vs no	1.22	1.0-2.1	**0.03**
Gestational age at birth	≥37 *vs* <37	1.12	0.87-1.43	0.34
Birth weight 2.5-3.9 kg	yes *vs* no	2.51	0.89-7.02	0.08
Rooming-in	yes *vs* no	13.67	3.76-20.62	**0.002**
Skin to skin	yes *vs* no	15.8	3.7-30.5	**0.009**
First latch-on within 1 hour	yes *vs* no	3.93	1.42-10.83	**0.008**
Received practical support by midwives	yes *vs* no	21.76	6.81-35.63	**p<0.001**

Table 3
Association between maternal and childbirth characteristics and a high satisfaction score

		OR	95% CI	p-value
Maternal age	18-25 *vs* >35	1.02	0.92-1.17	0.35
Master degree	yes *vs* no	0.87	0.53-1.42	0.59
Attended a birthing class	yes *vs* no	2.28	1.08-4.77	**0.03**
Previous births	yes *vs* no	0.72	0.21-2.36	0.58
Vaginal birth	yes *vs* no	2.63	1.02-7.02	**0.05**
Gestational age at birth	≥ 37 *vs* < 37	1.43	0.96-2.13	0.07
Rooming-in	yes *vs* no	8.64	3.92-20.63	**p<0.001**
Skin to skin	yes *vs* no	6.61	2.22-19.63	**0.001**
First latch-on within 1 hour	yes *vs* no	3.00	1.14-7.90	**0.02**
Breast-pump	yes *vs* no	0.14	0.06-0.31	**p<0.001**
Formula	yes vs no	0.10	0.04-0.23	**p<0.001**
Glucose solution	yes *vs* no	0.31	0.01-5.14	0.41

The multivariable analysis showed that women who attended birthing classes are more likely to have a high satisfaction score (OR=2.28, p=0.03), likewise, women who had a vaginal birth (OR=2.63, p=0.005) instead of an operative or caesarean delivery. Moreover, rooming-in during the hospitalization (OR=8.64, p <0.001), the skin to skin contact (OR=6.61, p = 0.001) and the first latch-on within 1 hour after birth (OR=3.00, p=0.02) were associated with a high satisfaction. Conversely,

mothers who were asked to consider using breast pumps (OR=0.14, p<0.001), and the integration with infant formula (OR=0.09, p<0.001), were less likely to have high satisfaction.

DISCUSSION

Our study explored the mother's perception of cares during hospital stay, showing overall a high satisfaction rate, in the first days after childbirth. Satisfaction is a multi-dimensional concept affected by several factors such as personal features, values and expectations [25]. Patient satisfaction during childbirth is one of the main outcomes frequently used for measuring the quality of care in health institutions affecting mother's satisfaction [26, 27]. In our results, this aspect is positively associated with the attendance of antenatal classes, vaginal birth, rooming-in, skin to skin contact and the first latch-on within 1 hour after birth. Most of these findings are in line with a study, which investigated maternal satisfaction regarding care during delivery [28]. The attendance to antenatal classes represents the first step for a positive birth experience and, moreover, improves women's awareness and empowerment [29]. A study which evaluated the effects of the antenatal classes on mothers' and babies' health and women's satisfaction, found that women attending courses were more satisfied with the experience of childbirth and had better health outcomes [30].

Another aspect emerged in our study is that women who had vaginal birth are more likely to be satisfied. These findings are consistent with other studies [31-34]. In this context, the father plays a key role in the delivery-room and, therefore, it is necessary also to consider the fathers' birth satisfaction and their role as a future parent and not only as the mother's partner [35, 36]. Bélanger-Lévesque *et al*. showed that mothers consider themselves more prepared and more supported during childbirth than fathers, and these ones were less satisfied with quality of care provision, their baby's health and the mother's health [37].

Our women seemed to be more satisfied with rooming-in during hospitalization. This result is in line with another Italian study on mother's views about rooming-in, showing that women were satisfied with rooming-in offered by the hospital, despite several difficulties with baby's management [38]. For this purpose, a continuous support and help from health professionals is important to create a positive rooming-in experience for postpartum mothers. Likewise, skin to skin contact reached the same results. In fact, it was positively associated with a high satisfaction score as also found in other studies [39, 40]. Research suggests that this aspect is also confirmed after caesarean section [41] and the association between skin to skin and birth satisfaction is especially strong for women who had operative births [42]. The high maternal satisfaction following skin to skin contact underlines the importance of increasing this practice, in addition to all others the health benefits [43, 44]. This approach is included in the framework of "Zero Separation" according to which keeping mother-baby together from birth, protects physiological and neurophysiological processes for both, and guarantees successful breastfeeding [45].

We found that women who were advised to use a breast pump or those who used the integration with infant formula were less satisfied. We may speculate that the use of mechanical support, as breast pump, make the mother feel inadequate, reducing her confidence in her body and ability to breastfeed. This is supported by research on breastfeeding self-efficacy perception, which is strongly associated to maternal breastfeeding satisfaction [46]. As for formula feeding, several qualitative and quantitative studies reported negative emotions experienced by mothers using breast milk substitutes [47-49]. As secondary outcome, our results reported a high prevalence of exclusive breastfeeding of the women included in the study and its association with best practices and receiving a practical support by midwives.

As confirmed by our study, decision makers and clinicians should invest in breastfeeding promotion and support programs, including good practices during pregnancy and childbirth, in order to improve maternal satisfaction, as provided by the Emilia Romagna Region policies [20]. It is known that the absence of support for breastfeeding in the workplace, the advertising of formula, and lack of knowledge of the women, partners, family members, healthcare providers and policy makers contribute to low rate of exclusive breastfeeding [6]. Thus, our organizational model [22], documented in literature [50] and based on "dedicated" personnel to support breastfeeding [51], was effective in promoting mothers' satisfaction and breastfeeding rates.

Among the limitations of this study, we acknowledge the reduced number of questionnaires, which is related to the fact that the 40% of women who give birth at the university hospital are foreigners, with a level of linguistic competence not compliant with the research. This certainly has an impact on the generalizability of our results. In order to offer an overview of the foreign population, we suggest a broader study using a questionnaire translated into multiple languages and with support of cultural mediators, in order to break down language barriers.

CONCLUSIONS

Mothers' satisfaction is one of the most important factors for a positive experience during hospital stay and for better health outcomes. Improving quality of care is fundamental to achieve Universal Health Coverage by 2030 [52]. Our results are in line with Academy of Breastfeeding Medicine protocol [53], which recommends, among other things, the skin to skin contact, rooming-in, support to breastfeeding, the non-use of formula feed, physiological labour and birth, and the non-use of artificial nipples. Furthermore, our organizational model ensured maternal satisfaction and good practices. To increase the number of mothers who received a satisfactory delivery provision of care, contributes to enhance the use of the services, especially for hard-to-reach women. It is, therefore, advisable to invest in pre-service and in-service training of dedicated personnel and guarantee one-to-one organizational models of care.

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Author contribution statement

All Authors participated in the interpretation of the study results and approved the final manuscript as submitted and they agree to be accountable for all aspects of the work.

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Health Belief Model efficacy in explaining and predicting intention or uptake pertussis vaccination during pregnancy

Francesca Zambri[1], Ilaria Perilli[2], Alessia Quattrini[2], Francesca Marchetti[1], Sofia Colaceci[3] and Angela Giusti[1]

[1]*Centro Nazionale per la Prevenzione delle Malattie e la Promozione della Salute, Istituto Superiore di Sanità, Rome, Italy*
[2]*Dipartimento di Biomedicina e Prevenzione, Università degli Studi di Roma "Tor Vergata", Rome, Italy*
[3]*Saint Camillus International University of Health and Medical Sciences (UniCamillus), Rome, Italy*

Abstract

Introduction. Pertussis is a highly contagious respiratory disease and vaccination of pregnant women seems to be the most effective strategy to prevent pertussis in infants. The aim of this study is to assess the acceptance by women of pertussis vaccination during pregnancy based on Health Belief Model (HBM) constructs.

Methods. A multicentre observational study was carried out with a convenience sample of 300 respondents.

Results. Most women were worried to contract or to transmit pertussis during the first months of the infant's life and perceived pertussis contracted in the first months of life as very serious. Parity appears to be a factor predicting this health behaviour, as nulliparous women tend to get more vaccinated or have a higher intention to get vaccinated (ORa 2.8 CI 95% 1.5-5.2 p<0.01).

Discussion and conclusions. HBM is an effective tool for identifying facilitators and barriers to health behaviours. Strategies to promote vaccination during pregnancy are needed, including educational interventions and communication campaigns.

Key words

- health belief model
- vaccination
- pregnancy
- health promotion

INTRODUCTION

Pertussis is a highly contagious respiratory disease caused, in most cases, by the Gram-negative coccobacillus Bordetella pertussis. Symptoms develop after an incubation period of approximately 7-10 days (range 5-28 days), with mild, moderate or severe symptoms [1] and the pathology persists from 6 to 12 weeks, or longer.

According to the latest WHO updates, there were 132,754 cases of pertussis in 2019, despite an 85% three doses vaccination coverage against diphtheria-tetanus-pertussis (DTP) [2]. In Italy, there is a decreasing trend of pertussis mainly due to the increase in vaccination coverage [3, 4]. The incidence ranges from 0.88 to 0.85 (2013-2015) and the decrease was observed also for 0-5 years children [4].

Pertussis in newborns and infants can be associated with an increased risk of morbidity and mortality, with a clinical manifestation that may differ based on age, immunization status and presence or absence of antibodies transmitted through placenta [1, 5-7]. This risk is higher in the first 6 months of life [8].

Several studies have shown that the source of infections for infants is usually a family member, in most cases the mother [9, 10]. Based on these observations, the cocooning approach involves the use of Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) for parents and people who come into close contact with infants to reduce the risk of pertussis transmission [10, 11]. Vaccination of pregnant women, however, seems to be the most effective and cost-effective strategy to prevent pertussis in infants who are too young to be vaccinated [12]. Tdap vaccination has not been associated with an increased risk of adverse outcomes for the mother or foetus, with the exception of a small increased risk of chorioamnionitis [13, 14]. Women should be vaccinated between 28 and 32 weeks of pregnancy, or, otherwise, during the postpartum [15].

Address for correspondence: Francesca Zambri, Centro Nazionale per la Prevenzione delle Malattie e la Promozione della Salute, Istituto Superiore di Sanità, Via Giano della Bella 34, 00162 Rome, Italy. E-mail: francesca.zambri@iss.it.

The Italian Ministry of Health in the "National Vaccinal Prevention Plan" (2017) and in a policy document, recommends the vaccine against diphtheria, tetanus and pertussis to all pregnant women, even if the woman has already been vaccinated or has performed ten-year boosters or has had pertussis [15, 16]. According to data from the Italian National Institute of Health, child vaccination coverage in Italy is on average 94.99% [17].

The choice of pregnant women to get vaccinated against pertussis is influenced by knowledge. The level of information is often low and increases with higher levels of education. Favourable attitudes also demonstrated to be associated with vaccination choice [18]. The main barriers include concerns on the vaccine safety, the belief that it is not necessary or effective, the fact of not being recommended by the healthcare professional (HCP), access problems, costs and conflicting advice [19]. Different conceptual frameworks have been proposed in order to predict health choices and behaviours, such as the Health Belief Model (HBM).

The HBM is a theoretical model that aims to investigate what factors influence the health choices and behaviours of an individual and the access to healthcare services [20]. The six constructs of HBM are: *risk susceptibility, risk severity, benefits to action, barriers to action, cues to action and self-efficacy* [21, 22]. The effectiveness of the HBM has been widely demonstrated as it has been used in different areas [23-25], also effective in assessing the vaccination degree of acceptance during pregnancy [26-28].

In Italy, despite the existence of a national surveillance system on other population groups [17], there is still no available data on pertussis vaccination in pregnant women. To our knowledge, there is no Italian study on HBM effectiveness investigating the factors that influence the choice to vaccinate against pertussis during pregnancy. Therefore, the aim of this study is to assess the factors that influence the acceptance by Italian women of pertussis vaccination during pregnancy based on HBM constructs and the characteristics associated with non-vaccination.

METHODS

Design

A multicentre observational study was carried out.

Participants and setting

Two days a week, all women at 2nd and 3rd trimesters of pregnancy attending the maternal clinic outpatient of two Italian hospitals were invited to participate to the study. The exclusion criteria was not being able to read and understand the Italian language. From October 2019 to January 2020 a convenience sample of 300 respondents was achieved. None refused to answer the questionnaire. One hundred and fifty women were recruited from an accredited Italian private facility, while the other 150 women were recruited from an Italian public facility. All participants gave their oral informed consent, following the explanation of the study's purpose and methods. A self-administered, anonymous questionnaire was provided to women at two different centres simultaneously, and full availability was guaranteed for any procedural clarifications during compilation.

Study instrument

The questionnaire, including validated items on the effectiveness of the HBM in predicting the levels of acceptance of pertussis vaccination during pregnancy [29], was divided into two sections. The first provided 6 socio-demographic items and 2 related to the intention to get vaccinated. The second section included the six HBM constructs using a 5-point Likert scale, ranging from "1-Completely agree" to "5-Completely disagree" (Cronbach's alpha=0.76).

Authorization and privacy

The Head of Health Department of both hospitals agreed for the administration of the anonymous questionnaire. The responders were informed and agreed to the use of anonymous data in accordance with Italian and European Data Protection legislation.

Data analysis

Descriptive and inferential analyses were performed. Frequency and percentage of demographic were determined and a bivariate analysis allowed to assess the presence of statistically significant associations. Logistic regression was performed to identify predictors of vaccination or the intention to be vaccinated against pertussis. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Statistical measurements were conducted using Epi InfoTM v. 7.0 (CDC). By convention, the significance level was set at 0.05 ($p<0.05$).

RESULTS

Demographic characteristics

The average age of the sample was 33.3 years (SD±6), 83.3% were Italian and 53.3% were married. About parity, 50% of women were nulliparous, the other 50% said they had 1 (37%) or 2 or more children (13%). Of 300 women, 48.3% were vaccinated or planned to get vaccinated against pertussis during the current pregnancy *(Table 1)*.

HBM and pertussis vaccine

The frequency of the HBM model dimensions is shown in *Figure 1*.

With regard to *risk susceptibility*, 57% of women declared that they were worried to contract pertussis during the first months of the infant's life with 23% unsure about this risk. The concern to transmit pertussis in the first months of the infant's life was expressed by 64% of women, while 76% were worried that someone else could transmit to both mother and baby. Furthermore, 80% perceived pertussis contracted in the first months of life as very serious (*risk severity*). In relation to the perceived *benefits*, 75% of the women agreed that vaccination against pertussis in pregnancy could reduce the mother's risk of contagion, with 23% of women unsure. In addition, 70% agreed that vaccination protects the baby's health in the first months of life, 25% were unsure. As for the perceived *barriers*, despite 54% disagreeing, there were 33% of women unsure whether the

Table 1
Women's socio-demographic characteristics and frequencies of pertussis vaccination or intention to get vaccinated

Data of participants	n (%)
Mean age in years	33.3 (SD±6)
Nationality	
Italian	250 (83.3)
Foreigner	50 (16.7)
Marital status	
Married	160 (53.3)
Unmarried	133 (44.3)
Separate/Divorced	7 (2.4)
Educational level	
University degree	143 (47.7)
Secondary school	132 (44)
Lower secondary	20 (6.7)
Primary school	5 (1.6)
Occupation situation	
Employed	201 (67)
Housewife	35 (11.7)
Unemployed	33 (11)
Student	4 (1.3)
Other	27 (9)
Parity	
Nulliparous	250 (50)
1 or ≥2	250 (50)
Pertussis vaccination or intention to get vaccinated	
No	155 (51.7)
Yes	145 (48.3)

vaccine could transmit pertussis. The perception of the vaccine as unsafe for the health of the foetus during pregnancy also had 33% of women unsure and 53% disagree. The fear of injections did not represent a serious barrier to vaccine (63% disagreement), compared to the lack of adequate information on vaccinations (55% agreement). This is confirmed by the fact that 74% of women agrees on the importance of the role of professional recommendations about vaccination. Only 15% reported that friends and family discouraged them to get vaccinated during pregnancy and 55% affirmed they trust the guidelines with 32% unsure. With regard to self-efficacy, 57% thought they had received all the information needed to decide whether to get vaccinated or not, 20% were unsure and 23% disagreed.

Most HBM constructs were associated with intent or getting vaccinated during pregnancy *(Figure 2)*, confirming its role in explaining or predicting health behaviours and choices.

Only the fear of injections and the role of friends and family did not affect the vaccination choice. A high educational level has been significantly associated with not being worried to transmit pertussis to infant in the first months of life (ORa 0.2 CI 95% 0.05-0.7 p<0.01) and with the perception of not having received all information needed to decide whether to get vaccinated or not (ORa 0.4 CI 95% 0.1-0.9 p<0.05). Being employed was significantly associated with the fact that injections do not represent an obstacle to vaccination (ORa 2.3 CI 95% 1.3-3.9 p<0.01), with not being worried to lack of knowledge on vaccinations during pregnancy (ORa 1.9 CI 95% 1-3.8 p<0.05) and with not having been discouraged by friends and family to get the vaccination (ORa 2.1 CI 95% 1.2-3.6 p<0.01). Having one or more children was associated with the concern of transmitting pertussis to infant during the first months of life (ORa 1.8 CI 95% 1.1-2.9 p<0.01). The Italian nationality was negatively associated with this construct (ORa 0.3 CI 95% 0.1-0.7 p<0.01) and showed a significant association also with not being afraid of injections (ORa 3 CI 95% 1.6-5.8 p<0.01), with not being discouraged by friends and family to vaccinate during pregnancy (ORa 2.9 CI 95% 1.6-5.5 p<0.01) and with the perception of not having received all information needed to decide

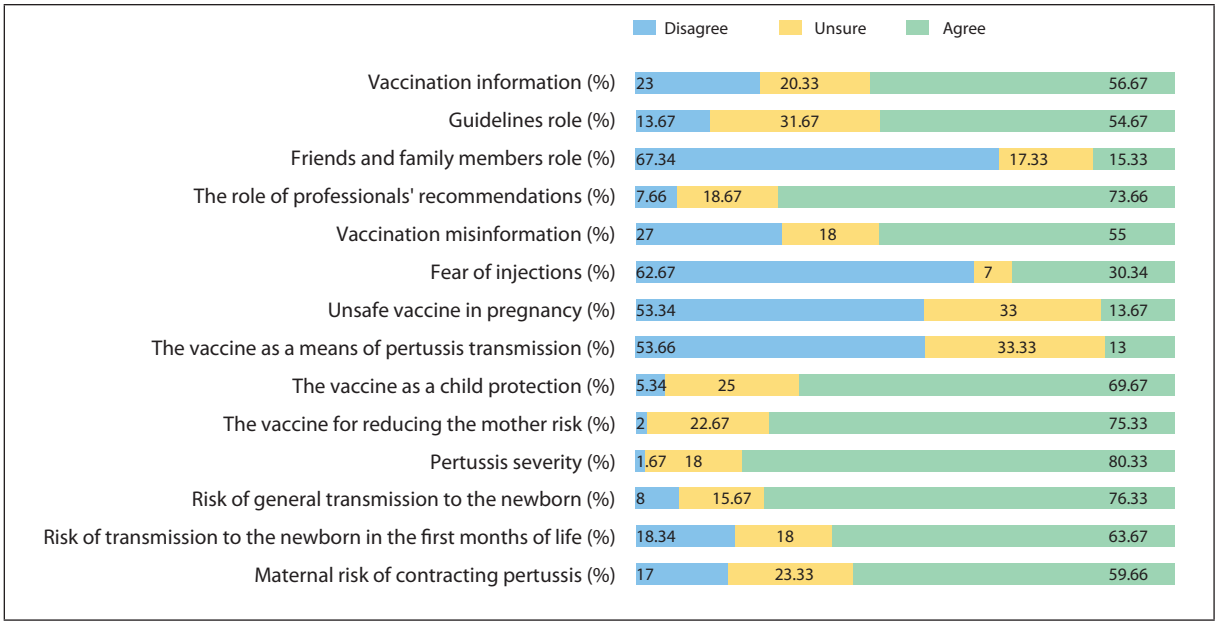

Figure 1
Frequency of the HBM model dimensions (n=300).

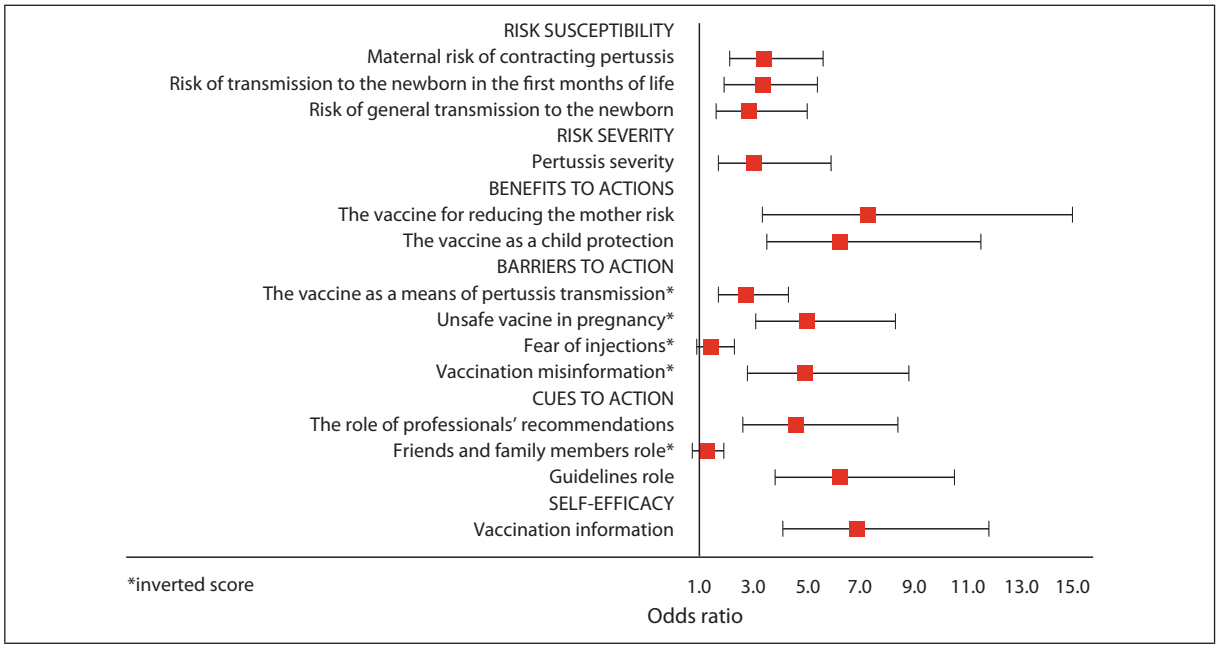

Figure 2
Frequency of the HBM model dimensions (n=300).

whether to get vaccinated or not (ORa 0.4 CI 95% 0.2-0.8 p<0.01). Fear of injections represented a barrier in women aged less than or equal to 31 years (ORa 0.4 CI 95% 0.3-0.7 p<0.01) *(Table 2)*.

The logistic regression model showed factors associated with intent or vaccination against pertussis during pregnancy *(Table 3)*.

Parity appears to be a factor predicting this health behaviour, as nulliparous women tend to get more vaccinated or have a higher intention to get vaccinated against pertussis (ORa 2.8 CI 95% 1.5-5.2 p<0.01). The other associated factors are healthcare related: receiving the recommendation to vaccinate from a health professional (General Practitioner, gynaecologist, midwife) (ORa 2.8 CI 95% 1.4-5.7 p<0.01), trust in guidelines recommending vaccination during pregnancy (ORa 3.5 CI 95% 1.9-6.4 p<0.01), and the perception of having received all the information needed to take an informed choice (ORa 5.8 CI 95% 3.1-10.7 p<0.01).

Table 2
HBM and social-demographic characteristics

	I am worried that I will transmit pertussis to my baby during his/her first months of life (risk susceptibility)	I'm afraid of injections (barriers to action)*	I'm worried there may be things I don't know about vaccinations in pregnancy (barriers to action)*	Friends or family members have discouraged me from getting vaccinated during pregnancy (cues to action)*	I believe I have received all the information needed to decide whether to get vaccinated (self-efficacy)
Educational level					
High	61.5%	–	–	–	54.9%
Low	88%				76%
Occupation situation	–	67.5%	29.8%	71.5%	–
Employed		47.2%	18%	80.7%	
Unemployed					
Parity					
1 or ≥2	70.7%	–	–	–	–
Nulliparous	56.7%				
Nationality					
Italian	60%	67.2%	–	71.6%	53.6%
Foreigner	82%	40%		46%	72%
Age					
≤31	–	51.3%	–	–	–
>31		69.9%			

*inverted score.
HBM: Health Belief Model.

Table 3
Logistic regression model

	Intention or uptake of pertussis vaccination during pregnancy (yes *vs* no) ORa (CI 95%)
Parity	
1 or ≥2	1
Nulliparous	2.8 (1.5 - 5.2)
Receiving the recommendation to vaccinate from a health professional (general practitioner, gynaecologist, midwife)	
Disagree	1
Agree	2.8 (1.4 - 5.7)
Trust in guidelines recommending vaccination during pregnancy	
Disagree	1
Agree	3.5 (1.9 - 6.4)
Perception of having received all the information needed to take an informed choice	
Disagree	1
Agree	5.8 (3.2 - 10.7)

DISCUSSION

Our results show that HBM is a good model to explain and predict the intention or actual uptake of pertussis vaccination in pregnancy. About half (48.3%) of pregnant women said they had been vaccinated or plan to get vaccinated against pertussis. This percentage is higher than in other studies. In a previous study that investigated knowledge, attitude and practice toward pertussis vaccination during pregnancy among 347 pregnant and postpartum Italian women, 21% of pregnant women expressed a willingness to be vaccinated [30]. It is possible that, despite vaccination rates in pregnancy are still not sufficient, the ministerial recommendations and health services campaigns have positively influenced the increase in vaccination coverage [15].

In our study, the high frequency of pertussis vaccination intention or actual uptake is associated to higher frequency of risk susceptibility and severity (concern of contagion or transmission to the baby, considering pertussis contracted in the first months of life as very serious). Previous studies investigated the knowledge about the severity of pertussis, showing that it is considered a serious threat to newborns [31, 32], with increased risk of hospitalization [33]. For this reason, most women consider the pertussis vaccination necessary for the newborn protection [33].

While knowledge and attitudes are determinant to health behaviour, in a previous study [30] 35% of women did not know that children <1y represent the age group with the highest risk of infection. Furthermore, although few, some women believe that the vaccine does not protect newborns from pertussis during the first months of life and that it is harmful to the development of the foetus [30].

Most of our women agreed that vaccination against pertussis in pregnancy was able to reduce the mother's risk of contracting pertussis but some were unsure. This is consistent with a previous study in which several women, despite being aware of the potential useful of the vaccine, were not convinced that maternal immunization should be done [33]. Although in most cases women disagreed on the perception of the vaccine as unsafe to the health of the foetus, some were unsure. This is also confirmed by a previous study that investigated attitudes, practices and perceived barriers by gynaecologists regarding vaccination against influenza and pertussis during pregnancy [34]. In this study, fear or scepticism about pertussis vaccination during pregnancy often led to rejection, despite a thorough explanation of the benefits. Agricola *et al*., show that some women considered the vaccine as harmful for the foetus' development and believed that the vaccination did not protect the infants against pertussis during the early months of life [30]. This attitude recalls the "good mother myth" regarding the use of medication during lactation, according to which the breastfeeding women tend to give up the medicine to avoid exposing the children to a risk [35].

Our results show that fear of injection did not represent a barrier to vaccine, despite some suggestions in the literature on blood and injection phobia among pregnant women [36].

Studies on the determinants of vaccine refusal indicated that low perception of immunization safety, poor information and lack of professional encouragement represent the main barriers to vaccination [31, 37, 38]. The HCPs are considered as a trustable source of vaccine information, followed by national Public Health Organizations and Scientific Societies, but only few women receive a recommendation by their health care professionals to receive pertussis immunization during pregnancy [30]. Safety information regarding the mother and the newborn are considered the most important information in deciding whether to be vaccinated and often gynaecologists were the preferred HCPs for the provision of information, followed by paediatricians, and local health unit staff [33]. The recommendation given by a HPC is positively associated to other women's health behaviours, e.g. the participation to cervical cancer screening, and considered among the most relevant factors for screening uptake [39]. The fundamental role of professionals is also recognized in our study, where women considered the recommendations to vaccinate given by a HCP as a cue to action, regardless their socio-cultural background, and show a greater intention or actual vaccination uptake. Thus, health systems should be encouraged to promote individual evidence-based communication interventions. The time dedicated to effective communication provided to women by HCPs produces results in terms of intentions to get vaccinated or vaccinated. This is confirmed by previous studies showing an increase in vaccine intention and coverage after the motivational interviewing intervention of 15-20 min [40, 41]. However, it is important to make sure that women truly have the perception that they have asked all the questions and resolved all the knots and all the doubts. To achieve this, the communication time must be considered within the care provision.

Our logistic-regression model shows that nulliparous women tend to get more vaccinated or have a higher intention to get vaccinated against pertussis than multiparous confirming what reported in another study which determined the facilitators and barriers to pertussis and influenza vaccine [42]. This could be explained by the fact that multiparous women do not consider necessary to repeat the vaccination in the next pregnancy, therefore they should be one of the main targets of vaccination campaigns.

This study has some limitations: the use of a convenient sample of women and a questionnaire that includes items from validated questionnaires, but overall it has not undergone a validation process.

CONCLUSIONS

Our study shows that theoretical frameworks such as HBM are an effective tool for identifying facilitators and barriers to health-generating behaviours, such as pertussis vaccination. Vaccinations during pregnancy are an important strategy to reduce morbidity and mortality from infectious diseases in women and their newborn and this is confirmed by the ItOSS report on maternal mortality, which reports that some maternal deaths from sepsis have been attributed to influenza in unvaccinated women [43]. Moreover, strategies to promote vaccination during pregnancy are needed, including educational interventions and effective communication campaigns. Recommending pertussis vaccination during preconception period can be a further strategy that allows higher acceptance of vaccination and therefore higher vaccination coverage. The action plan to increase vaccination levels in pregnancy must also start with the professionals training in the birth pathway. In this way, they will be able to provide adequate and standardized information to women in order to obtain an informed choice. Midwives play a fundamental role in protecting the health of the mother, the child and the community, and they can promote vaccinations during pregnancy.

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Author contribution statement

All Authors participated in the interpretation of the study results and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest statement

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ORIGINAL ARTICLES AND REVIEWS

Mortality temporal trends and cancer incidence profiles of residents in the petrochemical industrially contaminated town of Gela (Sicily, Italy)

Daniele De Rocchi[1], Amerigo Zona[2,3], Rosario Tumino[4], Viviana Egidi[5] and Roberto Pasetto[2,3]

[1]*Istituto di Ricerche sulla Popolazione e le Politiche Sociali, Consiglio Nazionale delle Ricerche, Rome, Italy*
[2]*Dipartimento Ambiente e Salute, Istituto Superiore di Sanità, Rome, Italy*
[3]*WHO Collaborating Centre for Environmental Health in Contaminated Sites, Istituto Superiore di Sanità, Rome, Italy*
[4]*Registro Tumori di Caltanissetta e Ragusa, Ragusa, Italy*
[5]*Dipartimento Scienze Statistiche, Sapienza Università di Roma, Rome, Italy*

Abstract

Objective. In 2000, a vast area in Gela (Sicily, Italy) was defined as a national priority contaminated site due to pollution from a petrochemical complex. This study is aimed at addressing the influence of the petrochemical complex on the health profile of residents in Gela.

Methods. Trend analysis by gender was performed for mortality for all diseases and malignant cancers, in the period 1980-2014 for residents in the municipality of Gela, by directly standardized rates and Joinpoint regressions, using, as a reference population, people resident in the Sicily region. SMRs were computed for 5-year periods in the same timespan. Since the beginning of the period analyzed, the share of population of Gela represents 1.5% of total residents in Sicily. Cancer incidence was analyzed for the period 2007-2012 applying a hierarchical Bayesian model to estimate Standardized Incidence Ratios (SIR). Ranks of these ratios were computed to highlight the most incident diseases affecting the population. Malignant neoplasms of lung, stomach and colon were selected because of *a priori* interest, as they are associated, in etiological terms, with the main contaminants found in the area. Malignant neoplasms of liver, pancreas and larynx were selected as "control diseases" since they share the same main risk factors (smoke and alcohol consumption) of neoplasms of *a priori* interest, but are not associated with the priority index contaminants identified in Gela.

Results. Mortality rates for all causes combined in both genders in Gela decreased over time, but they were higher than those of the whole Sicilian population. The trend of mortality rates due to all malignant cancers increased in men, especially from 1980 to 1987. This result was confirmed by the Joinpoint regression (annual percentage change (APC) 9.8). SMRs analysis showed significant excesses in mortality due to all diseases for both genders compared to the reference population. Other excesses were observed for mortality due to malignant cancers in men and for circulatory diseases in women. The trend for cancers in women in Gela increased from the mid-nineties but less than in men. SIR estimates were higher than 1 for all the diseases analyzed and in both sexes, and their ranks highlighted that cancer sites of *a priori* interest hold higher positions than "control diseases", although credibility intervals overlapped.

Conclusions. Results highlight that the health profile of residents in Gela is worse than the one of the reference population. Moreover, cancer incidence is in excess in all the sites analyzed and mortality due to all cancers combined has a trend compatible with a cumulative impact due to petrochemical contamination.

Key words
- contaminated sites
- petrochemical industry
- mortality
- cancer incidence
- temporal trends

Address for correspondence: Daniele De Rocchi, Istituto di Ricerche sulla Popolazione e le Politiche Sociali, Consiglio Nazionale delle Ricerche, Via Palestro 32, 00185 Rome, Italy. E-mail: daniele.derocchi@irpps.cnr.it.

INTRODUCTION

World Health Organization (WHO) defines contaminated sites as "areas hosting or having hosted human activities which have produced or might produce environmental contamination of soil, surface or groundwater, air, food chain, resulting or able to result in human health impacts" [1]. In 1998 (law 426/98), in Gela (Sicily), a vast area close to the town was defined as national priority contaminated site due to pollution from a petrochemical complex built in 1960 and active since 1962. It hosted a large oil refinery, as well as thermoelectric power and petrochemical plants for production of organic and inorganic chemicals. The oil processing waste polluted the close environmental matrices: air, soil and, due to long time disposal, the stocked waste polluted also the groundwater. Moreover, a specific chemical waste, the Petcoke, was reused as a fuel for the thermoelectric power plant instead to be treated as dangerous waste.

In 2000, with the Legislative Decree, the area covering the entire petrochemical complex and an extended sea portion was officially identified to be remediated [2] and data gathered since the same year by the Istituto Superiore di Sanità (ISS, the Italian National Institute of Health) documented heavy groundwater, soil and air contamination [3].

After a first seizure in 2002, the industrial complex was gradually downsized until the closure in 2014. Then, a conversion of a small portion of the industrial site to renewable energy production was begun. Meanwhile, in 2009, environmental matrices analysis showed the presence of arsenic and heavy metals like lead and mercury (and vinyl chloride) thousand times more than the threshold values permitted by law [4]. In September 2019, a new bio refinery unit started its operations.

Focusing on the health profile of people in Gela, previous studies on residents and petrochemical site workers, showed excesses lung cancer mortality for both genders, hospitalizations due to acute and chronic respiratory diseases and pneumoconiosis, and congenital malformations of the nervous, cardiovascular and genitourinary systems [2; 5-7]. Exposure to some of the priority index contaminants identified in the polluted area is associated to several non-malignant diseases. Long-term arsenic assumption can cause diabetes and severe neurologic diseases [8], while exposure to lead is associated to neurotoxic effects and circulatory system diseases (i.e. hypertension) [9].

This study is aimed at evaluating the risk of mortality and cancer incidence for the population residing in Gela associable with the pollutants found in the widespread petrochemical contaminated area.

METHODS

Mortality and incidence are analyzed in this study. A trend analysis of mortality was made to focus on the evolution of the health profile of the population of residents in the municipality of Gela. The period considered is from 1980 to 2014, beginning twenty years after the start of activities of the petrochemical complex. Mortality for all diseases, malignant neoplasms (ICD10 codes C00-C97), four groups of causes relatives to the main systems (circulatory (I00-I99), respiratory (J00-J99), digestive (K00-K93) and genitourinary (N00-N99) and for malignant neoplasm of bronchus and lung (C34) was analysed using different tools. The latter disease was chosen because of the consistent results on excess of risk observed in other studies [2, 3]. Analyses were computed for both genders and for all ages.

Age directly standardized rates of death due to all diseases and to malignant neoplasms were computed for both genders, year by year, for the population residing in Gela and the entire Sicily. Standardized rates, computed having the Italian population of 2011 as reference, were calculated considering the first two twenty-year age classes (0-19, 20-39), and the others of ten-year, excluding the last one (80+). Simple centred moving averages (5-year periods) of rates for Gela's residents were used to improve their statistical stability. The Jointpoint regression [10] was applied to estimate the annual percentage changes (APCs). This estimator allows to highlight how rates change year by year and if the percentage change is statistically significant.

Standardized Mortality Ratios (SMRs) by gender were computed, with 90% confidence level, for the health profiles of residents in Gela (75,668 individuals)[1] considering the whole regional Sicilian population as reference (5,002,904 individuals)[1]. The Sicilian population was chosen as reference to balance the trade-off between similarity with the population of interest (in terms of lifestyles and habits) and the number of residents large enough to ensure stability of rates for age classes and rare diseases. SMRs were computed by gender for all diseases, malignant cancers, bronchus and lung cancer and for four groups of causes relatives to the main systems (respiratory, circulatory, digestive and genitourinary) splitting the whole period in five-year sub-periods. SMRs were computed for all ages, and for three macro-age classes (0-29, 30-64, 64+) and the specific age class 45-69. The last age class was chosen to maximize the difference, during the time window observed, in terms of share of years of life with potential exposure to the pollutants from the petrochemical complex. In 1980, first year with data available, people deceased in that age class were potentially exposed only for the last twenty years of life, while in 2014, last year with data available, people deceased were potentially exposed for almost the entire life.

Standardized Incidence Ratios (SIRs) were computed to analyze cancer incidence using data of the Caltanissetta province cancer registry to assess the cancer cases in the population of Gela in the 2007-2012 period. The population of regions belong to the macro area "South Italy and Islands" as reference (20,619,697 individuals)[1], using the methodological approach for cancer incidence data, applied in the last report of SENTIERI, the epidemiological surveillance system of residents in Italian main contaminated areas [3]. This approach was among those promoted within the Industrially Contaminated Sites and Health Net-

[1] People resident in Gela and Sicily in 2011, year of the last Census in Italy.

work (ICSHNet; www.icshnet.eu) to conduct descriptive studies for providing health profiles of populations living close to or in contaminated areas [11]. Twenty-two cancer sites for men and nineteen for women were considered. These sites were chosen considering the epidemiological evidences of association observed with the pollutants from the complex and are mutually exclusive. Some cancer sites were selected considering the health effects of the priority index contaminants identified following the methods developed in SENTIERI [3, pp. 180-188]. Following the evaluation of the epidemiological evidence of the association between specific causes and environmental exposures in SENTIERI [12], with regards to the typology of the complex, cancer sites of lung, stomach and colon were selected as *a priori* interest. Moreover, they are associable, in etiological terms, to some priority index contaminants found in the area (e.g. Arsenic, Cadmium, Chromium VI, Nickel, Lead). Malignant neoplasms of pancreas, larynx and liver (only pancreas and liver for women because cases of larynx neoplasm were not enough in the observation period (< 3)) were selected as control diseases since they have the same main risk factors associated to lifestyle (smoke and alcohol consumption) of cancer sites of *a priori* interest, but are not associable to the priority index contaminants identified in Gela [13]. SIRs were computed by means of a hierarchical Bayesian model based on Monte Carlo Markov Chain [14, 15]. In the applied Bayesian model, the data information (likelihood) was used choosing a non-informative prior distribution. The number of observed cases Y_i, has a Poisson distribution with parameter λ_i, as a product of the expected and known number of cases E_i, and the parameter of interest, the SIR, θ_i. The hierarchical structure of the model, defines that θ_i is defined by an *a priori* distribution with hyperparameters. In this case, the log transformation of θ_i has a Normal distribution with non-informative hyperparameters μ and $1/\sigma$ distributed, respectively, as a Normal (0, 0.0001) and a Gamma (0.1, 0.1). The rank of the estimated SIRs was calculated, with 80% credibility level, to highlight which diseases have the highest or lowest ratios [16]. Given K diseases, the rank of the disease *i* is defined by number of times the SIR of that disease is higher than the SIRs of other diseases.

RESULTS

Trend analysis of mortality for all diseases show that rates for men and women in Gela were decreasing over time, but they were always higher than the Sicilian ones (*Figure 1*). Gela's rates decreased from 205 deaths per 10,000 inhabitants to 135/10,000 in men and, from 185/10,000 to 100/10,000 in women. Sicilian rates decreased to 125/10,000 for men and 88/10,000 for women. The results from the trend analysis of mortality for all malignant cancers in Gela show an increase of rates from less than 25 deaths per 10,000 inhabitants (1980) to 45 deaths per 10,000 (2000) in men. From 2000 rates started to decrease to reach about 38/10,000 in 2014. There was an increase also for women but lower than in men, with the highest value, 25/10,000 (*Figure 2*), in 2004.

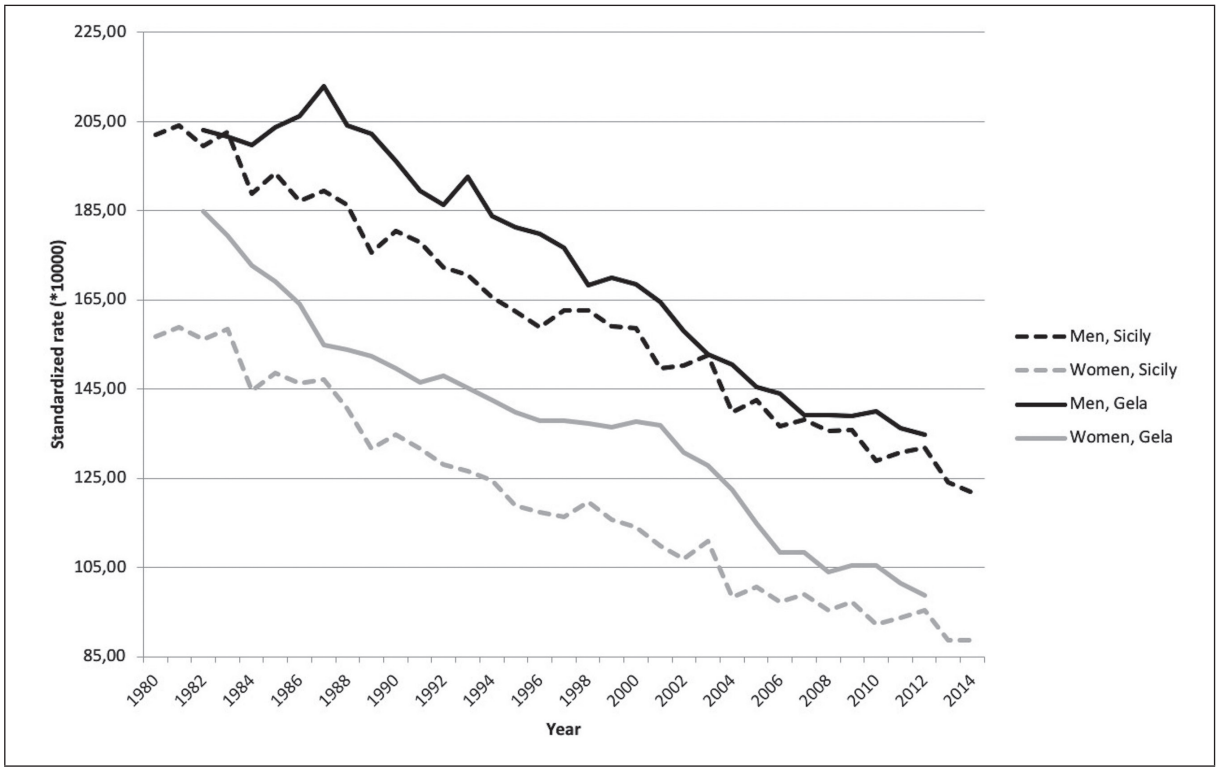

Figure 1
Directly Standardized rates: comparison Gela-Sicily, mortality due to all diseases, both genres, 1980-2014.

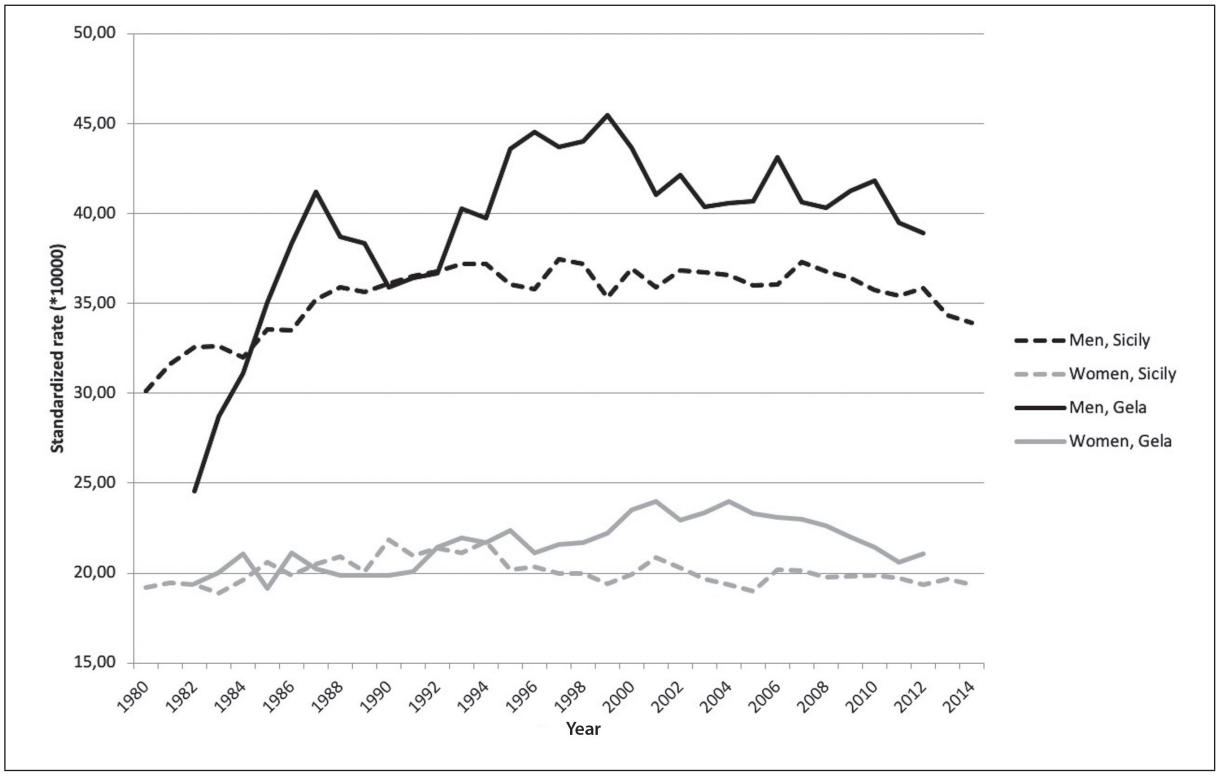

Figure 2
Directly Standardized rates: comparison Gela-Sicily, mortality due to malignant neoplasms, both genders, 1980-2014.

Main results of the Jointpoint analysis are reported in *Table 1*.

SMRs for all diseases, all ages, are almost always higher than one and statistically significant, both for men and women. For men SMRs have values between 1.04 [0.99, 1.09] in the period 1980-1984 and 1.17 [1.12, 1.22] in 1990-1995, since for women lowest value is 1.13 [1.07, 1.19] obtained for the period 1985-1989 and highest one is 1.25 [1.19, 1.31] in the period 2000-2004.

Focusing on mortality due to cancers for all age's men, the profile during the period analyzed is worse than Sicilian one, with SMRs higher than one from 1984 to 2014 with the highest value, 1.22 [1.12, 1.32] in the period 1995-1999. For women, instead, until 1994 values of SMR are lesser than one but since 1995 started to increasing over one until the period 2005-2009 (SMR=1.19 [1.08, 1.30]). Among all malignant cancers, the analysis was focused on the bronchus and lung cancer: for men, an increase of SMR estimates is observed since 1990, 1.00 [0.84, 1.20], until 2004, 1.46 [1.28, 1.67] among all ages. Focusing on results for specific age classes, SMRs in men show risk in excess between 30 and 64 years old in the last period of the study (2000-2014) with an average SMR of 1.36. In absolute terms, in these 15 years, 135 are the observed cases in men vs. the 95 expected. For men of 65+ an SMR of 1.51 [1.28, 1.76] is observed in the period 2000-2004. The SMR trend for women is more fluctuating showing two significant peaks in the periods 1995-1999 and 2005-2009 with values 1.62 [1.14, 2.30] and 1.52 [1.15, 2.00]. For women, the stability of the excess in mortality for circulatory system diseases is observed during all the years analyzed: since the beginning in 1980 until 2009 the values are always higher than 1.20, with confidence interval never contain the unit. Significant excesses in mortality due to genitourinary system diseases are also detected (*Table 2*).

Results of Bayesian analysis show SIRs in men for all the malignant tumours higher than one, but only the

Table 1
Joinpoint regressions, malignant cancer mortality APC, both genders, 1980-2014

	Years	APC	CI (95%)
Men, Gela	1980-1986	9.8**	(3.4 - 24.7)
Women, Gela	1980-2005	0.9*	(0.1 - 1.7)
Men, Sicily	1980-1990	1.8***	(1.3 - 2.2)
Women, Sicily	1980-1990	1.0***	(0.4 - 1.6)

* (P-value <0.05), ** (P-value <0.01), *** (P-value <0.005).

Table 2
SMR for mortality due to all diseases and malignant cancers for men and women, bronchus and lung cancers for men and circulatory system diseases for women, all ages, 1980-2014

	All diseases		Malignant cancers	
	Men (CI 90%) [n. cases]	Women (CI 90%) [n. cases]	Men (CI 90%) [n. cases]	Women (CI 90%) [n. cases]
1980-1984	1.04 (0.99-1.09) [1,239]	1.18* (1.12-1.24) [1,020]	0.90 (0.80-1.01) [201]	1.00 (0.87-1.14) [149]
1985-1989	1.17* (1.12-1.22) [1,383]	1.13* (1.07-1.19) [962]	1.18* (1.07-1.29) [308]	1.00 (0.88-1.14) [165]
1990-1994	1.09* (1.04-1.14) [1,320]	1.17* (1.11-1.23) [1,027]	1.00 (0.92-1.11) [301]	0.98 (0.52-1.48) [184]
1995-1999	1.13* (1.08-1.18) [1,392]	1.18* (1.12-1.24) [1,060]	1.22* (1.12-1.32) [398]	1.11 (0.99-1.24) [221]
2000-2004	1.10* (1.05-1.15) [1,387]	1.25* (1.19-1.31) [1,161]	1.16* (1.07-1.26) [421]	1.18* (1.06-1.30) [261]
2005-2009	1.05* (1.01-1.10) [1,447]	1.20* (1.14-1.24) [1,232]	1.15* (1.07-1.24) [476]	1.19* (1.08-1.30) [306]
2010-2014	1.07* (1.02-1.11) [1,599]	1.14* (1.09-1.20) [1,388]	1.11* (1.03-1.19) [502]	1.09 (1.00-1.20) [327]
	Bronchus and lung cancer, men (CI 90%) [n. cases]		Circulatory system diseases, women (CI 90%) [n. cases]	
1980-1984	1.07 (0.87-1.31) [64]		1.25* (1.16-1.34) [524]	
1985-1989	1.06 (0.88-1.28) [79]		1.20* (1.12-1.30) [479]	
1990-1994	1.01 (0.84-1.20) [87]		1.23* (1.14-1.33) [500]	
1995-1999	1.15 (0.99-1.35) [112]		1.22* (1.14-1.32) [508]	
2000-2004	1.46* (1.28-1.67) [154]		1.25* (1.16-1.34) [513]	
2005-2009	1.19* (1.03-1.37) [137]		1.24* (1.15-1.33) [530]	
2010-2014	1.16 * (1.02-1.33) [146]		1.09 * (1.01-1.17) [535]	
	All diseases (age class 45-69)			
	Men (CI 90%) [n. cases]		Women (CI 90%) [n. cases]	
1980-1984	1.05 (0.96-1.14) [401]		1.19* (1.07-1.32) [256]	
1985-1989	1.07 (0.99-1.16) [435]		1.12* (1.00-1.24) [244]	
1990-1994	0.99 (0.91-1.07) [422]		1.06 (0.95-1.18) [239]	
1995-1999	1.17* (1.09-1.27) [488]		1.07 (0.96-1.19) [236]	
2000-2004	1.04 (0.96-1.13) [407]		1.11 (0.99-1.23) [231]	
2005-2009	1.08* (1.00 – 1.18) [410]		1.13* (1.02-1.26) [242]	
2010-2014	1.02 (0.94-1.12) [374]		1.13* (1.02-1.26) [256]	

*SMR value statically significant with level of significance of 90%.

stomach and the lung cancers are statistically significant with the highest SIRs (1.08 and 1.07) and 80% credibility intervals that not contain the unit. For women, the highest SIR (1.09 [1.01, 1.20]) is observed for colon cancer. Also for women, the lung cancer presents the second-highest SIR among all sites. The SIR estimates resulting from rank estimates are similar with credibility intervals for different cancer sites overlapped (*Figure 3* and *Figure 4*).

DISCUSSION

Results of the analysis of mortality trends in Gela from 1980 to 2014 show that for all the period analyzed, and for both genders, the SMRs for residents are decreasing but they are higher than those of the Sicilian population by gender, although the gap is decreasing over time. Furthermore, the analysis of rates due to malignant tumours shows that in Gela, for men, the values grew up in the period 1980 to 2000, from 23 deaths/10,000 in 1980 to around 45/10,000 in 2000, then they decreased until reaching the value of 38 at the end of the analyzed period, while for the total of Sicilian men deaths reach a maximum of 37/10,000 in 1997 and in 2014 stands on 34. For women in Gela, the increase in rates was less evident than in men, but it lasted for a longer period: the decreasing trend started only in 2004, ten years after the one observed in Sicilian women. The gap in mortality from all cancers between men and women, especially between 1990 and 2000, could be the result of different risk in the occupational settings. Overall, the results on trends in Gela show an excess of risk, especially in the 1990s and mainly regarding mortality for all cancers.

The results of the SMR analysis suggest that, for both men and women of all ages, deaths in Gela are almost always higher than those observed for Sicily, for general mortality, all malignant tumours, and almost all large groups of diseases (circulatory, respiratory, digestive

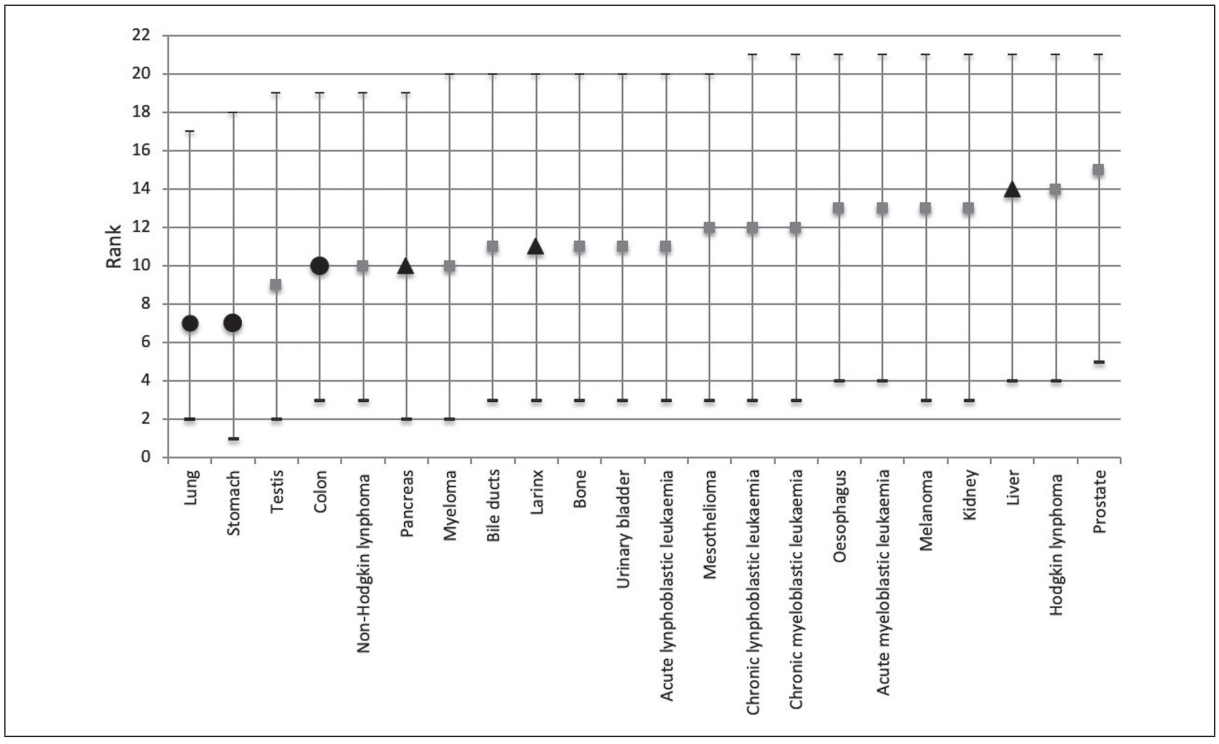

Figure 3
Rank of the neoplasm sites analyzed. *A priori* neoplasms as black circles and control neoplasms as black triangles, for men in Gela.

and genitourinary systems). An excess of mortality for lung cancer, in men in the 45-69 age class, has resulted since 1995. Excesses of mortality due to lung cancer identified are coherent with recent evidence from meta-analysis on risk for populations living close to petrochemical sites [17]. In the systematic revision made by Wong and Raabe limited to the analysis of the risk for workers in petroleum industry (not for the whole populations living close to petrochemical sites) [18] which considered also other outcomes, there were no identified increases in mortality due to digestive, respiratory or genitourinary cancers with meta-SMR estimates below unity.

The results of cancer incidence analysis show excesses of risk for all cancers combined for both genders and for lung and stomach cancer in men. Furthermore, neoplasms of *a priori* interest result as ranked in the first positions for both genders, while neoplasms selected as control are ranked in the subsequent positions. This result, although very weak in terms of statistical significance – credibility interval contain ones and ranks are overlapped, as above mentioned – are initial weak clues on the possible risk associable with petrochemical pollution.

Excesses in cancer incidence for people resident close to a petrochemical complex were identified in several previous studies and meta-analyses. These studies showed that lung cancer incidence, as well as mortality for those who lives near a petrochemical site is significantly higher compared to those who live farther [19, 20] and also the exposure to specific contaminants, mostly emitted from petrochemical complexes is associated to the increases in gastric cancer incidence [21] and leukaemia [22, 23]. Fernandez-Navarro *et al*. (2017) carried out a study in Spain with a design at municipality level analysing possible associations between industrial pollutants emission, estimated using data from the European Pollutant Release and Transfer Register (E-PRTR), and mortality risk for local populations residing in municipalities close to the sites. In a four-year time window (2007-2010), data on pollutants showed high levels of carcinogens also found in Gela's petrochemical site like arsenic, cadmium and chromium. The results of the study regarding cancers showed a mortality risk higher in exposed *vs* non exposed populations especially for pleura and colon-rectum cancers [24].

The notion of disease latency deserves some considerations. This study considered many diseases which could have different latency periods. Diseases associated to chronic exposure to environmental contamination, like cancers, could have long latency periods. The estimated minimum latency period for cancers can range from years to more than a decade [25], while the average latency between the beginning of exposure to cancer onset/diagnosis is usually of decades. For example, the estimated latency between the beginning of active smoking to the incidence of lung cancer was estimated ranging from about 10 to 30 years [26]. Furthermore, the latency period is influenced by several factors beyond the particular chemical or mixture of chemicals considered, including level and duration of exposure. To take this complexity into account in the present ecological study (outcomes available from routinely collected data or data from registries for the whole population without information at individual

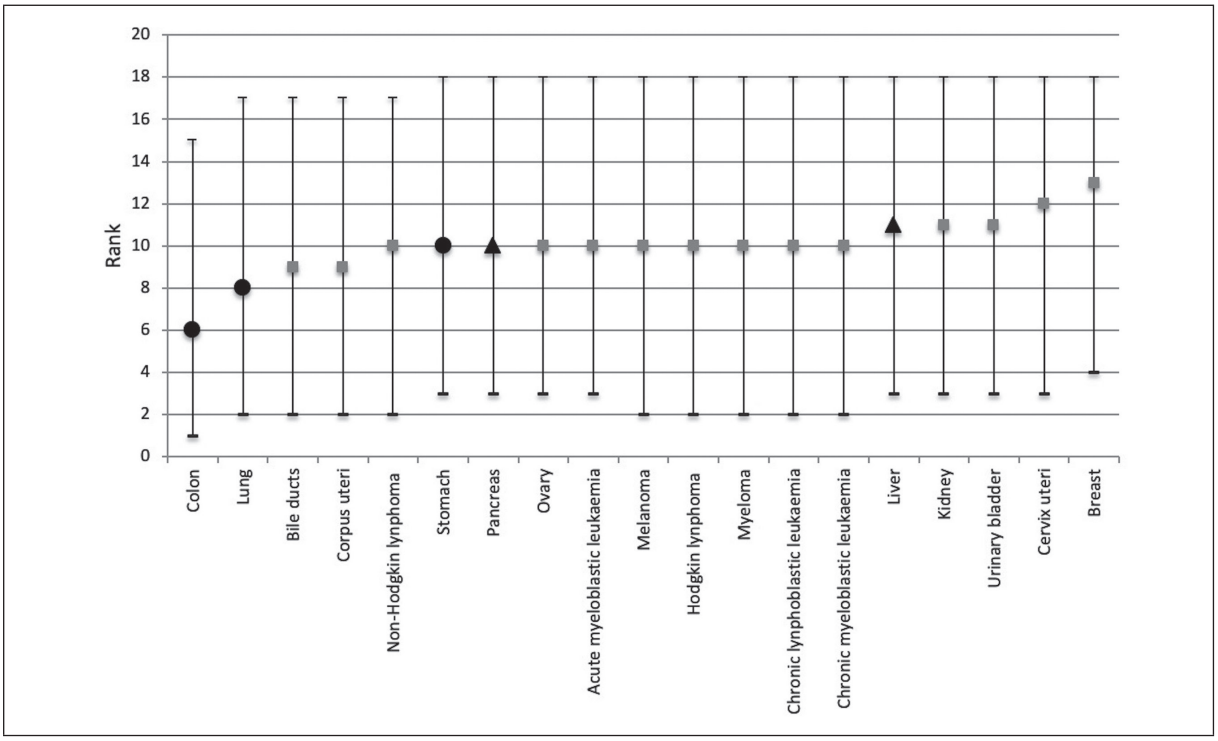

Figure 4
Rank of the neoplasm sites analyzed. *A priori* neoplasms as black circles and control neoplasms as black triangles, for women in Gela.

level), the mortality indicators were computed starting from 1980 (even because this is the first year of mortality data availability), twenty years after the beginning of the petrochemical complex operations (i.e. twenty years after the potential beginning of exposure at least for some contaminants, as for example, those in the air). Furthermore, the selection of the age class 45-69 was made to maximize the difference, during the time window observed, in terms of share of years of life with potential exposure to the pollutants from the petrochemical complex, as described in details in the methods section.

The picture on the risk in Gela resulting from the present study has some limitations. The selection of the Sicilian region population as the reference in the mortality analysis can be questionable, since the difference in risk factors other than the one at study (i.e. the pollution from the petrochemical plant) among the target and the reference population can affect the risk estimates and the inferences in comparing the risk among the populations. The choice of the regional population as reference for the study was pragmatic to balance the need of having quite similar populations in terms of risk and wellbeing factors and to obtain robust analysis in statistical terms also for rare diseases in computing indirect standardized indicators. This option of having the regional population as reference in descriptive epidemiological studies is common in the Italian context and is the one chosen for the SENTIERI monitoring [3].

As described in methods section, the Bayesian model was structured using non-informative prior distributions to give more importance to empirical data. In the case study, before data analysis, there were not specific information about specific diseases compared to others, therefore each cancer site has the same importance into the model. Another option to estimate SIRs would have been to use some informative prior based on, for example, *a priori* cancer sites knowledge, to check if empirical data had confirmed and eventually enlarged the differences between these SIRs and those of the others sites. Furthermore, representation of ranks of SIRs presents some limitations: above all, ranks are computed using SIRs estimated values which were computed having low statistical power due to the short time of data availability of cancer incidence data for the population of Gela (5 years). Nevertheless, the authors chose to present the methodology and describe results as the method applied to the analysis of cancer incidence data is quite innovative for its application to contaminated sites, expecting to provide more robust estimates in the future as longer series of data become available.

The results of this study confirm in general what is presented in the last SENTIERI report regarding the risk in Gela highlighting several excesses of risk in the resident population [3].

CONCLUSIONS

The study aims to evaluate the risk for the population residing in Gela associable with the pollutants available in the contaminated area. All the analyses computed highlight a disadvantage in terms of mortality and cancer incidence of the residents of the municipality of Gela, compared to the Sicilian population. Trends

in mortality due to all disease and to malignant cancers, the excesses in mortality highlighted by SMRs and Joinpoint regression, and the excesses of the cancer incidence for all sites, in particular, for those of *a priori* interest, coherently show excess in risk, although for some diseases or neoplasm small numbers do not allow robust estimates.

This study highlights the need to continue the activity of monitoring of the environmental matrices polluted by the petrochemical complex and epidemiological monitoring of the population living in Gela by integrating national and regional approaches [3, 27] with evidence from *ad hoc* studies.

Conflict of interest statement

There are no 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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Exploring methods for the assessment of temporal trends in mortality and hospitalization in Italian industrially contaminated sites

Vittoria La Serra[1], Roberto Pasetto[2], Valerio Manno[3], Ivano Iavarone[2], Giovanna Jona Lasinio[1] and Giada Minelli[3]

[1]*Dipartimento di Scienze Statistiche, Sapienza Università di Roma, Rome, Italy*
[2]*Dipartimento di Ambiente e Salute, Istituto Superiore di Sanità, Rome, Italy*
[3]*Servizio di Statistica, Istituto Superiore di Sanità, Rome, Italy*

Abstract

Introduction. The Italian contaminated sites of interest for remediation are monitored by SENTIERI, an epidemiological surveillance system describing the health status of populations living nearby these sites. There is an increasing concern on how to assess temporal changes in the health status of these populations.

Methods. A sequence of three statistical techniques was adopted to analyse temporal trends of mortality and hospitalization, by using different indicators and reference populations, in a sample of 36 sites with industrial sources of contamination monitored by SENTIERI.

Results. Positive temporal trends in health risks are detected reflecting mainly long term effects of industrial activities. The adopted methodology identifies multiple factors influencing the temporal patterns: type of health outcomes, type of disease, and its link with gender and type of emission sources.

Conclusions. Reliable methods to assess health profile changes in local populations attributable to contaminations are key elements to measure the impact of remediation activities.

Key words

- contaminates sites
- mortality
- hospitalization

INTRODUCTION

In Italy, the health status of communities identified as living close to major contaminated sites is periodically monitored by the SENTIERI epidemiological surveillance system, using data at the municipality level [1]. Most of these contaminated areas are registered as National Priority Contaminated Sites (NPCS) and many of them are contaminated by still active industrial complexes. The main aim of SENTIERI is to describe health profiles of communities living close to each monitored site by looking at different health outcomes (mortality and hospitalization, cancer incidence, prevalence of congenital malformations) in order to provide evidence for local public health interventions.

All 20 Italian Regions, excluding Molise, have at least one site monitored by SENTIERI, with an overall interested population of 5,900,000 inhabitants in 319 municipalities (2011 Italian Census) [1].

Industrial plants have contaminated most of these sites for decades, compromising the surrounding areas by polluting soil, water, air, and the food chain with several chemical substances. The main polluting sources found in the monitored sites are chemical plants, petrochemical plants and refineries, steel industries, electric power plants, mines, harbour areas, asbestos, landfills, incinerators [2].

The first figures published by SENTIERI documented an overall excess of mortality in the 44 monitored areas (298 municipalities), with around 10,000 exceeding deaths among the 404,000 observed (men and women combined, all causes of mortality) in an 8-year period (1995-2002) [3]. About 3,600 deaths were associated with pollution present in the contaminated sites. A subsequent overall analysis of cancer incidence data in 10 years (1996-2005), limited to the 23 sites served by cancer registries, showed an overall excess of 9% in men and 7% in women [4]. The last SENTIERI publication regarded 319 municipalities in 45 sites, with data on

Address for correspondence: Giada Minelli, Servizio di Statistica, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. Email: giada.minelli@iss.it

mortality, hospitalizations, cancer incidence (for the overall population and children, separately), and congenital anomalies. Data on mortality documented an excess for all causes of 2.5% (around 5,300 deaths) and 3% (around 6,700 deaths) in men and women, respectively, in a period of 8 years (2006-2013) [1].

SENTIERI has provided figures on health profiles in different periods, updating such figures on the basis of data availability. At present, no formal statistical analysis on changes over time of such profiles has been carried out.

This is an explorative study aimed at proposing a possible methodological procedure for assessing temporal trends in mortality and hospitalizations to be applicable to SENTIERI and other epidemiological surveillance systems based on data aggregated at a population level (i.e. ecological-area level data). This will be reached by exploring the informational benefits of some statistical analysis by their application to data regarding a subgroup of sites monitored by SENTIERI. An in-depth analysis of temporal trends in contaminated sites via model estimation and the application of statistical methods for comparing them with regional reference trends were carried out.

METHODS

Selection of contaminated sites

The present contribution is primarily focused on exploring methods for the assessment of temporal trends in different groups of sites, and to suggest some possible clues for further *ad hoc* analyses, while did not aim to analyze, discuss and interpret results concerning different contamination sources. To achieve this aim we limited the analysis to the large subgroup of sites monitored by SENTIERI having chemical/petrochemical or steel industrial plants among the main sources of contamination and excluding other contaminated sites characterized by asbestos or asbestiform fibers or having landfills as the only source of contamination or combined with asbestos. Thirty-six sites were identified and classified in the following 5 categories:

- Chemical: sites that present just a chemical plant or a chemical plant and a landfill. The chemical plant is predominant in the contamination process since the landfill, in these cases, is used for waste produced by the chemical plant itself;
- Chemical+: sites that present a chemical plant and other relevant plants, in terms of contribution to pollution in the air, such as electric power plants, steel industries or harbour areas [5, 6];
- Petrochemical: sites that present a petrochemical plant and/or a refinery and a harbour area;
- Petrochemical+: sites that present a petrochemical plant and/or a refinery and other relevant plants, in terms of contribution to pollution in the air, such as electric power plants, steel industries or harbor areas [5, 6]. This label includes sites that present at least three pollution sources, up to a maximum of seven, so the contamination level is considered high;
- Steel: sites that present a steel industry and a landfill. The steel industry is predominant in the contamination process, since the landfill, in these cases, is usually used for waste that is produced by the industry itself.

Out of the thirty-six sites, 17 of them were classified as "Chemical", 5 as "Chemical+", 2 as "Petrochemical", 10 as "Petrochemical+" and 2 as "Steel".

The selected sites have industrial sources of chemical contamination of soil and water environmental matrices. The presence of important industrial sources of air pollution is associated with petrochemical plants and refineries and steel plants and is highlighted with the "+" if other industrial sources of air contamination (i.e., electric power plant, harbour area, steel industry) are present in the site.

This paper does not provide the names of the contaminated sites included in the analyses, nor it describes where they are located. We intentionally anonymized the study areas since the main objective is to explore useful methods and identifying a process of analysis to be used in epidemiological surveillance systems, rather than to produce and interpret results from an environmental public health perspective.

Source and description of health data

Two data sources available at the Statistical Service of the Italian National Institute of Health (Istituto Superiore di Sanità) were used: the National Mortality Database (NMD) managed by the Italian National Institute of Statistics (Istat) and the National Hospital Discharge Database (NHDD) managed by the Italian Ministry of Health. The NMD contains the underlying causes of death, coded using ICD-10 Revision since 2003. The NHDD records data of all patients discharged from all Italian hospitals, including not only acute admissions but also planned investigation treatment units, on a "day-hospital" basis. For each patient, demographic data (e.g., sex, date and place of birth) are recorded with the primary and up to five secondary discharge diagnoses, codified according to the WHO International Classification of Diseases-Clinical Modification, 9th Revision (ICD9-CM).

Mortality and hospitalization data for each selected site were analyzed for the period 2005-2016. Concerning hospitalization data, every hospitalized patient was considered just once each year, even if they had been hospitalized multiple times in the same year, for the same disease. Also, only the primary cause of hospitalization was considered. This procedure avoids multiple counts for the same subject and reduces the distortion of risk estimates.

This study refers to data observed in Italian selected contaminated sites and in the regions where these are located; the NPCS data were cleared from their respective regional data to avoid their contribution to the reference (the regional data).

Selection of causes of death and hospitalization

Multiple causes of mortality and hospitalizations were considered in this work following a sequence of three different phases.

In the first phase, standardized mortality and hospitalization rates for the selected contaminated sites were computed (see the statistical analysis section below) for

each of the 52 causes of mortality (from the ICD-10) and 49 causes of hospitalization (from the ICD9-CM) selected in the SENTIERI study [1].

In the second phase, in order to compare the single NPCS figures with the corresponding regional reference values, hospitalization and mortality data were broken down into groups: all causes; all malignant tumours; trachea and lung malignant tumours; malignant tumours of the lymphatic-hematopoietic system; circulatory system diseases; ischemic heart disease; respiratory system diseases; digestive tract diseases; urinary system diseases; chronic lung diseases; acute respiratory diseases (asthma; acute respiratory infections, pneumonia and flu and chronic obstructive pulmonary diseases for hospitalizations).

These groups of causes were chosen due to prior knowledge on their association with the considered pollution sources, mainly petrochemical plants and refineries. Precisely, literature has been provided for lung cancer mortality [7] and incidence [8], risk of leukemia [9], respiratory symptoms [10] and hematological malignancies [11] on residents living near petrochemical industrial complexes.

In the third and final phase, with the aim of making comparisons between the contaminated sites and the reference regions, only the two larger groups of causes "General mortality" and "All causes of hospitalization" were analyzed in depth.

Statistical analysis

The three phases of analysis are here described.

In the first phase, for each cause of mortality (52 causes) and hospitalization (49 causes), standardized rates were computed for each year in 2005-2016, for males and females separately, marginalizing over the age factor and using the European population as reference [12].

The time series of standardized rates were studied by adapting linear regression models to the series, using time as the only covariate. The regression coefficients were evaluated to better describe hospitalization and mortality over time: a positive regression coefficient highlights increasing values over time, while negative regression coefficients highlight decreases. Significant linear trends can be detected by observing the p-value of each coefficient and setting a threshold: results are shown for a chosen threshold of 0.1. A chi-square dependence test was calculated for detecting the association between gender and significant linear trends, both increasing and decreasing.

In the second phase, the focus was on the selected groups of causes presented in the previous section. Increasing trends found among these causes were specified and further analyzed: time trends found to be associated with a specific gender in a contaminated site were compared to the corresponding region, to detect any differences or similarities between these geographical levels. This procedure was used to verify if increasing gender/cause time-trends are related to a specific site or if they are shared by all areas in the region where the site is located.

In the third phase, again, with the aim of comparing NPCS values and reference regional values, the focus was only on "All natural causes" of hospitalization and on "General mortality". For these two causes, ratios between rates in the contaminated sites and in the reference regions were computed, to detect possible risk excesses. With a ratio exceeding the threshold 1, the rate in the contaminated site is higher than the regional one, showing a risk excess; on the contrary, a ratio smaller than 1 correlates with a risk decrease; if the ratio equals the threshold, the site and the region have the same rate and no risk excess in either of them.

In addition, for the two groups of causes, a graphical comparison of the Local Estimated Scatterplot Smoothing (LOESS) curves built on the time series of the rates in the sites and in the regions was carried out in order to understand the general behaviour of the series. Confidence intervals were also calculated (with a 95% range) around approximations, to show the uncertainty surrounding these estimates.

By fitting simple regression models and using chi-square dependence tests, the first phase aims to get an overview of the trends in the time series of mortality and hospitalization.

In the second phase, a focus is made on increasing trends on a group of causes of interest, the ones that were chosen because of prior knowledge on their association with the selected sources of contamination, with the additional aim of comparing trends in the contaminated sites to those in the reference regions.

Focusing on an even smaller group of causes, the third phase gives further results on NPCSs-regions comparisons, through the application of rate-ratios analysis and LOESS curves graphical observation.

The three phases are displayed in *Figure 1*. Analyses were performed using the statistical software R and RStudio.

RESULTS

First phase

Out of 3,396 estimated regressions analyzing mortality rates, 768 (21.55%) show a significant trend, and among the latter 27.73% displays an increasing tendency. Significant gender differences in linear trends are also observed, as suggested by the chi-squared dependence test: there are more growing trends in the series due to women's death rather than men. The highest percentages of positive trends compared to the total for each type of site were observed for "Chemical+" and "Petrochemical", respectively 31.76% and 34%.

Out of 3,294 trends estimated for hospitalization data, 1,712 (51.69%) appear to be significant, 7.18% of which increasing; gender does not seem to influence the trend. Most significant trends have been observed for the "Chemical" and "Petrochemical+" sites, respectively 43.51% and 31.54% of the total.

Table 1 shows both significant and non-significant trends in mortality and hospitalization, which can be compared, for all causes. Regarding significant trends, although hospitalizations show a greater number of those, mortality has a four-fold higher percentage of increasing ones (27.7% *vs* 7.2%, respectively).

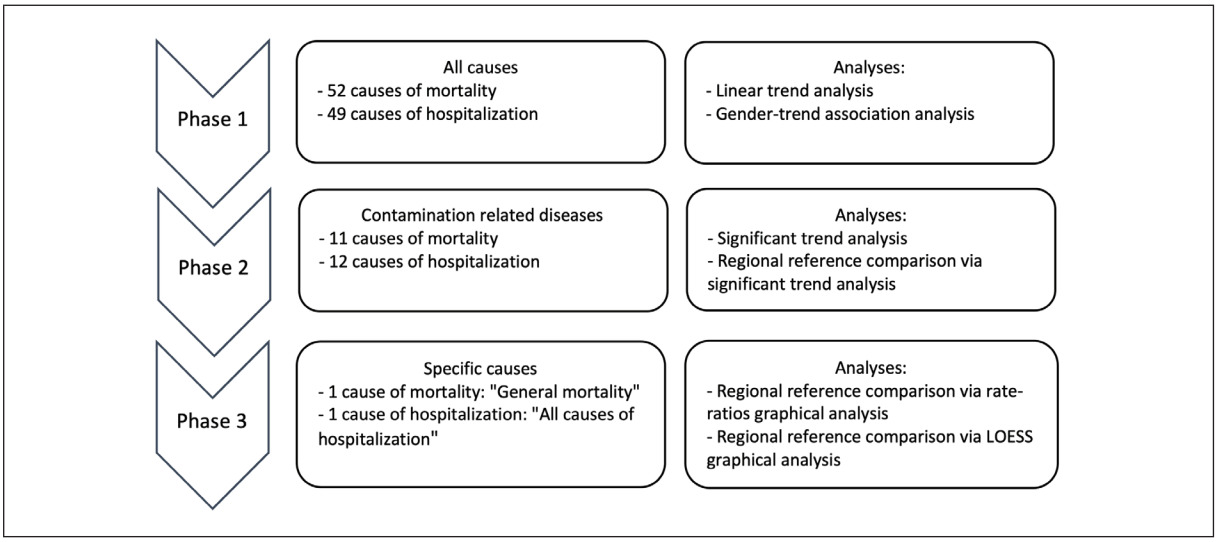

Figure 1
Diagram of the three phases of analysis.

Table 1
Significant and non-significant trends in mortality and hospitalization, for all causes. On each time series, a linear regression model is fitted and the regression coefficient, whether positive or negative, is evaluated; the coefficient is considered significant if its p-value is smaller or equal than the fixed threshold 0.1. For the five categories of NCPSs, absolute frequencies of the estimated trends are reported, both for hospitalization and mortality; frequencies are specified for both significant and non-significant trends, whether positive or negative, in both males and females

Significant trends												
Hospitalization	**Chemical**		**Chemical+**		**Petrochemical**		**Petrochemical+**		**Steel**		**Total**	**%**
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**		
Negative	356	320	98	101	49	46	270	236	61	52	1589	92.82%
Positive	33	36	4	7	1	3	14	20	3	2	123	7.18%
	389	356	102	108	50	49	284	256	64	54		
	745		210		99		540		118		1712	100%
Mortality	**Chemical**		**Chemical+**		**Petrochemical**		**Petrochemical+**		**Steel**		**Total**	**%**
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**		
Negative	130	109	35	23	18	15	95	91	22	17	555	72.27%
Positive	29	54	8	19	9	8	33	44	3	6	213	27.73%
	159	163	43	42	27	23	128	135	25	23		
	322		85		50		263		48		768	100%
Non-significant trends												
Hospitalization	**Chemical**		**Chemical+**		**Petrochemical**		**Petrochemical+**		**Steel**		**Total**	**%**
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**		
Negative	260	249	72	69	27	30	105	132	23	30	996	62.95%
Positive	128	171	54	48	15	13	71	72	5	8	585	37.05%
	388	420	126	117	42	43	176	204	28	38		
	808		243		85		379		66		1582	100%
Mortality	**Chemical**		**Chemical+**		**Petrochemical**		**Petrochemical+**		**Steel**		**Total**	**%**
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**		
Negative	365	364	93	111	35	42	197	192	46	47	1491	56.73%
Positive	268	262	98	68	34	31	168	153	27	27	1136	43.27%
	633	626	191	179	69	73	365	345	73	74		
	1259		370		142		710		147		2628	100%

Second phase

Results showing statistically significant estimated trends are reported, focusing on the selected groups of causes. Out of 792 estimated linear trends for the eleven causes of death, 290 are significant; of the significant ones, 30 (10.34%) are increasing. Of the 864 linear trends for the twelve hospitalization diseases, 685 appear to be statistically significant; only 7 (1.21%) of the significant ones increase, almost ten times smaller than the same percentage found for mortality results.

The absolute frequencies of the estimated decreasing and increasing significant trends, for each considered disease and type of pollution source, are described in *Figures 2a, 2b* and *Figures 2c, 2d*, for mortality and hospitalization, respectively.

In both scenarios, most of the estimated trends appear to be decreasing (89.66% in mortality, 98.79% in hospitalization), most of which are observed in "Chemical" (44.23% in mortality, 43.80% in hospitalization) and "Petrochemical+" (32.30% in mortality, 31.12% in hospitalization) types of sites. High frequencies of decreasing trends are also found for "Circulatory system diseases" and "General mortality" (*Figure 2a*), and for almost all hospitalization causes but "Trachea and lung malignant tumours" and "Lymphatic-hematopoietic system malignant tumours" (shown in *Figure 2c, 2d*).

Increasing trends are small in number, more frequent in mortality than in hospitalization, for a few selected causes.

All increasing mortality and hospitalization trends for the selected causes are shown in *Tables 2 and 3* by contaminated sites and gender; each regression coef-

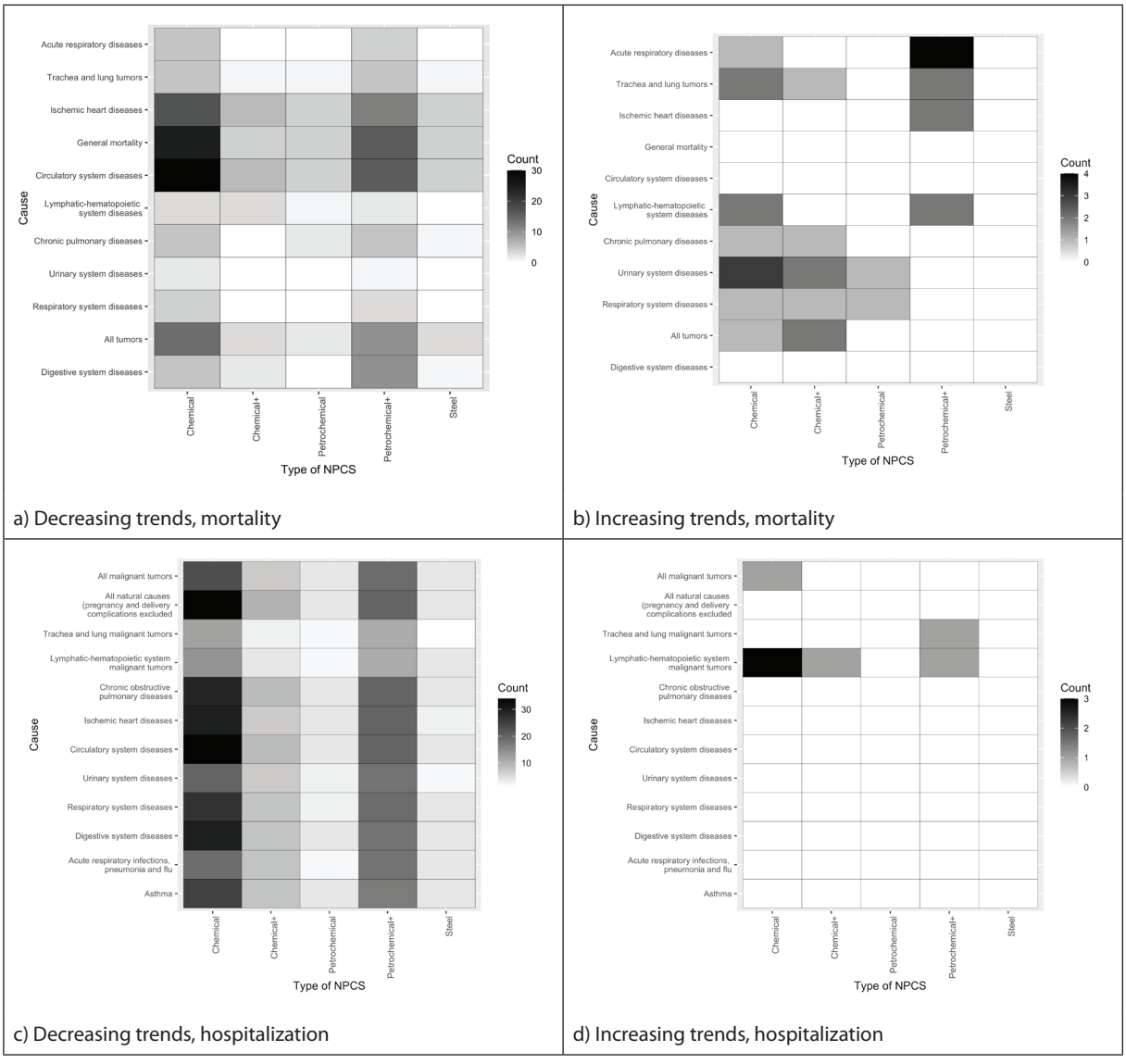

Figure 2

Absolute frequencies of the estimated significant trends, both increasing and decreasing, for mortality and hospitalization, separately. The shades of gray, ranging from white to black, correspond to the absolute frequencies. For the same phenomenon, whether hospitalization or mortality, the white shade corresponds to zero and the black shade corresponds to the maximum absolute frequency, depending on its value in decreasing or increasing trends.

Table 2
Increasing and statistically significant trends in mortality for the 11 selected groups of causes. When such a coefficient is estimated in a NCPS, for a specific gender and cause, a linear model for the same conditions is estimated in the region where the NCPS is located, as well. The regional coefficient is sided by an asterisk when statistically significant

Cause	Type of site	Gender	Coefficient	Coefficient in the region
Lymphatic-hematopoietic system diseases	Chemical	Male	2.03	-0.12
	Chemical	Female	1.50	-0.26*
	Petrochemical+	Male	1.43	0.08
	Petrochemical+	Female	1.11	-0.15
Respiratory system diseases	Chemical	Male	4.43	-1.08*
	Chemical+	Female	8.96	0.68*
	Petrochemical	Female	0.99	-0.44
Urinary system diseases	Chemical	Female	1.58	0.11
	Chemical	Female	0.82	0.075
	Chemical	Female	2.42	0.015
	Chemical+	Male	1.84	-0.009
	Chemical+	Female	2.68	-0.018
	Petrochemical	Male	1.20	-0.009
Ischemic heart diseases	Petrochemical	Male	5.16	-3.77*
	Petrochemical	Female	6.07	-2.60*
Chronic pulmonary diseases	Chemical	Male	5.16	-2.23*
	Chemical+	Female	4.93	0.44
Acute respiratory diseases	Chemical	Female	0.74	0.46*
	Petrochemical+	Female	0.57	0.057
	Petrochemical+	Male	1.95	0.40
	Petrochemical+	Female	0.81	0.099
	Petrochemical+	Female	1.09	-0.099
Trachea and lung tumors	Chemical	Female	1.56	0.50*
	Chemical	Female	1.33	0.42*
	Chemical+	Female	1.55	-0.02
	Petrochemical+	Female	1.10	0.55*
	Petrochemical+	Female	0.39	0.49*
All tumors	Chemical	Female	2.94	-0.11
	Chemical+	Male	15.02	-5.15*
	Chemical+	Female	2.33	-0.49

*Significant.

Table 3
Increasing and statistically significant trends in hospitalization for the 12 selected groups of causes. When such a coefficient is estimated in a NCPS, for a specific gender and cause, a linear model for the same conditions is estimated in the region where the NCPS is located, as well. The regional coefficient is sided by an asterisk when statistically significant.

Cause	Type of site	Gender	Coefficient	Coefficient in the region
Lymphatic-hematopoietic system malignant tumors	Chemical	Male	6.51	-1.8*
	Chemical	Female	3.39	-1.28*
	Chemical	Female	1.11	- 0.25
	Chemical+	Male	2.82	-3.38*
	Petrochemical+	Female	3.74	-1.28*
All malignant tumors	Chemical	Female	6.97	-6.18*
Trachea and lung malignant tumors	Petrochemical+	Female	0.67	0.25*

*Significant.

ficient can be compared to the regional one, which was estimated for the same disease and gender. An asterisk is placed beside the region coefficient if this happens to be significant as well, for a 10% threshold.

In both scenarios, 70% of increasing trends concern women, and no results are observed for "Steel" sites.

In mortality results, as observable in *Table 2*, the highest and positive coefficient is found for "All tumours" on a "Chemical+" site for men; its corresponding trend in the region, however, is negative, decreasing significantly.

In hospitalization results, the group "Lymphatic-hematopoietic system malignant tumours" shows statistically significant increases in 5 sites, whose corresponding regions show decreasing and significant disease trends.

In general, regional trends are much more stable than NPCSs in both scenarios, with slopes ranging between 0 and 1, if positive.

Third phase

Focusing on "General mortality" and "All natural causes" of hospitalization only, graphical analyses for more in-depth comparisons between contaminated sites and regions are provided.

Figures 3a, 3b and *Figures 3c, 3d*, available online as Supplementary material, showing rate-ratios for the two causes, where the rate in each contaminated site, for both mortality and hospitalization, for males and females separately, is divided by the corresponding regional rate, can be observed.

In both scenarios, for both genders, most of the ratios do exceed the threshold 1, highlighting risk excesses in the contaminated sites as compared to the regions where they are located, with higher frequencies in hospitalization results.

Some trends in the hospitalization ratios can be spotted in the *Supplementary Figure 3c*, e.g. in the "Chemical 15" site, with increasing ratios across time, and in "Steel 2" site, with decreasing ratios. Mortality ratios in the study period are extremely variable, with no trends to be detected (*Supplementary Figures 3a, 3b*).

Only a few sites show smaller-than-one ratios for the whole period; most of the "Petrochemical+" sites show risk excesses, especially in hospitalizations.

In addition to the evaluation of the relationship between site and regional rates, the time series of the "General mortality" and "All natural causes" of hospitalization rates were compared using LOESS. Smooth approximations of the series are obtained, helping us to capture their general behavior, and also confidence intervals are calculated around approximations to show the uncertainty surrounding these estimates.

In the following plots, two explicative examples of the LOESS curves are displayed.

Figure 4a shows males have very large mortality rates in the "Petrochemical+ 6" site, with respect to females; however, the two show similar trends in time: the rate in the NCPS has been growing, with respect to the regional one which has been decreasing linearly, and the two have started approaching only in the last years of the observation period.

Figure 4b shows the hospitalization rate for the "Chemical 15" site is always higher than the regional one, and the two do not seem to be approaching one another, even though both of them are decreasing. The ratio between the two rates, as observable in the *Supplementary Figures 3c, 3d*, appears to be increasing.

More explicative examples of LOESS curves can be observed in the Supplementary material.

Supplementary Figure 4c shows males and females present different trends in the mortality rates in the "Chemical 1" site: concerning males, the rate was decreasing at the beginning of the period and then has started increasing in the latest years, diverging from the regional one, while the rate for females appears to be much closer to the regional one, except for a slightly diverging trend in the final years of observation. The regional rate, in both genders, has a linear and decreasing trend.

In *Supplementary Figure 4d*, the regional general mortality rate is almost always larger than the NPCS' one, with wide uncertainty on the estimates, especially for females. This is also observable in *Supplementary Figure 3b*, where rate-ratios in this site are very small throughout the whole period.

In *Supplementary Figure 4e*, the hospitalization rate for the "Petrochemical+ 3" NPCS is always higher than the regional rate, with the difference between the two becoming smaller in the most recent years, and both rates decreasing. This trend between the two rates was observed in most of the cases.

Lastly, *Supplementary Figure 4f* shows one of the few cases where the regional hospitalization rate is higher than the contaminated site rate; this is coherent with what is observable in the *Supplementary Figures 3c, 3d* for this site, "Chemical 14".

DISCUSSION

Results from the three phases of analysis that were run on mortality and hospitalization data in contaminated sites allow multiple considerations on time trends of the rate series.

Findings of the first phase provide awareness on the differences between the two health outcomes in time: more significant trends were observed in hospitalizations than in mortality, and yet, the percentage of increasing trends in the latter was much higher than in the former. This finding shows mortality rates have been growing in time, from 2005 to 2016, due to the long latency of some death causes (the observed high mortality might be associated with exposure to contaminants many years before). In both scenarios, more increasing trends were detected in women than in men, and the gender difference was significant in mortality results, which could be a matter of interest for future work aimed at linking gender-related mortality to specific exposure settings in contaminated areas.

In the second phase, results are provided for the selected group of causes: most of the significant trends in the selected sites were decreasing. Concerning mortality rates, most of the decreasing trends were observed for general mortality and circulatory system diseases in "Chemical" sites; regarding hospitalization, almost all conditions showed high frequencies of decreasing trends in "Petrochemical+" sites. A small percentage of increasing hospitalization trends was observed for lymphatic and hematopoietic system-related diseases, all tumours and trachea and lung tumours, malignant or not, in mortality. The highest frequencies of increasing trends were observed for all respiratory diseases and urinary system diseases. In both scenarios, most of the increasing trends were observed for "Chemical" and "Petrochemical+" sites; for sites with only Steel plants increasing trends were never found.

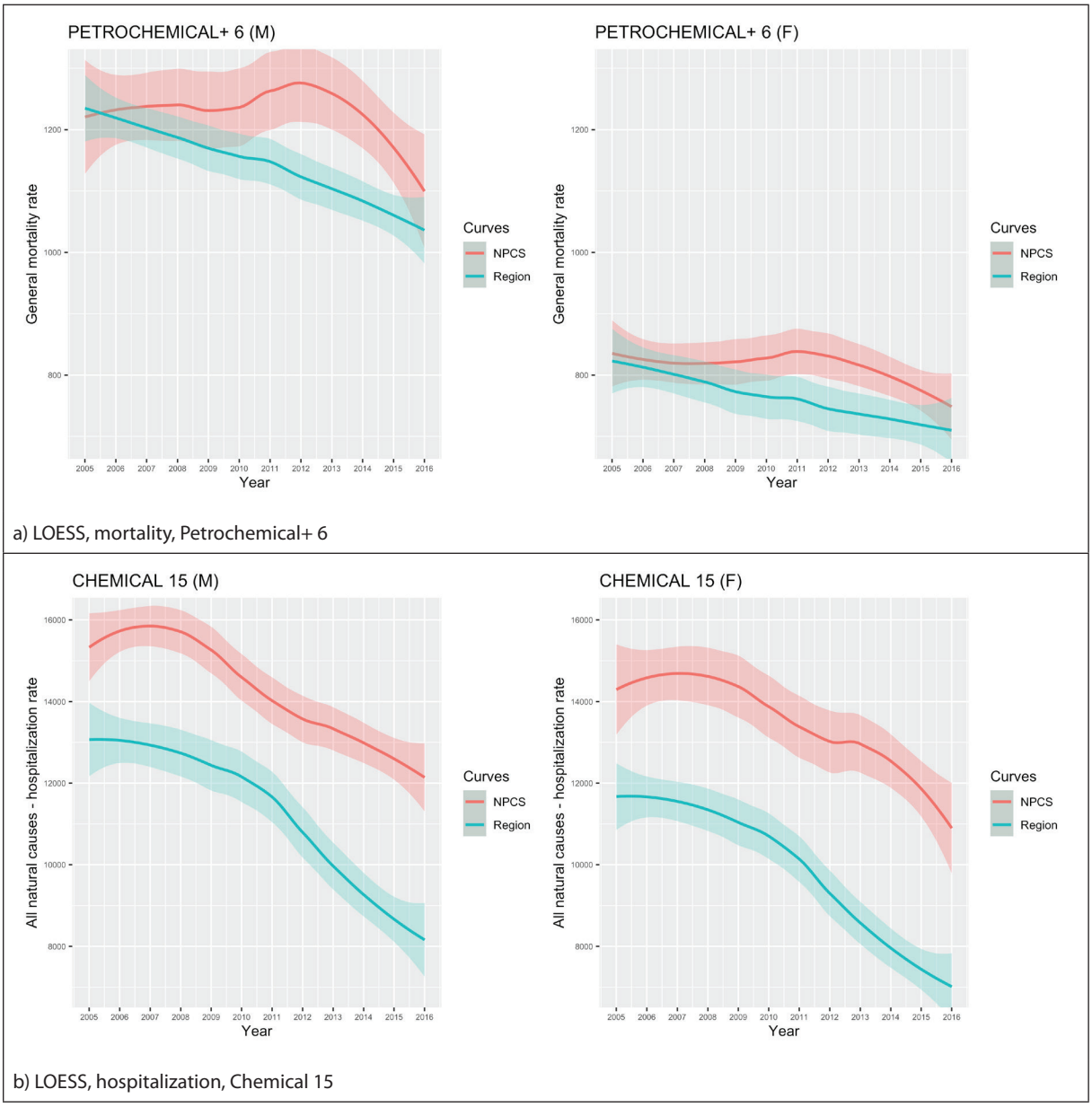

Figure 4
LOESS curves built on mortality and hospitalization rates, for the two selected causes (General mortality, All natural causes of hospitalization). A few explicative examples are shown, for four anonymized NCPSs. In each plot, the red curve is the smooth approximation of the rate series in the NCPS, while the turquoise curve relates to the rate series of the region where the NCPS is located. For each curve, a 95% confidence interval is computed.

In general, what is known from scientific evidence about the association between exposure to petrochemical plants emissions and certain health conditions, such as lymphatic-hematopoietic system-related diseases, lung cancer, and respiratory diseases, has been confirmed with the results of the present study. Also, risk excesses have been detected for the above diseases and also for urinary system diseases, chronic pulmonary diseases, acute respiratory diseases, and all malignant tumours in populations living in sites contaminated by chemical plants.

Through the second phase, comparisons between rates in the contaminated sites and their regions were made: in general, regression coefficients for the linear trends in regions were often negative or small if positive, whereas increasing trends were detected in selected sites.

In the third and final phase, a rate-ratio analysis and a graphical analysis (run via LOESS estimation) helped in capturing the general differences in temporal series when comparing contaminated sites with their regions. As expected, risk excesses for general mortality and all-natural causes of hospitalization have been detected comparing figures of the sites with those of their respective regions, except for a few cases. In most cases, the NPCS rates were higher than the regional ones, with

decreasing trends in both and decreasing differences by time between the two. Increasing trends, non-decreasing differences between contaminated sites' rates, and regional rates and regions with higher rates than in the contaminated sites were rarely observed.

STRENGTHS AND LIMITATIONS OF THE STUDY

Information on contaminated sites

The study areas were selected and grouped only based on the main sources of contamination (type of industrial setting). The study does not address the analysis of temporal trends in health outcomes concerning temporal trends regarding direct or indirect estimates of exposure.

The analysis of the associations between exposure and health effects in temporal terms, albeit important in contaminated sites for assessing both the risk associated with past exposure and the health benefit of environmental remediation activities or other public health interventions [13], is beyond the scopes of the present contribution. Nevertheless, the assessment of temporal trends of health outcomes in contaminated sites, especially in terms of comparison with temporal trends of the same outcomes in appropriate reference populations, helps in identifying priorities of interventions from a public health perspective.

A detailed evaluation of temporal trends of health outcomes in association with temporal changes of emissions/contamination, if feasible, strongly depends on the availability of reliable information. Furthermore, industrially contaminated sites are often characterized by mixtures of hazardous toxicants contaminating multiple environmental matrices, while an evaluation of the potential exposures over time in relation to the process of contamination is potentially possible only for air pollutants, whose data are usually monitored with long time-data. This is the case of the Taranto contaminated site, in southern Italy, hosting one of the largest steel factories in Europe, operating since the sixties. A detailed analysis of temporal trends based on available time-series of health and environmental data allowed to estimate a statistically significant increased risk in natural mortality per annual change of industrial PM10 emissions accounting for confounding factors [14].

A simplified approach in analyzing mortality temporal trends in association with potential cumulative exposure was proposed in a site followed-up by SENTIERI contaminated by a petrochemical complex [15]. In this study, an analysis of differential risk over time was performed considering, among the others, a specific age class maximizing the difference, during the time window under study, in terms of share of years of life with potential exposure to the pollutants from the petrochemical complex considering the year of starting operations of the industrial complex [15].

Other studies at ecological-area level analyzed the health risk considering the location of major Spanish industrial sources of contamination [16] or the presence of petrochemical sources of contamination at the regional level in Europe [17]. Such studies estimated the type and amount of pollutants using information available in the European Pollutant Release and Transfer Register (E-PRTR) [16, 17]. Nevertheless, to our knowledge, no study on contaminated sites with a national or international basis analyzed associations between emissions and health risk in temporal terms.

Selection of health outcomes and diseases

Mortality and hospitalization are health outcomes that present differences in terms of use in epidemiological studies.

Mortality is one of the most robust epidemiological outcomes and it is widely used to make geographical and temporal comparisons; it is expected to reflect long term effects of exposure and it is relevant when studying diseases with high lethality; long term effects of exposure showed in the results of the present study, since a large percentage of increasing and significant trends in mortality rates were found.

Regarding hospitalization, the following aspects should be highlighted: temporal changes in this outcome are hardly influenced by regional policies, concerning which diseases are considered to require hospitalization, since those might be different for different regions and they might change over time in the same region as well; this covariate is latent in the present study. Therefore, increasing trends in hospitalization rates might be due to changes in the policies.

These aspects limit the interpretation of results in terms of inferring considerations on the association between temporal trends of mortality and hospitalization and changes in exposure to industrial contamination in the study areas. However, it has to be stressed that the latter is not the objective of this study that aims at identifying new statistical methods in time trend analysis that can be adopted in epidemiological surveillance systems like SENTIERI.

Moreover, the analysis of temporal trends in mortality and hospitalization rate-ratios in the contaminated sites and in the reference regions is likely to identify changes that are, at least, suggestive of a possible impact of the industrial contamination when we can assume that this is one of the most relevant differences between the compared populations.

CONCLUSIONS

This exploratory methodological study proposes a sequence of statistical techniques to analyze temporal trends of mortality and hospitalization rates in industrially contaminated areas.

The obtained results highlighted changes over time in the health status of populations affected by long term exposure to massive pollution sources, compared to other areas in the same region that do not include NPCS.

The adopted methodology indicates some potentially relevant aspects that require further attention in the analysis of temporal trends in epidemiological studies in these areas. The various approaches show that the interpretation of the temporal changes is influenced by multiple factors: mainly by the type of health outcomes (mortality *vs* hospitalization), the type of disease, and its link with the gender and type of emission sources studied.

This work is a first attempt to propose a methodological path for the monitoring of time trends of health profiles in epidemiological surveillance systems like SENTIERI. This approach should be integrated with temporal trends of contamination and/or exposure estimates over time, by also considering drastic temporal changes in potential noxious exposure, such are for example those linked to industrial plants openings and closures.

The ability to detect changes over time in the health profiles attributable to changes in contamination/population exposure in highly contaminated areas is one of the most challenging objectives, as it could be potentially adopted as a measure of the positive impact of remediation activities and the negative impact of contamination processes on local populations.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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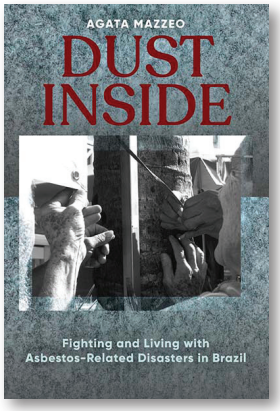
Book Reviews, Notes and Comments

Edited by
Federica Napolitani Cheyne



DUST INSIDE
Fighting and living with asbestos-related disasters in Brazil
Agata Mazzeo
New York - Oxford: Berghahn Books; 2020.
202 p.
ISBN 978-1-78920-931-0
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Dust inside, by Italian anthropologist Agata Mazzeo, from Bologna University, is a complex ethnographic study investigating health based grassroot activism aimed at countering an asbestos-related disaster occurring in Osasco, Sao Paulo, Brazil. Previous anthropological studies by the Author concerned asbestos exposed communities in Italy, starting from her hometown, Bari, and subsequently involving Casale Monferrato and Bologna (see also A. Mazzeo. Narrating and remembering as practices of care, community, and commitment in asbestos contaminated contexts. *Annali Istituto Superiore di Sanità* 55(1):94-9).

Differently from other disasters characterized by their high visibility, asbestos related disasters are regarded as "invisible" because they are not easily brought to light in the absence of *ad hoc* epidemiological surveillance or other appropriate procedures. The long latency time of asbestos related neoplasms among else contributes to uncouple the time-window of occupational and environmental exposures and that of disease onset and progression.

The founder of Osasco, initially an industrial district of Sao Paulo, then an autonomous municipality, was an Italian immigrant, who named the location after the name of his hometown, Osasco, Province of Turin. Many international companis opened their facilities in Osasco since the early Forties of the last century, among them Eternit, who built there the greatest asbestos cement manufacture of Latin America. The health impact of asbestos exposure on the workers and their relatives started to be perceived about forty years later, in the Eighties, like it happened in Italy.

In this frame, the ethnographic survey realized by the Author includes a series of interviews to patients of asbestos related diseases and their relatives, bringing to light suffering, anguish and the notion of "embodied past coming to the surface". In this frame, for many sufferers, engagement in activism has meant to contribute to "paths of care" for others. It can thus be stated that "reading and narrating the memories inscribed in the contaminated bodies coincide with practices of care and struggle". In the meanwhile, besides individual activism, a national network of Brazilian asbestos exposed subjects (ABREA) started to work with collective issues such as access to health care , social security, compensation, court litigations and new regulatory frames aiming at asbestos ban. This also implied Brazilian participation in international networks, including a strict cooperation with Italian associations of asbestos victims and relatives, especially with the town of Casale Monferrato, where the largest Italian asbestos cement plant operated for many decades.

Finally, after a thorough review of the multiple disciplinary contributions required in order to disentangle the different issues at stake, the Author depicts the important role of anthropology and ethnography in the recognition of invisible disasters, empowerment of asbestos exposed communities, commitment to give a response to sufferers, and pursuit of environmental justice.

Besides the obvious interest of this book, that can easily be understood, I would add a few remarks on the way it is written. Firstly, the book's template is directly derived from the notes written by the Author in her daily fieldwork; before starting, she achieved a good proficiency in Portuguese, in order to directly capture the interviewed subjects' thought without intermediation by interpreters. Secondly, she took by herself the pictures that integrate the book, being highly significant under several perspectives. Thirdly, she often took notes about general issues concerning ethnographic studies, documenting her solid cultural background, and her familiarity with the thought of many important anthropologists. I would thus like to conclude this rapid review of *Dust Inside* by quoting the American anthropologist Nancy Scheper-Hughes, reported by the Author, who wrote "If 'observation' links anthropology to the natural sciences, 'witnessing' links anthropology to moral philosophy".

Pietro Comba
formerly, Istituto Superiore di Sanità, Rome, Italy
pietro.comba@iss.it

MANIFESTO PER UN ANIMALISMO DEMOCRATICO
Simone Pollo
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12.00 €

[Manifesto for a democratic animalism]

The Istituto Superiore di Sanità is actively involved in the revision of the project proposals involving the use of animal models, as well as in the cultural and applicative aspects of the legislation concerning animals used in scientific procedures. We have witnessed how animalist movements have been instrumental in the growth of awareness, both in in the general public and scientific community, concerning the welfare of animals used in research laboratories. However, it is not perhaps wrong to say that most of us, when we hear the word "animalist" or "animalism", think about a bunch of very angry young people thrashing research laboratories, or hard-core vegans who refuse any kind of use of other animals for any purpose by humans. This vision simplifies a much more complex and interesting picture. Simone Pollo, author of this agile volume, argues that animalism is a very important movement flourished during the last decades, and essential for reforming our relationships with other animals. Furthermore, animalism can, and in some respects already is, entwined with the ways of democratic societies: the author maintains this concept as the theoretical backbone of this book.

Simone Pollo is not new to these topics. His previous, very convincing, effort was dedicated to different ethical aspects of our relationships with non-human animals. His voice in the Italian scenario of philosophers dealing with animal ethics is original, and in my opinion, quite necessary. Instead of taking easy "pro" or "cons" perspectives, Pollo is always ready to discuss different options, even contrasting among them, and deconstructing mental "status quo". This attitude could be perhaps easily pictured as too cautious sometimes, and unable to take clear positions, for example: "pro" or "against" the use of animals in biomedical research. Instead, in my opinion, it is the correct perspective to adopt for scenarios that cannot be approached by means of preconceived positions. Having said that, Pollo does not hold back himself when the occasion rises to criticise, for example, hunting practices or the use of animals in circuses.

The book develops in 13 short chapters (and few pages of conclusions). Each chapter discusses the notion of democratic animalism in relation to other concepts and issues, such as "transparency, "progress", "science", and so on. The starting point is that the perception we have of the other animals has radically changed, and the notion of "sentience" has become pivotal as an important concept to consider in our relationships with other animals. This implies the belief that other animals can suffer in sophisticated ways that resemble human sufferance (scientific evidence for this is increasing in a significant way). Darwin already suggested that and his concept of "gradualism", for different physiological as well as behavioural characteristics (and mental as well), serves very well a much-needed re-thinking of animal welfare. Simone Pollo is a fervent Darwinist, and successfully calls for the Great Man to support his thinking about transforming the way we think about animals.

The book is not a "manifesto" strictly speaking. It does not then propose a sort of political program, but argues in favour of animalism as being integral part of the dynamic characteristics of a democratic society. Animals have the right to be free. However, the evolutionary, social, cultural history of humankind is significantly based on the exploitation of other animals, in a way or another. For this reason, certain practices, such as scientific research with animal models or animal farming, cannot be so easily dismissed simply because "cruel" or "inhumane", but surely have to be re-discussed with all of the stakeholders included, in new terms of what animal welfare is today.

I found of particular interest, for its originality, the chapter dedicated to wild animals "invading" urban spaces, or spaces inhabited and/or used by humans. The author is very critical of notions such as "management" of wildlife, because this notion is linked with a limitation of animal freedom, and our inability to comprehend and relate to something that is different from us (think about the term "*alien* species"). Pollo also says that the right to freedom of, let say, bears or wild boar which find themselves interacting with humans must be discussed taking into account everybody needs and reasons. I agree on this, and it would have been useful if the author provided us with some practical examples here.

Therefore, "animalists" cannot be understood anymore as just some loonies who reasons with their guts and emotions, instead of their brain. Animalism is and must be part of the developmental and dynamic processes of democratic societies. This is an important message that must reach, for example, those colleague scientists who still have some prejudice. However, extreme and violent animalism is still out there, but it just concerns a section of a more complex reality of people who do sincerely care for the welfare of animals we use for our purposes.

The book is reader-friendly, written in a style that leads the reader by hand through the reasoning of the author. The author is a philosopher, but do not worry! Simone Pollo's style is simple and very clear. This volume can be of interest for anyone who has an animal in her/his life that is, a lot of us! But I would also strongly recommend it to members of ethical committees involved in evaluation of animal experimentation, as well as to the scientific community that use animal models, a community that increasingly care for the welfare of

their scientific study subjects. However, as already said, the book will be enjoyed by anybody sensible to the relationship we humans have with other animals. Finally, I agree with the central thesis of the book: we need to discuss, we need to confront different ideas, we need to understand how we have to change our relationships with other animals. However, we also need to distinguish different contexts, and adjust our arguments in relation to those contexts, but never lose the possibility to give voice to who thinks differently. And this should include other animals as well.

Augusto Vitale
Center for Behavioural Sciences and Mental Health
Istituto Superiore di Sanità, Rome, Italy
augusto.vitale@iss.it

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Publications from International Organizations on Public Health

Edited by
Annarita Barbaro

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS (FAO)

Adaptive management of fisheries in response to climate change. FAO Fisheries and Aquaculture Technical Paper No. 667. Rome: Food and Agriculture Organization of the United Nations 2021; 300 p. ISBN 978-92-5-133890-2. Based on 13 case studies across the globe, this report showcases a set of good practices for climate-adaptive fisheries management, including applying flexible and adaptable fishing seasons and establishing early warning systems for extreme events. Aiming to accelerate climate change adaptation implementation in fisheries management throughout the world, the report showcases how flexibility can be introduced in the fisheries management cycle in order to foster adaptation, strengthen the resilience of fisheries, reduce their vulnerability to climate change, and enable managers to respond in a timely manner to the projected changes in the dynamics of marine resources and ecosystems. The good practices reported are linked to one or more of the three common climate-related impacts on fisheries resources: distributional change, productivity change, and species composition change. Therefore, these three impacts can serve as practical entry points to guide decision-makers in identifying good practice adaptation measures suitable for their local contexts.

State of knowledge of soil biodiversity. Status, challenges and potentialities. Rome: Food and Agriculture Organization of the United Nations 2020; 618 p. ISBN 978-92-5-133582-6. This report is the result of the work of more than 300 soil scientists and experts on soil biodiversity from all regions of the world, and it presents the best available knowledge on soil biota and their ecosystem functions and services. It is organized into seven chapters and presents concisely the state of knowledge on soil biodiversity, the threats to it, and the solutions that soil biodiversity can provide to problems in different fields. It also represents a valuable contribution to raising awareness of the importance of soil biodiversity and highlighting its role in finding solutions to today's global threats.

Minimum dietary diversity for women. An updated guide to measurement - from collection to action. Rome: Food and Agriculture Organization of the United Nations 2021; 176 p. ISBN 978-92-5-133993-0. This guide follows and supersedes the 2016 Minimum Dietary Diversity for Women: A Guide for Measurement. The Minimum Dietary Diversity for WRA (MDD-W) indicator is a food-based diversity indicator that has been shown to reflect one key dimension of diet quality: micronutrient adequacy summarized across 11 micronutrients. The guide aims to provide guidance to a diverse range of stakeholders from low and middle-income countries who are interested in actionable data on women's diets. It includes guidance on the most accurate and valid methodologies on collecting, analysing, interpreting, and presenting data on women's dietary diversity, for use in research, impact assessment and large-scale, health and nutrition surveys such as the Demographic Health Survey (DHS), to generate nationally representative data, that are comparable over time and across countries. This guide is articulated into two parts: Part 1, The Indicator: from collection to action, provides an overview of the indicator; Part 2, Steps for field operations, includes basic steps on preparing for MDD-W data collection, selection of enumerators and planning and conducting capacity-development.

INTERNATIONAL SCIENCE COUNCIL (ISC)

Opening the record of science: making scholarly publishing work for science in the digital era. Paris: International Science Council (ISC) 2021; 88 p. This report is the first output of the ISC's ongoing project on The Future of Scientific Publishing and is aimed at the scientific community and its institutions. Opening the record of science is seeking to establish, as far as possible, a shared view of the principles and priorities of the system through which its work is disseminated, and as a precursor for action to promote beneficial change. It proposes a series of normative principles that should underlie the operation of scientific and scholarly publishing; describes the current publishing landscape and its trajectory of evolution; analyses the extent to which the principles are observed in practice; and identifies problematic issues that need to be addressed in realizing those principles.

UNITED NATIONS ENVIRONMENTAL PROGRAMME (UNEP)

Emissions gap report 2020. Nairobi: United Nations Environmental Programme 2020; 128 p. This eleventh edition of the United Nations Environment Programme (UNEP) Emissions Gap Report (EGR) as-

sesses the gap between estimated future global greenhouse gas (GHG) emissions if countries implement their climate mitigation pledges and the global emission levels from least-cost pathways that are aligned with achieving the temperature goals of the Paris Agreement of limiting global warming to well below 2°C and pursuing 1.5°C. This year, the report focuses on three areas that are highly relevant for our ability to bridge the gap and that have become even more pertinent in the wake of COVID-19: the role of COVID-19 fiscal rescue and recovery measures in the global transition to decarbonization; the role and opportunities for reducing emissions from the shipping and aviation sectors, where international emissions are not covered by the NDCs; and the role of lifestyle change in decarbonization. Reflecting the unusual circumstances, the 2020 report deviates from its usual approach of exclusively considering consolidated data from previous years and includes preliminary assessments of the implications of the pandemic and associated rescue and recovery measures.

Adaptation gap report 2020. Nairobi: United Nations Environmental Programme 2021; 120 p. The fifth edition of the United Nations Environment Programme (UNEP) Adaptation Gap Report (AGR) provides an update on the current actions and emerging results of global adaptation planning, finance and implementation, three elements which are critical for tracking and assessing progress towards the global goal on adaptation. This year's report features a number of innovative elements: the AGR – taking into account existing tools, assessments and provisions of the Paris Agreement – applies five criteria (comprehensiveness, inclusiveness, implementability, integration and monitoring, and evaluation) to review for the first time whether adaptation planning in 196 countries is adequate (sufficient) and effective (successful) in meeting adaptation objectives; the report explains how efforts to make the financial sector sustainable could help monitor adaptation and pro-actively support the shifting of capital towards climate resilient investments; a new chapter on implementation reflecting the importance of understanding which actions are being taken, where, by whom and in what form has been added. Another important innovation is that, considering the growing recognition of nature's contributions to humanity, this year's report focuses on nature-based solutions as key instruments for adaptation to the impacts of climate hazards.

Preventing the Next Pandemic: Zoonotic diseases and how to break the chain of transmission. Nairobi: United Nations Environmental Programme 2020; 82 p. The report – produced in partnership with universities, research institutions, UN agencies and the secretariats of several multilateral environmental agreements – identifies key anthropogenic drivers for the emergence of zoonoses, from agricultural intensification and increased demand for animal protein to the conversion of land and climate change. These drivers are destroying natural habitats and seeing humanity exploiting more species, which brings people into closer contact with disease vectors. Once established in humans, these diseases quickly spread across our interconnected world, as we have seen with COVID-19. Understanding these drivers is essential to inform effective strategies and policy responses to prevent future outbreaks. This report makes many recommendations, all based on the One Health approach, which unites experts from multiple disciplines – public health, animal health, plant health and the environment – to deliver outcomes that improve the health of people, wildlife and the planet. The recommendations include expanding scientific enquiry into zoonoses, regulating and monitoring traditional food markets, incentivizing the legal wildlife trade and animal husbandry to adopt zoonotic control measures, and radically transforming food systems.

EUROPEAN FOOD SAFETY AUTHORITY (EFSA)

EFSA (European Food Safety Authority), Maxim L, Mazzocchi M, Van den Broucke S, et al. **Technical assistance in the field of risk communication.** EFSA Journal 2021;19(4):6574, 113 pp. doi:10.2903/j.efsa.2021.6574. This report assesses peer-reviewed and grey literature on risk communication concepts and practices, as requested by the European Commission to support the implementation of a "General Plan for Risk Communication". A scoping review of social research studies and official reports in relation to risk communication was conducted in the following areas: understanding and awareness of risk analysis roles and tasks, reducing misunderstanding of the different meaning of the terms "hazard" and "risk", tackling misinformation and disinformation, enhancing confidence in EU food safety, taking account of risk perceptions, key factors in trade-offs about risks, audience segmentation and tools, channels and mechanisms for coordinated risk communications. The findings were structured as follows: definitions of key concepts, audience analysis and information requirements, risk profiling, models and mechanisms, and contributions to communication strategies. Several recommendations were made for consideration by the Commission, both in terms of actions to support the design and implementation of the general plan, and research needs that are considered crucial to further inform appropriate risk communication in the EU.

EFSA AHAW Panel (EFSA Panel on Animal Health and Welfare). **Ability of different matrices to transmit African swine fever virus.** EFSA Journal 2021;19(4):6558, 109 pp. doi: 10.2903/j.efsa.2021.6558. This opinion assesses the risk posed by different matrices to introduce African swine fever virus (ASFV) to non-affected regions of the EU. Matrices assessed are feed materials, enrichment/bedding materials and empty live pigs transport vehicles returning from affected areas. Although the risk from feed is considered to be lower than several other pathways (e.g. contact with infected live animals and swill feeding), it cannot be ruled out that matrices assessed in this opin-

ion pose a risk. Evidence on survival of ASFV in different matrices from literature and a public consultation was used in an Expert Knowledge Elicitation (EKE) on the possible contamination of products and traded or imported product volumes used on pig farms.

WORLD HEALTH ORGANIZATION (WHO)

Guidance for the surveillance of drug resistance in tuberculosis: Sixth edition. Geneva: World Health Organization 2021; 117 p. ISBN 978-92-4-001802-0 (electronic version) ISBN 978-92-4-001803-7 (print version). This sixth edition of the Guidance for the surveillance of drug resistance in tuberculosis (TB) is an updated version of earlier editions published between 1994 and 2015. This updated guidance incorporates experience gained from 25 years of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance, a project initiated by WHO and the International Union against Tuberculosis and Lung Disease, supported by a global network of Supranational TB Reference Laboratories (SRLs). The aim of this document is to assist national tuberculosis (TB) programmes in developing the strongest possible mechanisms of surveillance for drug resistance in TB. This starts from periodic surveys of sampled patients, moving towards an ultimate goal of continuous surveillance systems based on routine drug susceptibility testing (DST). This guidance promotes certain standardized criteria for surveillance to ensure that results are comparable within and between countries over time. The target audience of this document is national TB programmes and, in particular, the coordination team for surveillance ideally composed of the programme manager, a laboratory specialist, a logistician, and an epidemiologist/statistician. This document is articulated into two parts: Part I describes the principles of the Project that should be considered fundamental to routine continuous surveillance and periodic surveys, and the requirements to transition from the former to the latter. Part II describes the steps needed to plan and implement a survey to determine the burden of drug resistance, and to manage and interpret the data collected.

WHO Guidelines for malaria. Geneva: World Health Organization 2021; 210 p. These Guidelines bring together the Organization's most up-to-date recommendations for malaria, are a compilation of existing WHO recommendations on malaria and supersede two previous WHO publications: the Guidelines for the treatment of malaria, third edition, and the Guidelines for malaria vector control. The WHO Guidelines for malaria aim to provide the latest evidence-based recommendations in one reference to support countries in their efforts to reduce and ultimately eliminate malaria bringing together all recommendations for malaria, including prevention using vector control and preventive chemotherapy, diagnosis, treatment and elimination strategies. The guidelines are organized around the major interventions available for malaria: prevention (vector control and preventive chemotherapies), case management (diagnosis and treatment), and strategies to be used in elimination settings. These recommendations on malaria will be continuously reviewed and, where appropriate, updated according to the latest available evidence.

Instructions to Authors

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- the *brief note*, 3000 words, including about 15 references, one table and one figure;
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Articles in journal

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

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.

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

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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).

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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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