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PhD in BIOENGINEERING

"Digital Health: Usage of Innovative Mobile Technologies for Health and Wellness"

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SUMMARY

LIST OF ABBREVIATIONS

AAC	Augmentative and Alternative Communication
AD	Alzheimer Disease
ADL	Activity of Daily Living
AI	Artificial Intelligence
AO	Augmented Object
AR	Augmented Reality
ARPA	Regional Agency Environmental Protection
AP	Autonomous Province
API	Application Programming Interface
ASL	Local Health Agency
AT	Assistive Technology
BBT	Basal Body Temperature
BCI	Brain Computer Interface
BP	Blood Pressure
CAT	Cognitive Assistive Technology
CN	National Center
CT	Contact Tracing
DAMSA	Department of Health and Environment
DPA	Data Processing Addendum
EPHA	European Alliance for Public Health
EU	European Union
GDPR	General Data Protection Regulation
GIS	Geographic Information System
GP	General Practitioner
HCI	Human Computer Interface
HI	Hearing Impairment
HMD	Head-Mounted Display
HR	Heart Rate
IaaS	Infrastructure-as-a-Service
IADL	Instrumental Activity of Daily Living

ICT	Information Communication Technology
ICU	Intensive Care Unit
IMU	Inertial Measurement Unit
IoT	Internet of Things
ISS	Italian National Institute of Health
IT	Information Technology
IZS	Experimental Zooprophylactic Institute
LIS	Locked-In Syndrome
MCI	Mild Cognitive Impairment
MR	Mixed Reality
MRTK	Mixed Reality ToolKit
NCID	National Centre for Infectious Diseases
NHS	National Healthcare System
PEPP-PT	Pan-European Privacy- Preserving Proximity Tracing
QAS	Water Quality and Health
SaaS	Software-as-a-Service
SDK	Software Development Kit
SLI	Specific Language Impairment
SPO2	Peripherical Oxygen Saturation
ST	Territorial Structure
STT	Speech-To-Text
TISP	Innovative Technologies in Public Health
TTS	Text-To-Speech
UWP	Universal Windows Platform
VI	Visual Impairment
VR	Virtual Reality
Wbe	Wastewater-based epidemiology
WHO	World Health Organization
WTP	Waste Treatment Plant
XR	Extended Reality

ABSTRACT

This thesis work fits within the context of health digitalization phenomena, triggered by the recent diffusion and continues development of wearables and mobile technologies, that allows to support and/or monitor everyone's activity, at any moment wherever he is.

In the First chapter, a worldwide overview of technologies that are used in healthcare sector is being provided. Digital health (eHealth) and its related applications is being presented in healthcare sector, with special focus on mobile health applications (mHealth), on emerging technologies such as Geographic Information System (GIS) and XReality (Virtual Reality, Augmented Reality and Mixed Reality). Then, the chapter ends with a brief reflection regarding the changing in patient's role and problems related to online data sharing, such as security and privacy.

In the Second chapter some current health issues are being presented and discussed with their current utilized solutions for rehabilitation/support of fragile or disable individuals. The faced issues are, problems inevitably associated with aging, such as cognitive decline and sensory capacity decline; problems related to individuals that are showing verbal and motor disabilities. In the end, the current discourse regarding the global situation caused by SARS-CoV-2 diffusion is being faced by illustrating solutions adopted by various Countries, with reference toward the situation and solutions in Italy.

The Third chapter describes materials and methods employed during my PhD project, for which the proposed set-up and systems functioning are described to face health issues discussed in the previous chapter. A solution is being presented for cognitive and sensory decline that exploits Augmented Reality as a support technology for individuals during their daily living activities; a Mixed Reality solution is being proposed, that exploits a gaze detection system, for subjects affected by both motor and verbal communication disabilities; lastly, the development of a Geographic Information System is being described to contribute in the management of containing of Covid-2019 diffusion in Italy from two different point of views: first, Clinical, through a daily monitoring system that allows direct communication between patients and General Practitioner; and second, environmental, through a system able to gather and manage data on a national level that are deriving from the analyses of waste water taken from different sampling sites scattered on the Italian territory.

In the Fourth chapter is described the environmental surveillance project Entitled "Environmental Surveillance of SARS-Cov-2 through urban wastewater in Italy: indications on epidemic trends and early warning (acronym: SARI)". The project, after a first pilot phase, has obtained funding to become a real environmental surveillance at national level for the monitoring of the spread of SARS-Cov-2 infection. The preliminary results obtained from the analysis of the samples taken from the Waste Treatment Plant of different Italian regions are therefore reported and discussed.

Finally, a discussion is carried out on motivations for which I believe that these proposed solutions can effectively contribute in the monitoring of citizens and in the enabling/rehabilitative practice of fragile and disable patients, by showing strength points of the proposed systems and discussing the modalities in which these new technologies should be inserted in a well-defined social, economic and legal frame.

1 CHAPTER 1 – eHealth and mHealth

European healthcare and assistive systems must deal with important challenges, such as aging of population, multimorbidity, lack of sanitary/healthcare personnel and the rising problem of preventable non transmissible diseases caused by risk factors like tobacco, alcohol, obesity and other diseases, including those neurodegenerative and rare. An additional increasing threat is represented by infective diseases caused by a high resistance to antibiotics and to new or re-emerging pathogens (EUR-Lex, 2018). Across the world, the main cause of morbidity and mortality are chronic conditions, those who are widely preventable through consultancy, modification of risk factors and adherence to drugs (WHO, 2011). The implementation of this kind of intervention though is hard in contexts with limited resources (Mechael et al, 2010).

The relative costs of public healthcare system and long-term assistance are constantly increasing in the EU member states and it is expected that they will continue to rise in the next years (EUR-Lex, 2018). In most of the European member states life expectancy exceeds 80 years, but this life expectancy record is not always equalized by years of life in good health. Therefore, in order to guarantee to everyone a fair and inclusive access to healthcare assistance (Giedrojc, 2017) that allow in the first place the clear tracking of patient since the very first day in which the interaction with healthcare network there is in need for new solutions. In 2017, the European union report (https://ec.europa.eu/health/state) about the global health status in Europe has concluded that only a new conception of healthcare and assistive systems will allow them to stay adequate to their purposes, that is continuing to promote the sanity, prevent diseases and provide support focused toward the patient satisfying the citizen's needs. Therefore, Sanitary and supportive systems require reforms and innovative solutions to become more robust, accessible and effective in providing high quality assistance to European citizens (EUR-Lex, 2018). To date, this is possible through the development of an integrated services system online (Information Communication Technologies, ICT) that allows, in real time, the control and systematic evaluation of parameters such the clinical risk, diagnostic and therapeutic procedures with particular reference to their direct quality, to the employed resources, to the utilized technologies and to the satisfactory level perceived by the citizen (Italian Ministry of Health, 2014). Through cloud systems, infrastructure-as-a-Service (IaaS), the sanitary organizations and the medical personnel may test the reliability, accessibility and the availability of a determined service (Garai et al, 2016).

The development of the "digital revolution" creates enthusiasm within European citizens, which at the same time makes them feel overwhelmed by the digitalization of society. The wide range of technologies that is simultaneously introduced on the market interrupts the familiar ways of operating and communicating. As outlined in a 2018 CE communication (European Commission, 2018), the digital transformation of health care is just a small element of a much larger transformation that is becoming always more tangible and includes technologies such as for example, Big Data and Artificial Intelligence (AI) (Hindle, 2019). Big Data gives the capability to analyze a variety of data set (non-structured) from a wide range of sources. This requires the capacity to connect the data and extract potential precious information from non-structured data in an automized and convenient way. These data might be a vital element for the epidemiological research since it could allow researchers and scientists to improve the treatment of patients by searching models on broad standards or draw new conclusions, for example, on the relation between the development of a medical conduction and environmental factors. Moreover, Big Data could contribute to the reduction of the test periods or the development of more advanced mechanisms for early diagnosis and diseases prevention. Maximize the potential of healthcare data may lead to more productivity and a cut of health care system costs, with a prospective of hundreds of billions of Euros per year (EC COM, 2014b).

Healthcare system and public health are often indicated as delayed in comparison to other economic sectors like Online Banking, travels or shopping (Hindle, 2019). As underlined previously by the European Alliance for Public Health (EPHA), the reasons of this delay are various and have mainly to do with the fact that the union between digital and non-digital elements have been so far relatively dysfunctional, in a sense that the final users – health professionals and patients, managers of the health care system, contributors (tax payers) and public in general – did not receive evidences regard costs and real benefits from the digital health (Marschang, 2019). The developments in other sectors will inevitably bring changes in the healthcare attitude, for example, towards the protection of data and privacy (Hindle, 2019). In order that healthcare systems could evolve in a fair and sustainable way, it is important to exploit the potential of digital solutions in the most realistic and inclusive possible way. The risk is in fact that digitalization may lead to more exclusion, by satisfying the minority and creating additional cracks/splits between socioeconomic groups (Hindle, 2019).

The European union has an action plan for electronic healthcare for the period 2012-2020, in which is stated that the promise made by ICT to increase the efficiency, improve the quality of life and unlock the innovation in health markets (European Commission, 2012). The 2011 directive regarding "The application of patient's Cross-border healthcare right", the establishment of an electronic healthcare network and initiatives such as large-scale pilot projects have increased the interest in utilizing ICTs in healthcare environment, but the action plan has identified numerous obstacles to digital healthcare diffusion, including (Cowie et al, 2016):

- Lack of awareness and trust in the digital solutions;
- Lack of interoperability;
- Lack of legal clarity for mobile applications for health, wellness and lack of transparency regarding the usage of the gathered data, including data that crosses international borders;
- Inadequate or fragmented legal frameworks;
- Lack of reimbursements;
- Regional differences in accessing ICT services, with limited access in the disadvantaged areas.

The importance of digital solutions seems destined to increase in an exponential way during the new European Commission mandate (CE, 2019-2024), with significant investments announced in many political areas (Hindle, 2019).

1.1 Information and Communication Technologies

Starting from the 80s, technological innovation has taken giant steps enough to fully hit businesses that have the need to implement informatic services inside corporate processes to respond to the new challenges presented by the world. From here was the birth of ICTs. If from a perspective it turns out possible to identify those that are essential elements of ICT, on the other side it is complicated to give to it a univocal definition, being that of ICT a dynamic world which is in a continues evolution, anyway, generally with ICT it is meant the combination of hardware and software technologies of Information Technologies (ITs) services with the methodologies Communication Technologies (CTs): the ITs part manages the data, processes and manipulates it, while the CTs part allows its transmission through wireless, network installations or telecommunication services. The growth in computing power has triggered the development and strengthening of digital devices, as well as peripherals that expands its capacity. These devices are able to acquire, register, organize, recover, visualize, manipulate and above all to spread information. ICTs strength point is the interoperability, that is the capacity of two or more systems to exchange data based on a common protocol. The development of ICTs during the last quarter of the XX century has marked an information era in which the economic and social activity has been expanded, deepened and transformed. The more optimistic projections suggest that an informatized and network-connected world not only would guarantee a more rapid and diffused growth of occupations, productivity and production, but would even improve the access to structures responsible of improving the quality of life (Chandrasekhar and Ghosh, 2001). The growing interest in the development and usage of electronic instruments based on Internet for healthcare purposes has been facilitated by an enormous increase in the last two decades of accessing Internet in the whole world. To date, more than 50% of global population has an Internet connection compared to the only 1% in 1995 (https://www.internetlivestats.com/internet-users/) and with reference to Europe an increase of 500% was registered in the Internet usage from 2000 to 2017, with a utilization percentage that have reached approximately 87% of European population (https://www.internetworldstats.com/stats.htm). This creates a new prospective and it is important to underline that this phenomenon involves even elderly people (LaMonica et al, 2017).

The noticeable growth of ICTs in the last decades has favored the development of new and innovative healthcare applications, that kick started the phenomena of digital health (or more commonly called eHealth). Healthcare authorities in the European countries are very interested in the implementation of new models of care assistance with the migration from traditional and local healthcare environment (for example, hospitals) toward remote or omnipresent scenarios, resulting in improving the support and the treatment experience especially for those who are living with chronic conditions (Pena and Gil, 2007). The development of ICTs may lead to health improvements in at least three ways: as an instrument for continues formation, allowing healthcare operators to be informed and trained on knowledge progresses; they could improve the supply of remote services, ranging from the improvement of education toward healthcare to emergency consultancy, including advices to face and mitigate natural disasters consequences; in the end, they may enhance the governance transparency and efficiency, which consequently should improve the availability and supply of public healthcare services (Chandrasekhar and Ghosh, 2001).

The production of ICT services in healthcare has permitted to improve the quality of services provided to the citizens (even in terms of house assistance), to rationalize the resources and reduce the costs, while continuing at the same time to guarantee high quality services. These instruments have the potential to (Cowie et al, 2016):

- Improve the patient's quality of life even when dismissed from the hospital structure thanks to telemonitoring, which is the monitoring of vital parameters even from home;
- Promote house assistance (homecare): the patient is being assisted from home allowing to rationalize the costs related to occupying a spot in the hospital by patients that can be cured remotely;
- Sharing information (data and media) to allow the analysis by experts both in real time and not;
- Provide support in emergencies (tele-aid).

A typical example of ICTs usage to advance the health status is the rising field of telemedicine, which commits to provide the best advices and medical treatments to patients independently from their position. In addition to the advices based on standardized symptoms, works are ongoing concerning how to provide a high-level medical assistance via satellites or remote sites or in response to a disaster, such as earthquakes. The main constraints are accessibility to services and the cost of the bandwidth required for the transmission of physiological data and complex medical images (Chandrasekhar and Ghosh, 2001).

If designed and implemented adequately in an effective way from a "costs" point of view, healthcare solutions and digital assistance can enrich the well-being of millions of citizens and radically change the way healthcare services and assistance are delivered to the patients (WHO, 2015). To date, the main critical issues faced in the usage of ICTs in public healthcare fields are:

- Physical access limits to new technologies;
- High costs;
- Lack of necessary competences to use technology.

These constraints suggest that, instead of contributing to improve social services delivery, ICTs revolution may, generate a new "digital gap" (Jacobs et al, 2014). Educate health professionals and patients to the potentials of ICTs and provide them with adequate access would spread the benefits to a larger group of final users so it could then contribute to reduce the digital gap (Chandrasekhar and Ghosh, 2001).

1.2 eHealth

During the 90s, when Internet has taken consensus within the public, a certain number of electronic terms started to appear and proliferate (Buccoliero, 2010). For example, the term e-mail for the electronic post, which offered new possibilities to communicate rapidly and share experiences; e-commerce, which has proposed new ways to conduct commercial and financial transactions through Internet. For the introduction of ICT for the purpose of improving health and healthcare system the term eHealth has been coined (Alvarez, 2002). eHealth is a relatively new and interchangeable term, which includes a wide range of definitions (Roberts et al, 2010). Despite the growth in the research regarding electronic healthcare and the wide usage of it by many persons, academic institutions and professional organisms, a lack of consistency remains in the usage of the term and poor consensus on the taxonomy of digital health technology (Black et al, 2011). The main cause to the lack of clearness is the lack of consent on the meaning of the word health itself, whose definition varies from "disease restrictive opposite, infirmity or lack of diseases" to the concept health all-encompassing of the world health organization (WHO): "status of complete physical, mental and social well-being".

According to the European commission definition, eHealth includes all ICTs applications with its wide range of own healthcare system functions and that concern medics, hospital managers, nurses, data management specialists, social security administrators and, naturally, patients through the prevention of diseases or a better management of it (Di Carlo and Santarelli, 2012). More formally, World Health Organization, in accordance with the International Telecommunication Union defines electronic healthcare as "the usage of electronic technologies of information and communication necessary to make the healthcare system work to improve health and human well-being, and to enhance healthcare systems services in terms of more quality, security and possibility to obtain treatments, with a positive relapse in terms of human resource reduction and social and economic costs" (WHO, 2006). Electronic Health instruments can be utilized for the screening of "at risk" persons, offer help through interventions based on the Web or provide proactive and guided interventions (La Monica et al, 2017). With the term eHealth it is meant then the usage of instruments based on ICTs to support and promote prevention, diagnosis, treatment and monitoring of the diseases and the health management of the individual's lifestyle.

As in most neologisms, the precise meaning of eHealth varies in function of the context in which the term is used (Oh et al, 2005). Many authors have referenced to distance concepts, geography and position, as they see eHealth as an instrument through which is possible to break down physical barriers and provide healthcare assistance independently from where participants are (Brommey, 2004). Technology can meet the necessity of health operators and patients of communicating between themselves through digital healthcare services, including virtual consultancies, telemedicine clinics and group forums based on Web, by using several telecommunication software and Web-based conferences to interact and be connected in real time.

Physicians have explained how network connection increases the opportunities of carefully evaluating a patient in critical conditions remotely, limit the non-necessary transfer to a central structure and begin advanced treatments promptly.

Speech therapist have indicated social media as useful platforms to the rehabilitation of communication in patients with traumatic cerebral lesions. Social media reduces the need of literacy, by conceding time to the comprehension and messages elaboration since they provide the possibility to send photos and hypertextual links, that can be of notorious advantage for whom with communication issues.

Exercise physiologists are providing remote consultancies and support services for rehabilitation. Physiotherapists can, through Web based activities, offer interventions for musculoskeletal lesions to patients from all over the world. Moreover, through the usage of Applications it is possible to personalize therapy programs with personalized advices, teaching material and high-quality video demonstrations (Shaw et al, 2017). Specialists involved in rehabilitation see in eHealth the possibility to create robot and the development of digital games (*Serious Games*) and virtual and augmented reality applications for the promotion, prevention, cure and health maintenance (Borelli and Ritterband, 2015).

The combination of appropriate changes at an organizational level with acquisition of new skills could lead eHealth to contribute and develop more effective prevention systems at less costs, easily accessible with greater informed participation by the patient (Di Carlo and Santarelli, 2012). Shaw's group (Shaw et al, 2017) have carried out an interview collection to professionals, scholars and eHealth influencers with the purpose of developing a model to guide the development of technological innovations in healthcare field. The proposed model is constituted by 3 overlaid domains:

1) health in our hands: use of digital technologies for information, monitoring and tracing;
2) interaction for health: use of digital technologies to facilitate communicative meetings among parties interested in health;
3) data enabling health: use of data to improve health and healthcare services.

In order that the intervention possesses the maximal potential impact, during the planning of eHealth interventions the three domains should be taken into consideration. For example, the developer of a service aimed to the self-management of a chronic health condition will have to consider the way the user interacts with technology to monitor and manage his own condition (health in our hands); offer the opportunity to communicate and interact with health operator for coaching, support and for monitoring (interacting for health); an appropriate platform collection, management and analysis of data for an immediate decisional support and for a personalized healthcare assistance with an always higher precision (data enabling health) (Shaw et al, 2017).

To recapitulate, the key characteristics of digital health solutions are multiple, but can be summarized with the following points:

- **Connectivity** with network;
- **Accessibility** for all population groups;
- **Portability:** Laptops and mobile devices facilitating data transmission between entities that function as a new communication technology.
- **Wearability:** the miniaturization has allowed the creation of wearable devices that can be worn in contact with the own body for 24 hours a day, allowing innovative solution such as monitoring heart rate frequencies or the quality of sleep (sleep tracking);
- **Privacy**: the data exchange is a strong instrument to potentiate the national healthcare system services, however, it is necessary first of all that user's privacy is being respected by following strict rules such as dictated by the GDPR and by other specific standards for eHealth;
- **Cyber-security**: any digital health solution cannot be considered such if it is not capable of offering to its users an acceptable level of cyber-security according to the practice established by the sector (based on the guidelines and the ''best practices'') in addition to specific regulations.

1.2.1 Use of eHealth

WHO recommend the development of digital intervention to strengthen healthcare systems in a way to improve coverage and quality of healthcare services (WHO, 2019). At the same time, the European Commission considers digital health as a key factor for the creation of more robust healthcare systems (EC COM, 2014a). In public healthcare, the digitalization contributes to more transparency, to a more rational use of resources and to the designing of more effective services from both health operators and patients point of views. Digital interventions are not thought to substitute the fundamental components of healthcare systems, but rather to contribute as a complementary instrument for health operators aimed to improve their performances, improve the service quality for healthcare recipients and allow administrative processes and healthcare operations to function more efficiently (Hindle, 2019).

eHealth has multiple advantages compared to traditional interventions (Ritterband and Thorndike, 2006; Portnoy et al., 2008; Budman et al, 2013, Lustria et al, 2013; Borelli and Ritterband, 2015):

- More access to both assistance and experts' feedback;
- Uniformity diffusion and data collection;
- Reduce the inequalities by adapting to different necessities and levels of literacy;
- Possibility to send personalized messages and calibrate the intervention intensity based on each single user's performance.

Literature studies confirms that eHealth interventions can be effective since they are complex long-term programs appropriate to modify habits that require a behavioral change (Aalbers et al, 2015). eHealth intervention have demonstrated to be effective to help persons to improve/keep a variety of healthy behaviors and for the management and/or the treatment of symptoms in a series of health issues, from which anxiety depression (Andersson and Cuiipers, 2009; Andrews et al, 2010), diabetes (Cox et al, 2008), diet problems (Kraschnewski et al, 2011), alcohol abuse (Cunningham et al, 2009), insomnia (Chan et al, 2017; Christensen et al, 2016) and promotion of physical exercise (Irvine et al, 2013). Even though the entity of the pre-treatment condition and the change in the behavior tend to be from small to average according to meta-analytic conventions, the changes are compared favorably with other health and medical interventions commonly implemented (Portnoy et al, 2008). Moreover, it should be considered that, from a public health point of view, even small changes are significant on a population scale (Rose, 1992).

eHealth therefore has the potential to improve the quality of healthcare assistance while reducing its costs (Elbert et al, 2014). To date, the entity of effectivity and efficiency tests of electronic sanity is not proportional to the number of interventions conducted regularly (Enam et al, 2018) and the use of eHealth is mostly guided by hypothesis on the benefits of electronic health rather than by results obtained by scientific studies (Rigby and Ammenwerth, 2016). The numerous efforts done on research regarding electronic healthcare are still to be considered disconnected and so are not able to create a synergetic effect on the growth of eHealth (Enam et al, 2018).

Multiple systematic revisions and meta-analysis have demonstrated that intervention programs based on technology aimed to the change of healthcare behavior may have a positive impact on population (Wofford et al, 2005; Portnoy et al, 2008; Ekeland et al, 2010; Lustria et al, 2013; Elbert et al, Jacobs et al, 2014; Enam et al, 2018; Kisekka and Giboney, 2018), but they are often obstructed by the heterogeneity between single studies in terms of study population, intervention components, control groups and results measures with consequent difficulties of comparison and results generalization (Elbert et al, 2014).

Due to the lack of effectiveness proves, reliability, electronic health solidity to facilitate a secure and affordable assistance, the potential of eHealth have been questioned (Rigby et al, 2016) and this could trigger reluctance in investments and in the development of electronic health related policies in organization and countries (Al-Shorbaii, 2013). Before the interventions in electronic health could be a changing intervention of the future's behavior, it is necessary to identify components and effective mechanisms, rigorously test them and establish its cost/efficacy ratio in different contests (Jacobs et al, 2014). The academics are working to reduce the time necessary to create and test eHealth applications without losing scientific integrity, for example, through the usage of new methods (Klasnia et al, 2015; Mohr et al, 2015; Nahum-Shani et al, 2015). The development of a more solid and complete evaluation of electronic health studies or a better validation of evaluation methods may facilitate the transferability of results within studies (Enam et al, 2018). In fact, the introduction of technology in healthcare field must occur as part of a collaborative process based on gaps of healthcare services in particular on the needs of final users: the objectives of improving services of healthcare system will not be achieved if acquired technologies will not properly work in the eyes of its users (Hindle, 2019). Healthcare operators must judge digital technologies as easily interactable and as a support instrument to create new advantageous routines. If, by the way, are being imposed from the top of the scale to the bottom and without previous consultancy, it is probable that the introduction of the technology fails during its implementation phase (Hindle, 2019). The adoption of the technology must be viewed as a iterative process that involves all the parties involved (Shaw et al, 2018), including the citizen, who is not seen any more as a patient but as a health consumer that actively participates in the health assistance process (patient empowerment). This unified and transdisciplinary approach is translated in effective applications based on the theories, validated empirically that are translated to a health improvement (Borelli and Ritterband, 2015). From these necessities, recently a new model has been proposed to evaluate eHealth interventions, the model ‘’Evidence in eHealth Evaluation’’, that shows evidences accumulation by evaluating some aspects of the evaluation in distinct intervention phases, the model is composed by 6 phases (Enam et al, 2018):

1) **Designing**: evaluation of the technological aspect and technological development costs;
2) **Pre-test**: evaluation of the technological, human, social, financial aspects;
3) **Pilot study**: the evaluation focus moves primarily based on the clinical aspect followed by the human and social, technological, ethical and legal aspects. Depending on the evidences gathered in the pilot study, the intervention could proceed to the next phase or relegate to the designing phase;
4) **Pragmatic study**: evaluation conducted to identify if the assistance enabled by the technology could be executed by the realistic layout of an organization;
5) **Evaluation**: evaluating all the aspects related to the study, including the transferability of results;
6) **Post-intervention**: the evidence that reaches its peak in the summative evaluation phase and it is used in the post-intervention phase to take future decisions.

The utilization of this model increases the complexity of the evaluation process, since an eHealth intervention that includes all the phases presented in the model will become intricate due to the high consumption of resources, but it should guarantee the generation of solid proves of effectiveness and efficiency.

In conclusion, due to the increasing importance with the increasing of patient’s number and the international circulation of citizens (Italian Ministry of Health, 2014), the most important challenge that eHealth must face, according to EPHA members, is the way in which it is being inserted in the actual fragmented panorama, that differs not only from country to another, but often even between a region and another (Hindle, 2019). By focusing the attention on Italy, from a European Commission investigation it is evinced that we are in line with the European countries in the usage of technology by General Practitioner (GP), but in significant delay in the usage of online health applications (only 3% of GP exchanges administrative data with other subjects against 10% of the EU average). This is due to the poor online connection between GP and other subjects of the healthcare system, consequence of a heterogenous development between different local and regional structures. The decentralization of the National Healthcare System (NHS) makes it difficult to national detections to pick effectively the different modes from which the addresses of the central government are being actuated on a regional level; the other reason is because each single entity of NHS (regions, local health companies and hospital companies) are adopting their own informative systems, like ISTAT that has its own informative system concerning healthcare (Di Carlo and Santarelli, 2012). The collection, conservation and elaboration of these data is a result of decisions made by single entities in the NHS and the same applies when carrying out ad hoc investigations. Since the initiative is mostly entrusted to local projects, the purposes of the investigations are often different and the data collection is done through different criteria (sampling draws, interview type, definitions and variables classification, treatment of missing data). This makes it complicated even to provide a totally exhaustive description on the diffusion of ICT applications in healthcare.

To date, the principal technological areas of eHealth are (Cowie et al, 2016):

- Online health information;
- Telemedicine and telecare: disease management services, remote monitoring of patients, teleassistance and home assistance;
- Clinical information systems: electronic health record and monitoring of clinical and institutional practice;
- Advanced diagnostic, assisted by artificial intelligent algorithms and Big Data;
- Medical Robotics;
- Digital Therapeutics;
- Personalized Healthcare: adapting the intervention to the necessity of a single individual;
- Mobile health: providing healthcare and informative services regarding health and the treatment using mobile technologies, laptops and wearables.

1.3 mHealth

Until a few years ago customized interventions based on Web were disbursed almost exclusively by computer, thus, one of the principal problems with eHealth interventions resulted to be the high dropout rate (Christensen et al, 2009). To make interventions even more accessible, and therefore decrease the possibility of dropouts, professionals health promoter are always more interested to use mobile technologies, that allow health institution to communicate with other persons, monitoring their behaviors and conduct health promotion interventions remotely throughout portable or worn devices during daily living activities (Lupton, 2013).

The unprecedented spread of mobile technologies, as well as the progresses in its innovative application to face healthcare priorities, have evolved in a new eHealth field known as mHealth (Cameron et al, 2015). As for eHealth, there has not been established any standardized definition of mHealth. According to WHO (WHO, 2011) with mHealth it is meant the supply with health-related and informative services regarding the monitoring and evaluation of user's health condition supported by mobile devices (for example, smartphones) and wearable devices (smart watches, bracelets, clothes, virtual and augmented reality devices/viewers , etc.) connected with a wireless modality (for example, SMS, Bluetooth, GSM, GPRS/3G/4G, Wi-Fi), commonly indicated as *Internet of Things* (IoT), for the transmission of health related data. The definition focuses on technology and networks that drives the transition and potential impact on healthcare assistance in general thanks to the greater connectivity. However, technology is the catalyst and it needs to be incorporated in a system for healthcare assistance to be effective (Cameron et al, 2015). So far, in fact mHealth is evolving as a mosaic of incompatible applications that are not interoperable: mobile devices, medical hardware and often health information cannot communicate between them and share the data. Healthcare operators will have to face the possibility of being submerged by patients' data stream, that would create a series of hard challenges, including the potential requisite of a 24/7 supervision, the necessity to summarize multiparametric data gathered continuously in a clinically significant and utilizable format. Even for consumers the big quantities of potentially available data may easily overwhelm even the more active and informed healthcare consumers. Research then will have to focus on the challenge of utilizing in an efficient way the large quantity of data by defining objective indexes for the measurement of assistance quality that integrates the technique currently used based on the subjective perception of single individuals through questionnaires (EC COM, 2014b). International collaboration between industry and research institutes is fundamental for the development of approved standards by all interested parties.

Allowing mHealth systems to share information between itself and with more broad eHealth systems could increase the effectiveness and efficiency of assistance to patients and reduce the costs associated to data collection (Becker et al, 2014).

Reviews results that have collected data published about interviews conducted on mHealth users suggests that it is worth to continue investing in the field of online health, as patients believe that sharing information between health operators has a precious capacity in providing assistance (Kisekka and Giboney, 2018). mHealth solutions could in fact help to detect the development of diseases in an early stage through auto-evaluation instruments or by remote diagnostic, thanks to the possibility to share data with health operators that would facilitate a prompt intervention (EC COM, 2014b). Information regards physiological status are clearly fundamental to prevent, identify and deal with medical conditions. Attention toward prevention has the potential to improve the people quality of life and even extend life expectancy, thanks to mHealth it is possible to actuate new methods to promote "healthy behaviors" (EC COM, 2014b). Mobile technology can be used to acquire, archive, analyze, manage and present data on a population level, including data of the Geographic Informative System (GIS). The surveillance used for public health or medical purposes operates at different levels, from an individual clinical level, interpersonal on a national populational level or global. Therefore, on a global or national level, health surveillance systems are utilized to register and monitor cases of illness, severe conditions such as obesity or infections to maintain the records of epidemiologic changes of illnesses or in the illness model (Lupton, 2012). Moreover, these technologies are used in clinical studies to collect data and support patients during daily living activities in natural environments with a consequent load reduction on participants. The monitoring and remote detecting may in fact allow researchers to recruit and follow patients without the necessity and associated costs of transportation in a research environment or health assistance. Consequently, it is possible to obtain a higher quality of data at a lower cost (Kaplan and Stone, 2013). In the end, mobile technologies can be used as an enabling/ rehabilitation instrument for patients affected by disabilities of various kinds, in a way to carry out rehabilitation treatments even from home or to use it as a support/substitutive instrument of the absent/lost ability. As noted by these examples, a great potential for mHealth exists to re-design almost every aspect of healthcare assistance and significantly improve the comprehension of human physiology in healthy and disease conditions. The greatest potential of mHealth could be allowing the complete re-definition of the "normal" physiological answers and improving the comprehension of chronic conditions roughly defined from a perspective based on a population that compares an individual with thousands of others and from a time-based perspective that compares an individual with himself before the presence of a sign or a disease symptom (Steinhubl et al, 2015). In fact, these technologies are increasingly used even from "users not patients" outside the professional sphere of health promotion as part of voluntary strategies of auto-tracing (Lupton, 2013).

mHealth is considered as one of the main instruments that could help EU member states to maintain healthcare systems sustainable inasmuch it may support a more efficient delivery of cures, contribute to a more fair access to healthcare as technologies are spreading in remote areas and toward persons that otherwise would not have an easy access to healthcare, including individuals with disabilities (EC COM, 2014b). Moreover, it could keep patients who are affected by chronic diseases outside of hospitals and help in facing the lack of healthcare professionals in Europe. It is estimated that about 15% of utilization costs of healthcare assistance could be saved throughout remote monitoring, by using mHealth solutions (Steinhubl et al, 2015). However, mHealth is not currently utilized at the maximum of its potential in European HealthCare systems (EC COM, 2014b). Now, high quality tests are missing that would support the adoption of many new technologies and there are diverse financial obstacles, regulations and security limits to be overcame. Most published tests supporting the clinical use are limited by an undersized pilot data and they are mostly anchored to a specific technology or an individual device, rather than based on a new assistance system built around what the technology allows. Considering the many promises, without rigorous tests in clinical studies, mHealth is taking the risk of following the same path of Robotics use in surgery, megavitamins or commonly used therapies without clear data in support (Steinhubl et al, 2015). Healthcare operators and potential payers could need additional proves of its clinical and economic benefits before increasing its adoption (EC COM, 2014b). Luckily, noticeable efforts are in progress to establish the real capacity and value of mHealth field (Steinhubl, et al, 2015).

1.3.1 The role of Smartphones

Today, a portable device that fits in the palm of your hand is able to connect to the network and exert a computing power that, several decades ago, would had cost tens of millions of dollars and would have required instruments that would fill entirely a room (Markoff, 2011). The increasing in computing power and mobile connectivity have created the base for mHealth technologies that are able to transform the modality and the quality of clinical research and health assistance on a global scale. However, only now mobile technologies for health purposes are making their first steps in healthcare assistance by providing the basis to radically transform the assistance practice and research activity, facilitating at the same time patients to access to their own health information whenever and wherever they are (EC COM, 2014b).

As noted by WHO, the costs of communication technologies (principally thanks to an easy access to smartphones) have precipitated as years go by and as for today, they are within the reach of almost everyone. One of the key characteristics of smartphones is exactly their capillary diffusion. From an International Telecommunication Union (ITU, 2010) estimation, the number of mobile phone subscribers in the world has reached around 5 billion, with a commercial wireless signal coverage for more than 85% of the population. The use of smartphones has been that much an integrated part of our daily routine that to date, in average, on daily basis we spend more time looking at our smartphone's screen than our TV screen (Steinhubl et al, 2015). Based on the increasing usage of smartphones as a lifestyle device, the number and efficacy of mHealth interventions may increase noticeably (Dennison et al, 2013; Lathia et al, 2013).

The integrated and added functions – Cameras, GPS, accelerometers, voice recorders, internet mobile, Bluetooth, Apps and many others – of smartphones, are supporting the supply of mHealth for almost everyone or almost every location, at least in theory (Giedrojc, 2017). In this context, smartphones play a double role:

- They could be utilized directly to improve communication between patient and healthcare system by using a messaging Apps or by specially developed Apps to communicate directly with the medical authorities;
- They could function as transmitter/receiver of biometric data registered by wearable devices.

Users are potentially always digitally connected and so always reachable and, if necessary, geographically traceable. For example, automatized SMS or e-mail could be targeted and individually personalized or specially developed Apps could send patients notifications to remind them to adhere to treatment programs (Garai et al, 2016).

1.3.2 App for mHealth

From a technological point of view, a mobile application (App) is the result of an intertwined chain of many hardware and software components, of which complexity increases every time a hardware component is being added and a software version is updated (Becker et al, 2014).

The increasing diffusion of smartphones and 3G, 4G networks has incremented the usage of mobile Apps that provide health services which offer the possibility to improve security and patient's autonomy. The number of mHealth Apps has significantly increased over the span of few years, reaching according to European Union's estimations almost 100.000 health dedicated App currently available on different platforms of the global market. The most rapidly growing category is "health and fitness", occupying about 70% of the market. The remaining 30% is aimed towards health operators, by facilitating patients access to data, consultancy and patients monitoring, images diagnostics, information about medicines, etc. (EC COM, 2014b). These Apps are providing a various range of medical and health information, from informing the user about his health conditions, to assistance with disease auto-diagnose as well as patient's monitoring during his daily living activities or conditions. Health related data can be easily and frequently collected by users' devices every time they access the relevant App or, prior acceptance by the user, even in background (Lupton, 2013). If a trigger event is verified, an immediate response is provided to the user's device and a notification can be sent even to a nominated person (as a partner or caregiver, professional consultant or psychologist) (Shaw et al, 2017). In the stores there are Apps available to evaluate visual, auditory and mnemonic functions; Apps that predicts data inserted by the user to register information such as quality of sleep, ovulation, alimentary habits, states of mind, health status or onset and pain severity, blood glucose readings for diabetic patients, medicines assumption, adherence to treatment and results; Apps that take advantage of GPS information to allow researchers to comprehend the relation between environmental factors and health in specific locations compared to a predefined region or consent individuals to better monitor the quality of their environment to protect their own health (Lein, 2012).

One of mobile Apps strength points is sending of feedback to the user based on his own performances. For example, by using accelerometers and GPS systems to localize individuals and inform them, for instance, of the presence of a park nearby for physical activities or to make notice that they have not moved much lately and so then they might need to action for the best interest of their health (Lupton, 2012). Many Apps are including integrated reward systems or the possibility to share their own results with other users, including social media platforms assuming an openly competitive form that can further motivate the user.

As said, smartphones are equipped with integrated technologies that can contribute to monitor user's health conditions. In many situations, however, it cannot be relied only on surveys filled by users for different reasons. First, wherever it is required by the user to provide many information and insert as much data, problems of bureaucratic nature can occur (in terms of time and use) and of privacy, with consequent App abandonment. A more serious problem regards the possibility that patients could cheat and over rate their efforts or conceal their real health status. The increasing of social network use has led to a general competences' embellishment by persons that tend to report only positive facts and neglect negative ones, so there is a real danger that this may become the standard even in healthcare environment.

To overcome this last problem, the tendency is that of developing digital wearable devices that directly measures parameters from the human body while being connected on-line with alarm systems and with healthcare instructions (Giedrojc, 2017). In general, wearable devices are equipped with sensors that collect and send a data flow to the user in a continues and real time manner and, with the help of Machine Learning approach, are capable to transmit even the minimum change within the paths of biometric data of a patient (Sallay, 2013). This potential offers new modalities of monitoring, measuring and representing the human body: from the standard monitoring via static data to the tracking of healthcare metrics during daily living activities. In the last years a variety of wearable biometric sensors have been designed and developed, such as bracelets, watches, skin patches, electrodes bands, smart glasses and clothes with the common objective of allowing a discrete and, when appropriate, continuous passive monitoring. A key characteristic of wearable devices is their capacity to track and transfer all the biometric data to the smartphone through a dedicated App so it can be sent to healthcare operators, researchers, family members or uploaded on social media platforms.

Even though Apps can turn out to be a passing clamor due to the inexorable rhythm of digital innovation (for instance, AI, IoT, Big Data), it is probable that the new way of how individuals have access to their own health related information that is the new conception of mobile devices as "health mates" will remain as such (Giedrojc, 2017).

1.4 Innovative technologies for mobile health

As seen in the previous paragraph, with miniaturization of technology the number of devices developed expressly to monitor physiological parameters has increased significantly. In addition to these devices, designed and developed to have success in fields nonrelated to medicine it can be employed effectively in health. These technology can contribute to the monitoring of public health as well as the recovery of a single individual's health by functioning as a support tool in rehabilitation for patients who have to recover a lost functionality caused by an adverse event, such as incidents or diseases, or of a substitution in case of a disabling conditions, cognitive or physical.

In this thesis work, within the emerging technologies in healthcare field, we will deepen these technologies that are being commonly indicated with Extended Reality (Reality X), in particular Virtual Reality, Augmented reality and Mixed Reality, and the Geographical Information System (GIS).

1.4.1 Extended Reality (XR)

Extended reality X (XR) is a coined term to group all these technologies that foresee the combination of real elements (physical objects) and virtual elements (generated by a software). XR covers the entire spectrum that goes from "real completion" to "virtual completion": Virtual Reality, Augmented reality and Mixed Reality.

1.4.1.1 Virtual Reality (VR)

Virtual Reality (VR) is a simulated reality, that is a completely digital environment that substitutes the more realistically possible the physical reality. The modality with which a VR application is being delivered to an individual depends from the type of hardware device that is being utilized, based on which it is possible to distinguish between:

- Non immersive VR: a monitor function as a window on a digital 3D world in which the user can interact through appropriate joysticks;
- Immersive VR: the user is being totally isolated from the surrounding physical environment, perceiving to be really and completely in the digital environment.

VR is born and finds its field in the most of gaming application. The possibility to experiment totally analogous situations to those whom an induvial is experimenting on a daily basis, but in a safer and controlled environment, has caused health and rehabilitation sector (on both a mental/cognitive problematic level and on a motor level) to start being interested in this technology and begin to insert VR applications in rehabilitation protocols.

1.4.1.2 Augmented Reality (AR) and Mixed Reality (MR)

Augmented Reality (AR), unlike VR, does not "teleports" the user into a virtual environment, but rather predicts the enrichment of the surrounding physical reality by means of information created by a digital software in real time (Augmented Object, AO) capable of enrich the sensory perception, in particular user's sight sense. Based on the utilized technology to provide information to the user in the right moment and place, we can classify AR application in:

- Marked-based: based on the utilize of markers. At the moment in which the marker (tags, images, 3D models, etc.) fall within the field of view of an integrated camera in a personal device (tablet, smartphone or smart glasses), the AO (texts, images, audio files, 3D objects, etc.) associated in the programming phase, are being overlaid in real time on the physical reality.
- Marker-less: the AO appears to fluctuate on the display of a device endowed with a camera based on computer vision algorithms capable to associate the recognition of the environment (image recognition) through a Simultaneous Localization and Mapping method.
- Location-based: to each AO a couple of geographic coordinates is being associated, in the developing phase. When users find themselves in proximity of that place, they will perceive the AO presence through a personal device.

Mixed reality (MR) is the most recent XR technology and it can be seen as an advanced form of AR. In fact, the user can interact with AOs that are enriching the surrounding environment through predefined hand gestures, voice commands or gaze tracking. Digital contents do not usually appear on the device display but they seem completely ''submerged'' in the real environment enough to be able to interact between them and physical objects (https://docs.microsoft.com/it-it/windows/mixed-reality/mixed-reality).

As VR, AR and MR were born for applications in the gaming sector, by reaching the diffusion peak within the global population with the App "Pokémon GO", developed by Niantic in 2015. Moreover, since the introduction of AR/MR headset in the market, it has found different consensus in applications even in military field, in safety (for example, for aircrafts pilots), in remote supervision during personnel operation and in supporting daily activities (for instance, driving an automobile or a motorcycle).

In the last years, various applications are emerging in the medical field, from which Apps for the formation of medical personnel, Apps that allow surgeons to keep under control vital parameters with a simple blink via AR headset or to be assisted by specialized doctors in case of critical issues, in addition to Apps in the rehabilitation context and for treatments on both a physical-organic level (ex. Articular mobility) and on a cognitive-psychological level (ex. Mental disturbs) aimed to recover, improve or substitute the compromised functionality.

1.4.2 Geographical information system (GIS)

The idea of associating a certain type of data to its geographic location on the earth's surface is not to be considered recent. In fact, without considering informatic notions, already in 1854, year in which in a London neighborhood called Soho an epidemic had spread, a study executed by the British Medic John Snow that was localizing on the cartographies of the city of London regarding the various cases of contagion, by placing in relation the geographic distribution and the number of detected cases. From which the idea of georeferencing a determined characteristic was born, so that conclusions can be drawn on how to operate. Already in 1986 Peter A. Burrough coined one of the first definitions of geographic information system GIS: "*The GIS is composed by a series of software tools to acquire, archive, extract, elaborate and visualize spatial data in the real world*" (https://www.esriitalia.it).

With the recent development and miniaturization of technologies and the ease of exchange data online, GIS systems have taken a new role and have a great potential for the management of remote situations, in particular in emergency cases in which it is fundamental to promptly intervene. WHO defines GIS as a "technology that aim to the organization and management of digital cartographies and informatic database, that organizes and archives large quantities of information for multiple purposes; GIS adds the dimension of the geographic analysis to informatic technology, throughout an interface between data and cartography. This makes it is easy to present information to decision takers in a rapid, efficient and effective way" (https://www.who.int/lep/monitor/gis/en/).

To date, a GIS system is composed by the following elements: software instruments (GIS software, networks, archives); hardware equipment (computers, tablets, smartphones, printers, plotters, GPS devices); human resources (analysist, users). Application procedures and work methodologies of a GIS system are developed in the following phases:

1) Data acquisition

2) Data return/restitution
3) Data update
4) Sharing
5) Data elaboration
6) Data presentation
7) Creation on simulation models
8) Elaboration of representation models

A characteristic of GIS is to integrate data originated from multiple sources. Data might vary in terms of format, type or structure and can be generally summarized in two categories:

- Spatial data (geometric, topological): polygons, lines, dots, pixels, symbols and annotations
- Non spatial data (thematic, attributed): traditional data, which means referring to the characteristics of geographic objects such distribution of population, distribution of diseases and users of a service.

The process by which GIS associates a geographic univocal reference to an object, is by placing it univocally in a map, in an explicit manner through coordinates (x, y) or in an implicit way, through for example, the address, postal code, and so on, it is called *geocoding.* A peculiar and extremely versatile aspect of GIS is given by the possibility to overlay layers or informative levels, each one of these describing a category of information (for example: roads, hospital position and health centers, morbidity, mortality); this process consents the performance of different types of analysis and the ''construction'' of digital maps (Fortino and Candura, 2006).

GIS is an instrument that permits to represent and analyze events occurring on the territory. In the present technology inside the geographic software it is integrated with the common operations which can be carried out by the database, such as researches, statistical analysis, graphs, functionality like memorizing territorial data, their treatment and above all their representation in the form of cartograms or tables relative to territory portions more or less extended. These capabilities distinguish geographic systems from any other informatic system by allowing users to have an instrument with whom visualize and analyze information to explain events, plan strategies or design territorial infrastructures. For all the problems that have geographic components, GIS allows to create maps, integrate information, visualize scenarios even in 3D, solve complicate mobility problems and elaborate more efficient solutions.

Localization services are important because they allow an accurate territory planification and intervention to be executed on it, home after home, street after street, in an extremely detailed and complex manner. GIS systems are providing real time operative awareness for the field, which helps to improve efficiency and safety of workers. These services find application in many fields: in territory management, urban planification, implementation of Civil Protection plans, rescue and aid in case of calamities, to document the frequency and distribution of health/disease phenomena, with Police for a better awareness of the situation and in large events such as marathons or parades. The position monitoring can offer the opportunity to save human lives by monitoring the activity in order to verify and consent a better public security. Predefined levels of precision of the majority of "position collection" technologies to date, creates sets of data that re-enter in privacy and compliance regulations (ESRI, 2020).

1.5 New role of the citizen: patient-customer

Digital health carries out an increasing role in the way how persons are managing their own health and interacting with healthcare system, since online instruments allow persons to connect with others by sharing similar health interests, participate to interventions or find healthcare service (Shaw et al, 2017). This implicates that the potential of eHealth/mHealth resides in functioning as a mediator between the provider of health services and the beneficiary, while promising to be a more efficient medium to provide specific healthcare services and become useful to support the reorganization of healthcare system in a way of making it more efficient. However, due to the mediatic role, the effective impact of technologies on health does not only depend on health administrators will, but on the diffusion and the access to an ICT network within the different segments of healthcare systems (Chandrasekhar and Ghosh, 2001).

Many persons believe that diagnosis in medicine may derive exclusively from biological tests and, for many years, doctors have ignored most of the information provided by their patients during the clinical visit. However, it became clearer and clearer that the relations provided by patients are providing the key to comprehend many important diseases and risk factors. In fact, in most cases, patients are consulting doctors because they are experimenting symptoms and problems, and in this way, they could deeply influence the delivery of healthcare assistance (Kaplan and Stone, 2013). The big challenge for public healthcare sector is to make the most out of opportunities provided by technologies and avoid the tendency of all institutions, including those medical, to keep things as they are, by facing the fact that patients are changing, so even medicine has to change. A big effort and involvement is necessary by public healthcare sector in this evolving and revolutionary era to minimize the risks and enhance the benefits of a process that cannot be stopped as long as patients are free to share their experiences on the Web (Orizio et al, 2010).

Internet is becoming even more a fundamental medium to obtain information and health services. For instance, health social networks are becoming always more an important entity of influence in the medicine of tomorrow, for their nature of being generated "from the bottom to the top" from those who make medicine exists, who are the patients, instead of "from the top to the bottom" (Orizio et al, 2010). An increasingly number of person is frequently looking for information in an active way regarding his own health and disease conditions, at the same time, he would like to be actively involved in taking decisions on his own health (ex. Pharmacological or therapeutic cures), in such a way to eliminate the so called "informative asymmetry" that often characterizes the medic-patient relation. The European patients Forum claims that electronic health solutions have the potential to bring a better assistance to the patient's life and guarantee a better coordination through the exchange of information and data between health operators, but only if trust and acceptance conditions by users are satisfied (European Patients Forum, 2016). According to a study conducting by the Ministry of Health in collaboration with University La Sapienza (Italian Ministry of Health and University La Sapienza, 2010) an important number of individuals consults the internet when facing health problems: this tendency is higher among young people and for persons with a high educational qualification, meanwhile the study that have involved older people (Forester Research Inc, 2003; Marquiè et al, 2002) have showed their tendency to be less positive principally due to the more resistance toward changes and the weak experience with technology associated to this population of individuals, that have led them to describe their experience with technology as frustrating and challenging (Steinhubl et al, 2015).

eHealth and mHealth solutions have the potential to support the mutable role of patients from a passive role rather to a more participative one, by increasing citizens awareness concerning health issues and at the same time patient's responsibility on his own health. The passage to an assistance focused on the patient may require the redesigning of existing infrastructures and health organization, currently organized around health operators, healthcare systems will have to open themselves to the possibility of receiving data from patients and guarantee an omnipresent access to cures, for example, throughout online health platforms accessible to both patients and medics. This implicates a changing in professional's role that could more often have to remotely monitor patients (EC COM, 2014b). The direct access to authoritative, personalized and immediately utilizable health information is one of the key elements of the phenome defined as *patient empowerment,* which is "*the process for which the patient/individual is being provided with knowledge, capacity and awareness that allow him (in general or in part) to auto-determine himself in relation to his own health, within a process in which healthcare professional can become, as the patients prefers, a facilitator that operates inside a partnership relation, not an authority anymore*" (Buccoliero, 2010). Patients empowerment is considered as a powerful tool for healthcare assistance changing and, for some experts, the redefinition of traditional patients as "no Patient" is probably the main changing factor in healthcare assistance (Pena and Gil, 2007).

1.5.1 Patient empowerment

Patient empowerment's concept is based on a series of hypothesis, including the idea that patients wants to have the control over their own health assistance and that such control will produce benefits since informed and empowered patients will presumably take more care curing their own health. The empowerment can occur on different levels and patients have different ideas on the meaning of taking the responsibility and taking part in the decision making: some patients wants simply to receive information about their conditions, while others want to have full control in all medical decisions (Pena and Gil, 2007).

The European experience on patient's empowerment is oriented toward:

- Provide citizens to access information and advices by reliable and authoritative sources;
- Facilitate the accessing process and management of the own healthcare data;
- Healthcare literacy to take part in decisional processes;
- Increasing the security regarding patient's data.

The fundamental prerequisite is that both patients and health operators must have a certain level of digital competences to be able to search, understand, act and so, benefit from eHealth/mHealth solutions. Without a basic understanding and the capacity to draw useful relevant conclusions from digital health information, eHealth and mHealth can even generate negative effects (for ex. Creating misunderstandings and stress or exacerbating the exclusion). Patients education appears as a strategic key action that promotes patients' competency which is fundamental to guarantee the equality in accessing healthcare assistance (Giedrojc, 2017).

Health literacy is the grade on which individuals can obtain, elaborate and comprehend information and healthcare services basically needed to take the appropriate health decisions (U.S. Department of Health and Human Services, 2010). Examples of ICT for the management of people's health are including patients' portals, telehealth systems and online support system, for which eHealth literacy requires a mix of health, informatic, scientific and mediatic literacy (Chan and Kaufman, 2011). Considering the rapid development of ICTs, competencies and knowledges that make up eHealth literacy are continuously in evolution and individuals must constantly keep developing their own capacities and knowledges to maintain their own competency in matter of digital health (Watkins et al, 2014). Devices of common use and the more user-friendly interfaces can noticeably help to facilitate the implementation and execution of patients' empowerment.

However, if not used correctly it can function as an amplifier of existing problems or create new ones, since health assistance is a service, it is important to understand user's perception and the perceived quality of the service in order to maximize the efficacy (Kisekka and Giboney, 2018). Most digital health applications have been designed to support organizations and professionals rather than to support the patient/user, but experience has demonstrated that a key factor for eHealth success resides in the involvement of all interested parties in the design phase. Users will be more motivated to utilize a system that produces visible benefits or in which they see a potential efficiency for the resolution of real necessities (Pena and Gil, 2007). To evaluate patients propension in adopting electronic services the so-called model «ACM» has been proposed, which considers this propension as function of three principal factors: access, competency and motivation.

The major concern in matter of eHealth/mHealth regards the possibility of errors in diagnosis that leads to therapeutic choices that put into play the security and trust of the patient (WHO, 2011). The auto diagnosis and auto treatment based on online information can be dangerous and harmful, especially when the quality of information is doubtful, and patients are taking decisions without an advice by qualified health professionals. Highly expert patients in health matter can be particularly problematic since their interpretation of online information could differ from that of professionals (Giedrojc, 2017).

Another strategic action line is by working on accessibility, by keeping present necessities of elderly people and of disables in line with the politics of e-inclusion of EU (Pena and Gil,2007). Often, specifically in the past, intrinsic inequalities that are created have been ignored in using medical information and monitoring technologies. These inequalities are including problems of differential access to these technologies: aspects as disability, aging, chronic diseases, lack of knowing informatic technologies and economic disadvantage can limit the access or the will to participate (Nettleton e Burrows, 2003). However, regarding patient's responsibility it is assumed that while developing the technology, it is being considered that all individuals should have the same access and knowledge of these technologies. (Lupton, 2012).

EPHA has proposed the following recommendations, addressed to politics responsible and regulation authorities that are working on a national and European level, solution's developer for digital health, as other interested parties involved in the development of guidelines, standards and legislation in this sector:

1) A significant involvement of final users means establishing a co-creation process effective for digital health tools, in order to guarantee that the development and implementation of digital health politics are guided by real health needs and persons practices (patients and their caregivers, consumers, health operators) rather than from the market requests;
2) Guaranteeing the inclusive and ethic integration of digital health in national healthcare systems to improve the access toward healthcare assistance, in addition to that on a transborder level;
3) Improving digital health literacy and expand the digital competences between professionals, patients and population in general;
4) Instructing national and European archives about solutions for digital health (for example Apps) as a guide for patients and health operators who are looking for secure and tested solutions;
5) Guaranteeing that considerations regarding patients' security and assistance quality are linked in all initiatives of digital health;
6) Promoting research on the usage and usage results of digital health to guarantee continues improvements in this emerging field.

The new conception of the citizen seen as a consumer rather than a patient tend to move responsibilities of a large part of health assistance at patient's charge, by placing new expectancies on the patient to manage his own health in ways that are traditionally considered as prerogative of health operators. Consequently, health data keepers are not the government anymore neither the provider of health services, yet individuals themselves, but not all patients would like to become empowered consumers. To date, it seems that the concept of patient's empowerment is in the best interest of institution and health administration rather than of patients themselves (Pena and Gil, 2007).

1.5.2 Protection and data processing

Another aspect of the changing in the patient's role that deserves attention is that related to legal rights. In health environment they have introduced the right declaration of patients, the legal treatment for informed consensus, patients' representatives in hospitals, the rise of litigation for negligence and other legal aspects (Pena and Gil, 2007).

In literature there is a lack of empiric research that evaluates technology from the security of information point of view and, with the increasing of data violations and concerns related to privacy, the success of eHealth/mHealth depends as well from the level of privacy protection of patient's health data that is able to be guaranteed (Rainie et al, 2016). The rapid development of the mHealth sector rises concerns regarding the appropriate treatment of data collected by app or individuals' solutions, app developers, health professionals, advertisement companies, public authorities etc. Solutions and mHealth devices can gather large quantities of information (ex. data memorized by the user on the device and data from different sensors, including position) and processing it, even in third parties' countries outside the European economic space (EC COM, 2014b).

Previous studies have suggested that privacy concerns are influencing not only patients' perceptions on the quality of assistance to themselves, but even the tendency to use technology (Meingast et al, 2014). Different research groups have committed to analyze population's position in relation to health technologies regarding the use and protection of personal data. According to statistics only 23% of consumers has utilized a mHealth solution while 67% has affirmed that he would like to do ''nothing'' on his own cellular phone in support to his own health due to the concern for the possibility of an unwanted sharing with third parties (for example employers or insurers) of personal data when using mobile devices for health related activities. WHO has reviled that the barrier to Big Data adoption are including privacy and security (71%), lack of integration (63%) and information sharing (50%) (Wyber et al, 2015). One of the worse concerns resulted being the possibility of devices to collect and process large information in third countries even outside the regulation of the European market (EC COM, 2014b).

In order that mHealth promises can be fully realized, consumers, supplier and healthcare system must be able to trust the reliability, of the privacy and security of their own data, nevertheless of devices that are collecting and sharing them. To implement a successful model of healthcare system, the following determinant of quality and patient's assistance must be guaranteed (Kisekka and Giboney, 2018):

- *Trust in security of information:* user's perception that data provided by the organization will be accurate and available;
- *Concerns for privacy*: perception of the lack of confidentiality of personal information provided by the organization;
- *Trust in health information*: reliability of provided health information

The collection of health data must be carried out within the respect of legal requisites, even for protection of personal data and it can give rise to ethic issues, in particular concerning the respect of the informed and explicit principal consent, not buried in the universally utilized terms that are often not read and then accepted, with users that are required to explicitly consent every time their data before being sold or transmitted to others. (EC COM, 2014b). Services providers must be transparent with patients by providing clear information on how security and privacy of patients' data is being preserved, in which circumstances data is being shared and with whom (Palermo et al, 2014). A high level of transparency, combined with an adequate communication, can reduce concerns for patients' privacy and the reluctance to share information, by consequently increasing technology adoption and patient's assistance quality.

Due to the sensitive nature of health data, mHealth solutions should contain specific and adequate security measures such as data cryptography and authentication mechanisms of data to mitigate security risks (EC COM, 2014b). The loss or theft of devices that memorizes sensible information might be a serious security issue. With an average of 4,5 million lost or robbed smartphones per year, it is not difficult to imagine the security disaster that would derive if each of these phones memorizes sensitive information regarding personal health or, a more concerning issue, that it could potentially function as a portal toward an electronic system of clinical folders (Steinhubl et al, 2015). Organizations must increase the trust by actuating security and privacy controls, by undertaking activities that guarantees data accuracy, availability and by developing controls to protect confidentiality of users' data (Maconachy et al, 2001). From a political point of view it is important to keep in mind the correct actuation of, existing and in evolution, European and national legislation, as well as non-binding orientation documents within areas that have an impact on eHealth and mHealth, including the new General

Data Protection Regulation (GDPR), ePrivacy directive, the new guidelines for mHealth evaluation and potential future guidelines on Big Data (Giedrojc, 2017).

1.5.3 General Data Protection Regulation (GDPR)

Treatment of patients' health should rigorously respect EUs norms on data protection (EC COM, 2914b). Personal data protection is a fundamental right in Europe, stated by article 8 of fundamental European union rights, as well as article 16, paragraph 1, of the treaty on functioning of European Union (TFUE). Compliance with rules of personal data protection, the interested party information of data security and legal treatment of personal data, including medical and health data, is therefore fundamental to create trust within eHealth/mHealth solutions (EC COM, 2014b).

GDPR is a European Union (EU) regulation in matter of treating privacy and personal data, entered in force the 24 May 2016 and operational since 25 May 2018, with whom the European Commission proposed the objective to reinforce personal data protection of EU citizens, for both inside and outside EU borders, giving back to citizens control over their own personal data, by simplifying the legal context regarding international affairs, unifying and making privacy policy within EU homogenous (EUR-Lex, 2016). In the text, health data export theme is been addressed by obliging owners of data treatment (even with legal venue outside of EU) who are dealing with EU residents' data to observe and fulfill the obligations foreseen. Moreover, it is favorably considered the introduction of *privacy by design* (privacy must also be protected during software elaboration's phase or, in general, of the system), *privacy by default* (privacy measures must be implemented for predefined settings).

Inside the regulation there are also specified cases for which the same regulation may not be applied:

a) Treatments carried out for activities that does not re-take part within the scope of the Union's rights;
b) Treatments carried out by member states within the exercise of activities that take part within the scope of title V application, header 2, of the EU treaty (foreign policy and security);
c) Treatments carried out by competent authorities for prevention purposes, investigation, assessment, prosecution of crimes or execution of criminal

sanctions, including the safeguard and prevention against threatens to public security (see directive 2016/680);

d) Treatments carried out by a physical person for the exercise of an activity of an exclusively personal or domestic character (see personal use exemption).

Security of collected data must be guaranteed by the treatment owner and by the treatment responsible, they are required to put in act technical and organizational measures suitable to guarantee a level of security adequate to the risk. To that end the owner and the treatment responsible are guaranteeing that whoever accesses to collected data must do it in respect of the powers conferred by them and after being purposely trained, unless it is asked by the Union's right or by Member States (Article 32). To guarantee the interested party, EU Regulation 2016/679 regulates also the case of the transfer of personal data toward a third country or an international organization (Article 44 and following) and expects that the interested person gets promptly informed if there is a violation that puts at risk his rights and his freedom (Article 33).

1.5.4 Are mHealth technologies considered as medical devices?

The number of mHealth solutions is rising exponentially, but only few have been systematically evaluated. In fact, unlike pharmaceutical products or medical devices, that must undergo in-depth tests regarding security, accuracy and coherency before receiving a certification, the majority of mHealth technology are complexly nonregulated (Kaplan and Stone, 2013). It is in progress a discussion on how much technology related to health assistance require a conformity evaluation and on how to better communicate quality standards to consumers (Becker et al, 2014) and many authors have discussed the need of a government body, for example, The World Health Organization, to certificate open standards and consent countries the access to standards that satisfies key criteria (PLOS medicine Editors, 2013) (Becker et al, 2014).

In the EU there are no constraining rules regarding the delimitation between "Lifestyle and well-being" Apps or wearable technology that gathers physiological data and a medical device, diagnostic or therapeutic. It is not clear if there are associated risks with health apps and who should answer it from a legal point of view. Health operators themselves are not sure of the value of those technologies and are not able to evaluate the available solutions for which they are reluctant to integrate those systems in their decisional process. Moreover, the lack of reimbursements of the new technologies constitutes a serious obstacle to an appropriate use. Since January 2012, in order to help software developers and producers to identify whether their products are included or not in the directive on medical devices, European Commission services (European Commission, 2012b) have facilitated the cooperation and the exchange of scientific information between EU Member states through a voluntary network of national experts regarding the evaluation of health technologies and they have published the guide line MEDDEV dedicated to medical App developers in which is being stated that the classification of a smart device or an App as medical device depends on its intended use described by the producer. Although is not legally constraining, it could be very useful to interpret the appropriate European regulation.

It is always necessary that a producer obtains a CE tag for a product that is part of the directive on medical devices before he can present it on the market. This CE trademark can be assigned only after the product is being successfully subjected to appropriate evaluation procedures of compliance. Details of regulatory process, however, varies according to the risk category of which the product has been assigned (Becker et al, 2014). Apps can therefore be classified as medical products, but since they present limited risks for users they should not necessarily be submitted to regulatory procedure (EC COM, 2014b). those who are developing new mHealth technologies don't have the need of any medical input for their developing programs and then they can provide non optimal "solutions" (even harmful) that patients or citizens can assume to have a proven benefit. Independently from their purpose, in fact, utilized App in a medical context must be reliable, secure and the user interface must consent an efficient use. When the Apps are being utilized from health professionals while working on patients, regulatory aspects become relevant since these apps may lead to legal consequences for both the provider of health assistance and his employee, for example, health operator that utilizes the app (Becker et al, 2014). More concerns about security problems arises when citizens can utilize results of a solution or mHealth app to take decisions that can potentially put their health in danger, like for instance a mHealth solution that wrongly claims that the person is healthy (EC COM, 2014b).

Certification schemes may also be reliable indicators for health operators and citizens inasmuch they could verify if the app of the mHealth solution provides believable contents, contains protections for user's data and works as expected (EC COM, 2014b). Probably the approval by the national healthcare system can provide doubtful individuals with an additional level of reassurance regarding the fact they are using a high-quality product (Hindle, 2019).

On the other hand, in addition to the increase in costs, this poses a significant problem for the development of medical devices: according to regulations, any changes within the medical software leads automatically to a new certification process [50,51]. This is further compounded by the installation of additional versions or new apps on smart devices, sometimes not even voluntarily but rather caused by automatic updates running in background. There is therefore the risk that a medical application running on a mobile phone must be recertified several times a week. (Becker et al, 2014).

An international picture for the evaluation of mHealth programs, including significative and measurable indicators, would be an important step toward data collection. This would include a results database based on research studies of monitoring and selected evaluation within mHealth in all the world, with emphasis on data collection on a national level. Without such data, mHealth wont rapidly become part of the government politics neither protected by legal guidelines for privacy. If these barriers are overcome, very probably investments in mHealth would be strengthened, by putting associated expenses within the competing costs that every healthcare system must face (WHO, 2011).

2 CHAPTER 2 – State of art of targeted health issues

eHealth and mHealth technologies are getting involved more often in citizen’s daily living activities, these technologies can provide solutions for citizens affected by disabling, temporary or chronical conditions. health issues related to aging of population. The rising problems represented by chronic conditions and multimorbidity are at the base of a constant increase of healthcare services demand, which have to develop different approaches in order to provide more efficient assistance and confront with the complexity of various services that patients are required to know (EUR-Lex, 2018). In addition to patient empowerment, that is necessary so users can be put in a condition that allows them to utilize technology, during the technology development phase it is necessary to consider as well disabling conditions that can make it difficult to utilize hardware for the target population for which technology has been implemented. Large revisions have examined the impact of a series of technological innovations to improve elderly people or disabled individual’s assistance, often called “Assistive Technologies”, that includes elements that improve mobility, monitor security and facilitate communication in case of emergency. International Organization for Standardization defines Assistive Technology (AT) as “any product (including devices, equipment, instruments and software), especially produced or generally available, used by or for persons with inability or disability, for participation, to protect, support, train, measure or substitute of body functions/structures and activities, or to prevent impairments, activity limitations or participation restrictions” (Besio and Salminen, 2004).

In this thesis work two types of pathologies are being specifically faced, pathologies that influence citizens’ quality of life: disabling conditions due to cognitive and sensory decline related to aging; disturbs on a verbal language level in persons affected by motor disabilities. A general framework is done with the description of AT involved until today. Lastly, the recent global diffusion and spread of Sars-CoV-2 is being addressed with the presentation of systems put in practice by various countries.

2.1 Age-related impairment

Global population is rising exponentially: in 1800 global population was around 1 billion, in 1930 of around 2 billion, in 1974 became around 4 billion, 1982 around 5 billion, 1999 of around 6 billion, 2011 of 7 billion and its rise is predicted to rise up to 9 billion within

2045 (Suttie et al, 2011). Historically, high birth rates were associated with high death rates. However, today due to the improvement of hygienic conditions, healthcare assistance and food supply, there is an increase in life expectancy to which corresponds a shift toward a higher average of the global population's life. With focus on Europe, population is progressively aging, in particular in the second half of the twentieth century, that much to until counting 19 out of 20 countries from the most elder in the world in terms of populations age and, according to estimations, it is predicted that it will continue to age at much higher levels in the next 25 years: according to the populations' reference office, almost 25% of EU people in 2030 will have more than 65 years, against almost the 17% in 2007 and there is a high probability that up to 10% of European population may have more than 80 years within 2050 (Suttie et al, 2011).

As aging progresses, every person suffers from modifications in the structure and functionality of his own organs and is forced to face a variety of challenges: decline of cognitive capacity, sensory (mainly sight and hearing) and motor; multimorbidity and chronic diseases. Cognitive and sensory disturbs are very diffused among elderly people (older than 65 years) and, because of population aging, in the next decades the incidence of such disturbs is destined to increase (Preschl et al, 2013). According to predictions within the next two decades, either age related hearing disturbs (HI) or visual related (VI) will be placed within the first 10 disease charges in middle-high revenue countries while cognitive deterioration, from which Alzheimer diseas (AD) and other forms of dementia, will find itself within the first four (Mathers and Loncar, 2006).

It is well documented that AD and other forms of dementia are associated to progressive performance drop during Activity of Daily Living (ADL) and Instrumental Activity of Daily Living (IADL), of cognitive capacity and visuospatial, mobility, general quality of life, and to a higher depression index and load on the individual responsible to take care of the patient (*caregiver*). It is important to underline that recent proves suggests the evidence of an association between sensory and cognitive impairments and, in particular, an increased risk of cognitive decline and dementia is linked to age-related HIs (Lin et al, 2013) or VIs (Chen et al, 2017). For example, in these studies it has been demonstrated that age related HI is linked to an increased risk of cognitive decline and dementia, including imaging studies which proved that individuals with HI have higher cerebral atrophy rates in their right temporal lobe and reduction of their total cerebral volume, compared to individuals without HI. In the same way, an increase of probabilities has been detected of a poor cognitive punctuality among individuals with sight problems (Guthrie et al, 2018). People affected by one or more than one of the previously mentioned diseases are considered as vulnerable groups who are at increased risk for unmet social, environmental, psychological, and medical needs and are associated with a worse quality of life. One of the best ways to maintain the functionality of people in an old age state for the longest possible period is to mitigate the degeneration by stimulating cognitive and physical functions (Lin et al, 2018). Actions are therefore needed to stimulate the functionality of the human body and to facilitate active participation in social life, physical and mental well-being throughout life, or to promote active aging: “Active Ageing is the process of optimizing health, participation and safety opportunities in order to improve the quality of life when people get older" (WHO, 2002). Elderly people should train their cognitive and motor skills daily. It is advisable for them to carry out the following activities: physical exercises (e.g., walking), take care of their own house, reading, playing musical instruments, taking part in social events and group activities (e.g., playing cards), learning new skills (López-Martínez et al, 2011), etc. Several studies suggest that enough physical activity can effectively prevent numerous chronic diseases and mental health problems (Scully et al, 1998; Warburton et al, 2006; WHO, 2010). About 6-10% of worldwide deaths caused by non-transmissible diseases, such as cancer, cardiovascular disease and diabetes, can be attributed to physical inactivity (Lee et al, 2012) therefore, interventions are needed that increase the level of physical activity and can reach a large population in a convenient way (WHO, 2015). While planning interventions it is also necessary to take into account the strong preference of the elderly to age on the spot (that is to remain in their homes and communities) compared to other forms of care, such as nursing homes or other long-term care facilities (Mihailidis et al, 2004). In addition, several studies have found that older adults benefit from aging in environments to which they are accustomed since familiarity of the environment can provide cues of memory and a stimulus to be more active (Bryant, 2001; Cutchin, 2003; Intille, 2004). On the other hand, moving to home care means increasing the burden on family members and informal health workers, resulting in debilitating levels of stress and social isolation for the caregiver. It has been found that even small reductions in burden alleviate the prevalence of depressive symptoms in caregivers of individuals and this can lead to more successful informal care, with reduced medical costs (Mihailidis et al., 2008). A growing line of activity refers to remote monitoring to enable older people to continue living in their homes, through the use of sensors installed in different areas of the home or wearable sensors able to monitor any physical signs that must be kept under control by sending this information to a central medical service or to a center of virtual assistance (Pena and Gil, 2007).

2.1.1 Sensory impairments

The most common sensory deficits associated with older people are related to hearing and vision. Although impairment of these senses is not an imminent danger to the person's life, the impact of vision or hearing loss on an individual's overall health is critical in terms of the assistance required, reduced quality of life and increased risk of death (Schneider et al, 2012).

Approximately one over-65-person out of three is affected by visual-reducing eye disease. In 2019, WHO (WHO, 2019) has reported that at least 2.2 billion people worldwide have a visual impairment or blindness. People with Visual impairment (VI) have been linked to multiple adverse outcomes including an increased mortality risk, independence difficulties in ADL and IADL activities, mobility difficulties and reduced social participation (Guthrie et al, 2018).

Hearing impairments (HI) are one of the most frequent sensory deficits among human population (Mathers et al, 2003). In 2012, WHO (WHO, 2012) estimated that there are 360 million people around the world (5.3% of the world's population) with HI of which about a third are over 65 years old. However, the statistics are not well defined, in part due to the employment of different classification systems, such as differences in the definition of HI, different measurements of HI and difficulties in measuring the consequent limitations of activities and restrictions on social participation. Age-related hearing loss is primarily related to a functional loss of sensory and neural elements with consequences in both cognitive and psychosocial spheres (Roth et al, 2011). Auditory capacity decreases with age: physiologically starting from the third decade it mainly affects high frequencies (ISO, 2000) and, by the fifth decade, it begins to affect the entire spectrum of speech frequencies (Roth et al, 2011). As with VI, HI is also associated with poor self-rated health, difficulty in performing daily life activities (ADL; e.g., eating, bathing, dressing up) and IADL (e.g., using the telephone, managing finances), difficulty with memory, fragility and falls (Guthrie et al, 2018).

2.1.2 Age-related cognitive decline and Dementia

As age progresses, in each person a change in his/her brain structure and functions occurs which can provoke a cognitive decline (Canadian Task Force on Preventive Health Care, 2016). The ageing of the world's population will result in an increase in the number of people diagnosed with dementia, from the current estimation of 46 million individuals to over 130 million by 2050 (Hayhurst, 2018). There are over 100 forms of dementia and the most well-known is Alzheimer disease (AD) (Aruanno et al, 2017). The main cause of dementia is aging, however other conditions including family history, education level, brain injury, exposure to pesticides or toxins, physical inactivity, and chronic conditions such as Parkinson's disease, heart disease, stroke, and diabetes may cause cognitive impairment. People with cognitive impairment are reported as being three times more hospitalized compared to individuals who are hospitalized for other conditions (Centers for Disease Control and Prevention, 2011). In many developed countries healthcare costs have overtaken those related to cardiovascular disease and cancer (Valenzuela and Sachdev, 2009), with an estimated cost around 160 billion dollars per year (Koumakis et al, 2019).

Cognitive age-related decay occurs in a continuum, starting with aging-related cognitive decline followed by transition to mild cognitive impairment status, and ultimately to dementia. Mild cognitive impairment (MCI) does not substantially affect daily function, however the subjects diagnosed with MCI are associated with a decrease of quality of life and self-esteem, as well as greater social isolation and over time MCI patients are considered at higher risk for dementia (Zhao et al, 2018), so much that about 45% of people with MCI convert to dementia within 5 years (La Monica et al, 2017). The most common symptoms that indicate the onset of cognitive decline are:

- Memory Loss, especially short-term;
- Frequently asking the same questions or repeating the same story repeatedly;
- Communication difficulties (for example, difficulties to find words);
- Getting lost in familiar places;
- Losing track of time, including daytime, month, year, etc.;
- Having difficulty making decisions and managing personal finances;
- Difficulty in performing ADL;
- Changes in mood and behavior.

As the disease progresses, the limits become clearer and more restrictive until the individual becomes totally inactive and dependent on others. Dementia is devastating not only for the person suffering from it, but also for operators who must take care of the person with impairment (WHO, 2012). Caregivers can be formal, referring mainly to medical and nursing staff, or informal, in most cases family members or life partners. In most cases, caregivers tend to be informal and mostly family members who are not trained for the demanding task that is assigned to them. It is important to note that these informal caregivers often suffer a psychological burden themselves, with more than 40% of them reporting emotional stress and 74% reporting concern for maintaining their health since they became caregivers (Koumakis et al, 2019). As there are currently no treatments available to treat or alter the progressive course of cognitive decline (WHO, 2012), efforts are increasingly focused on targeting potentially modifiable risk factors (Richard et al, 2009; Vellas et al, 2014; Ngandu et al, 2015), with particular emphasis on intervention in the early stages of the disease (Naismith et al, 2009). Recent meta-analytical data shows that about one third of the weight of Alzheimer's disease can be attributed to seven key modifiable risk factors, including stress, depression, diabetes, middle-aged hypertension, middle-aged obesity, smoking habit, poor physical activity and low level of education (Norton et al, 2014). Increased psychosocial stress can lead to burnout or depression, which negatively affects a person's cognitive functioning (Aggarwal et al, 2014): attention, concentration, flexibility and memory deteriorate with a greater amount of perceived stress and the speed with which this decline occurs is correlated with the tendency to experience stress (Wilson et al, 2006; Wolf, 2009). Arterial hypertension and obesity are negatively related to cognitive functioning in general and more specifically to executive functions, motor vision and memory (Gunstad et al, 2010). Physical activity is also associated with cognitive performance: older people with better cardiovascular function, who are more physically active, have less chances of suffering from cognitive decline (Abbott et al, 2004; Colcombe and Kramer, 2003). Managing these modifiable lifestyle factors could be a useful protective factor against neurodegenerative syndromes such as dementia. Proper information and proper stimuli to change one's health behavior can be an effective protective factor when it comes to dementia (Almeida et al, 2012). So, elderly people should train their cognitive and motor skills daily. It is advisable for them to carry out the following activities: physical exercises (e.g., walking), take care of their own house, reading, playing musical instruments, taking part in social events and group activities (e.g., playing cards), learning new skills (López-Martínez et al, 2011). In fact, the risk of dementia increases with a lower participation in leisure activities carried out by the person (Verghese et al, 2013). Previous studies highlighted that consistent physical and social activities help maintaining neuronal plasticity and help increasing brain activity of elderly people (Verdelho et al, 2012; Hagovska and Nagyova, 2016; Hauer et al, 2017; Shimada et al, 2017; Lin et al, 2018; Kou et al, 2019).

Although prevention is the ultimate goal, support programs for people suffering from cognitive decline or dementia and their caregivers (often fragile people themselves) are also essential to reduce the risk of further cognitive decline, medical comorbidity, mental health problems and functional decline, as well as to promote a better quality of life, healthy brain aging and general well-being. (Lamonica et al, 2017). Early diagnosis of the disease is of great importance in order to have greater possibilities to start the treatment as soon as possible and to carry out other forms of disease management interventions (Dodge et al, 2012) resulting in the postponement of its onset and slowing its evolution (Kikkert et al, 2016). Too often, however, the initial phase of decline is overlooked, as relatives and friends (and sometimes even professionals) associate the effects only to "old age", that is, only as a normal part of the aging process (WHO, 2012). Through a wide range of physical, psychosocial and cognitive outcomes in gerontology and geriatric medicine, it is of paramount importance to be able to detect significant changes over time, in particular for the practice of proactive health care and for the timely implementation of prevention strategies (Kaye et al, 2011). In this direction, signs of mild cognitive deterioration should not be ignored, as it is an early indicator of cognitive deterioration that can further advance towards Alzheimer's disease (AD) (Koumakis et al, 2019). Traditional methods for detecting clinical changes expect for relatively short period visits by persons at intervals that can vary from every 6 months to every 2 or 3 years. Additional methods include mail questionnaires or telephone interviews that rely primarily on forced-choice questions to elicit self-reporting of changes in physical and cognitive function. In general, the questionnaires and the episodic examinations are inadequate because they depend on the memory of events or on an instantaneous observation of the function and because they are based on the assumption that the observations recorded during the examination represent the typical functional state for relatively long periods prior to the assessment. Recorded observations are also often limited to indirect inference as to how one state or event may be related to another because there is a limited accuracy in the relative time of events. Therefore, the qualities of many activities, such as sleep, exercise, and socialization, which can affect health outcomes, cannot be readily marked with time, and therefore associated with effects on specific outcomes of interest.

People cannot remember with high fidelity significant changes that are rare and short-lived, that occur irregularly or that evolve slowly over time; on the other hand, events or syndromes that progress slowly over time often have a poor demarcation on the onset and transition to new states, making it difficult to recognize the transition to a new condition (Kaye et al, 2011). In addition, the self-reported performance of participants is unreliable because, as several studies have shown, older people tend to overestimate their level of competence in relation to their actual performance (Diehl et al, 1995). All these limitations make it very difficult for a geriatrician and other physicians to provide precise answers regarding transitions or events that may occur in the cognitive or physical functionality of older people. Therefore, traditional methods make it difficult to identify changes or events with detailed time accuracy by ensuring detection of the onset of cognitive or functional decline that precedes many important geriatric events or syndromes (Kaye et al, 2011).

An alternative approach is to introduce assessment into a person's daily activity in their home environment: this changes the type of assessment from short, episodic or intermittent assessments, often temporalized by the availability of the evaluator to assessments, at least theoretically, in continuous and real time with minimal intrusiveness in daily activities of the individual (Kaye et al, 2011). Significant research and development efforts have recently been made for the design of assistive technologies for the elderly in general, and for the management of patients with dementia in particular, with the aim of stimulating and/or monitoring the patient during ADL (Koumakis et al, 2019). These techniques range from the identification of a person's general activity by detecting electrical activity at home (Gupta et al, 2007; Berenguer et al, 2008; Noury et al, 2009), to the detailed identification of particular activities using sensors worn on the body (Logan et al, 2007; Min et al, 2008; Park and Kautz, 2008; Atallah et al, 2009) or health monitoring by means of sensors installed at various points in the home (Virone et al, 2002; Kaushik et al, 2007; Hayes et al, 2008; Hagler et al, 2010).

2.1.3 Related works

The increase of the number of people with cognitive impairment demands to identify a methodology able to detect and limit the decay of cognitive function in an economic and easy way (Konig et al, 2015). Currently, to mitigate the effects of cognitive decline, most common interventions are based on medications' administration; however, it has been also reported the benefit of non-pharmaceutical intervention in elderly (Zhao et al, 2018).

One of the best ways to maintain the functionality of people in an old age state for the longest period possible is to mitigate the degeneration by stimulating cognitive and physical functions (Lin et al, 2018), in fact it has been shown that prolonged engagement in cognitive stimulation activities has an impact, even in the long term, on the neural structure in elderly (Ball et al, 2002). Cognitive training exercises have been shown to slow down cognitive decay ratio and potentially even reversing it (e.g., Ball et al, 2012), even if traditional programs of psycho-stimulation have several aspects that make their application difficult, such as high load in human and financial terms (López-Martínez et al, 2011). In general, researchers have not implemented the strategy of directly observing the performance of older people when performing tasks in the real world, but rather participants are presented with a problem and asked to identify the problem or provide a solution for it. This is a potential research limitation for several reasons. First, paper-and-pencil tests or interviews introduce an artificiality and unfamiliarity that can negatively affect the performance of the elderly. Secondly, the greater the need to read, write and speak the greater the introduction of bias in performance, caused by literacy level of the user. (Diehl et al, 2005).

The use of Information and Communication Technologies (ICTs) in this area allows, in principle, to overcome these disadvantages since it has made possible the development of computer-based low-cost psychostimulatory programs with the following potential (Lopez-Martinez et al, 2011):

- Development of flexible programs, easily adaptable to user impairments;
- Increase in the number of therapy hours, since the therapist can apply psychostimulatory programs to different users at the same time;
- Increased effectiveness of treatment thanks to shorter sessions (to prevent the patient from getting bored) performed more often;
- Fast and appropriate feedback;
- Recording the results so that they can be seen and analyzed not only by the therapist but also by the patient, immediately after the session;
- Task difficulty can be changed depending on each individual user's performance.

Recent studies have assessed the effectiveness of Serious Games designed for people with cognitive impairment from which it emerged that cognitive stimulation by means of Serious Games can decrease the rate of intellectual decay and potentially reverse cognitive age-associated decline (Rodríguez-Fórtiz et al, 2017). The results showed an improvement in cognitive abilities, an improvement in reaction time, a greater sense of well-being and greater self-esteem in the elderly when they "play" at the Serious Games (Chi et al, 2017). Serious Games are defined as computers or video games developed with a main purpose different from that of ‘’pure fun’’, but rather a "serious" purpose such as to maintain and train the executive functions of users: memory, attention, ability to generate execution plans, follow the rules and make decisions based on the situation in order to achieve a predetermined goal (e.g., the management of own finances) (Lopez-Martinez et al, 2011) and at the same time to collect data that will allow the therapist to assess the cognitive state of the user, such as the time taken to perform a given action/make a decision, the number of errors, what are the tasks with minor performances, etc. Another technology that is recently spreading for the maintenance and stimulation of the cognitive abilities of people with cognitive disorders are the training systems in Virtual Reality (e.g., Manera et al. 2016; Serino et al, 2017; Repetto et al, 2017). Virtual Reality (VR) offers the opportunity to experience situations completely like those of everyday life, in a safe, controlled and low-cost environment generated by a Software with a high degree of realism and interactivity, to provide the patient with an adequate sense of presence.

The artificial nature of laboratories (or in a VR environment) enhances the internal validity but reducing the ecological validity aspect. Traditional measures, being out of the context of real life, could limit elderly performance and improvement by avoiding the benefit of the experience and the confidence gain expected by a familiar context (Diehl et al, 2005). Various non-technological solutions aimed to support elderly people during real ADL have been proposed. For example, the use of a diary (I. G. Hanley and K. Lusty, 1984), or the modification of the physical environment by removing cabinet doors or employing clear plastic on drawer folders (Beard et al, 2009). The advancement of technology results in the possibility of supporting the people with cognitive impairment in their own house with the aim of improving the quality of life of older people and to help them remain independent, or at their own home, as long as possible (Wherton and Monk, 2005). Improvements in communication, information transfer, mobile health, monitoring and sharing of clinical data all have the potential to help the elderly and their families manage their health at home (Fischer et al, 2014). The common ground of these initiatives is to make the domestic environment active, intelligent and cooperative by promoting self-Home care, in contrast to hospital/institutional care thus prolonging independent life and helping to face the rising costs of healthcare systems in aging societies (Preschl et al, 2011).

A solution is offered by Smart Homes and by so-called Cognitive Assistive Technologies (CAT) that, together with some form of artificial intelligence, allow to control patient's health status and detect specific events, and provide support during ADL (Intille, 2004) thus improving user autonomy (Pollack, 2002). The idea behind automatic ADL monitoring is to acquire further information on physical and mental health conditions and to identify problems, for the development and targeted implementation of prevention and support measures. There are two main monitoring approaches (Preschl et al, 2013):

a) Measure biometric signals such as blood pressure or body temperature in people with chronic diseases using wearable devices. The data are sent and recorded in a local base station and provided to health care professionals with information on the health status of the elderly person, allowing them to initiate (emergency) care where necessary.

b) Using built-in sensors in the home environment for video monitoring, door monitoring, bed alarms, pressure mats for detecting falls, smoke and heat alarms that can increase safety, security, and the ability to complete ADL.

Several initiatives have been reported, focusing mainly on the monitoring and analysis of people's behavioral patterns with the aim of providing support. Machine learning algorithms combined environmental and physiological data for the analysis of patients' behavioral patterns and well-being. Using real-life data, the authors supported the efficiency of the proposed algorithms by conducting assessments based on classification and prediction (Koumakis et al, 2019).

The ISAAC study (Kaye et al, 2011) foresaw the continuous collection of data without obstructing normal activities of the subject by installing a set of sensors at the user's home of different nature: passive infrared wireless motion sensors in the most populated areas of the house; sensors to measure walking speed, using sensors placed sequentially on the ceiling in areas such as corridors; magnetic sensors, located on each door, to trace the presence in the house. In this way it was possible to analyze different signals, such as the activity carried out during the day and night, the time activity, the speed of walking and the time spent away from home. Another study (Enshaeifar et al, 2018) presented a system that involves the installation of sensors in patient's home and the acquisition of a set of physiological data with the use of Bluetooth-enabled medical devices.

These technologies can then use the collected data to support users by means of input, ranging from single simple prompts (Quintana and J. Favela, 2012; Chandrasekera et al, 2017) to more complex input sequences (Mihailidis et al, 2008; Wood and Mccrindle, 2013). For example, systems such as Autominder (Pollack, 2006) or Gator Tech Smart House (Helal et al, 2005) use artificial intelligence planning to schedule events such as drug taking and use environmental sensors to provide, if necessary, reminders concerning unattended activities. Another example of a dementia project is the COGKNOW project (Dröes et al, 2009), an electronic assistant prototype that provides elderly people with mild dementia with support in the domains of memory, social contact, daily activities and psychological discomfort, such as the system reminding the user to call a significant person or to close the front door. Another project regards the development of the ALADDIN platform (Haritou, 2009) which aims to support patients and their caregivers in terms of self-management of disease by monitoring patients' health parameters and assessing cognitive and behavioral functions, and the activities of daily life.

Other systems have been developed to provide support during specific ADL, such as preparing a meal since the kitchen is a complex and dangerous environment. The number of instruments is high, and the type is complex, often requiring instructions before being used. In addition, tools, despite their degree of automation, rarely provide feedback on their status or give input to users for interaction. Kitchens are natural candidates for augmented reality interfaces because there is a high need to stay in touch with physical reality while using sophisticated tools that use digital information. Augmented reality can therefore help people to cook more safely and effectively. The Pigot Group (Pigot et al, 2008) has developed Archipel, a cognitive modeling system for kitchen activities that recognizes the plan intended by the user and adapts the suggestions to a predetermined level of cognitive deterioration, by means of sensors (tags and RFID readers) in the kitchen environment that detect which objects have been used and provide audio or video signals to help users at every stage of the activity. A more complex system was presented by Lee and colleagues (Lee et al, 2005), called Counter Intelligence, able to monitor the most commonly performed activities in a kitchen and give information by projecting them on objects and surfaces (e.g., virtual recipes, temperature of pots and pans, contents of the refrigerator, lighting of the drawer handles).

So, Smart Homes can offer an evaluable environment, efficiently from an ecological point of view (Jekel et al, 2016). The disadvantage is the demand of many sensors, which is generally associated with a high financial expense. In addition, ethical and legal issues and individual needs deserve special consideration in this context, especially regarding monitoring devices. Privacy can be enhanced by using less invasive technologies, such as monitoring systems that do not allow the user’s face to be clearly identified (Preschl et al, 2013). Even most of the currently available CATs also require extensive sensor and/or input distribution and maintenance by a cognitively intact individual. Caregivers should learn to operate and maintain a potentially complex planning system (Mihailidis et al., 2008).

A cheaper solution for patients’ monitoring during ADL is the use of wearable sensors such as Head Mounted Displays (HMDs) for augmented reality, where a user’s view or vision of the real world is enhanced or augmented with additional information generated from a computer model without precluding the vision of the surrounding physical environment. HMDs are also suitable for the provision of cognitive stimulation exercises, like those presented with

VR, but in a more user-friendly mode since it does not isolate the user from his/her environment. Furthermore, AR technology allows us to combine both cognitive and physical exercises.

So, we developed an AR marker-based Application designed for smart glasses to support the elderly during ADL that allows the user to navigate their home environment - but also away from home - in a more secure and controlled manner. The app also makes use of text-to-speech (TTS), speech-to-text (STT) and tactile feedback (vibration) technologies to support older people who, in addition to cognitive decline, have visual or auditory impairment.

2.2 Communication disorders

Communication disorders lead to language, speech, and communication problems. The language includes the use of a system of symbols such as sign language, spoken words, written words, and images that help people to communicate in a form governed by rules. Communication includes verbal and non-verbal behavior (Wolk, 2019). During interpersonal communication, in fact, the message is divided on three levels:

- *verbal communication*: consisting of the words we use when we speak or write. It is generally the level we are most aware of and the one we care for most carefully.
- *Paraverbal communication*: in oral communication, the indicators are tone, speed, timbre, and voice volume. In the case of written communication, we have for example punctuation and length of periods, elements that give the text rhythm and speed.
- *non-verbal communication*: all that is transmitted through one’s own posture, movements, the position occupied in the space with respect to the interlocutor. The "non-verbal" language is also present when we communicate in writing: if we write by hand, the calligraphy or the type of paper used can reveal our state of mind or the care we have placed in writing the message; in an email, the type of font, the color, the possible use of images are important indicators.

The psychologist and university professor Albert Mehrabian (Mehrabian, 1971) formulated the so-called model “55, 38, 7”, according to which 55% of the communicative message is deduced from non-verbal language, 38% from paraverbal aspects and 7% from verbal content.

In accordance with the Diagnostic Statistical Manual, Fifth Edition (DSM-5) (American Psychiatric Association, 2013), communication disorders include:

- *speech impairment*, which involves problems of articulation and pronunciation of one's native language. The language is produced by a coordinated and precise muscular action in the neck, head, chest, and abdomen. Language development involves years of learning how to adjust these muscles to produce comprehensible language.
- *linguistic disorder* characterized by difficulties in using and learning the language caused by vocabulary and grammatical problems and difficulties in composing sentences properly. This problem can occur both in the receptive form (comprehension of language) and in the expressive form (production of language).
- *disorder of social communication (pragmatic)*, which involves difficulties in the social use of verbal and non-verbal communication in representative contexts. This concerns the understanding of dialogue and the development of social relations.
- *Childhood onset fluency disorder (stuttering),* which involves interrupted fluency and rhythm of speech. It often causes the repetition of syllables and whole words, and sometimes includes pauses within words, avoiding the pronunciation of difficult words and / or prolonging syllables and words. Childhood-onset fluency disorder causes other associated communication problems and may end up interfering with social benefits and communication, both at school and at work.

Over 190 million people worldwide have severe disabilities that limit their ability to interact with everyday devices and engage in communication and social activities (Zhang et al, 2019). Focusing on younger population, statistics estimates that about 7.5% of children (age 3-17), have a clinically significant language disorder that is a direct cause that impedes learning (Wolk, 2019). On the other hand, 2.3% of children with language impairment presents an associated medical diagnosis and/or intellectual disorder (Norbury et al, 2016). Developmental language disorder is considered a cause of public health concern. It implicates an increased risk of school failure and can be a cause of social, emotional, and behavioral issues. Specific language impairment (SLI), one of common developmental disorders (7-8% incidence in kindergarten) is a communication disorder characterized by issues in acquiring and usage of the most common communication channel, written and oral language. Even though this disorder's causes are unknown, studies suggest that it has genetic routes. In fact, approximately 50-70% of SLI patients have at least one relative with language disorder (National Institute on Deafness and Other Communication Disorders, 2019). In addition to the above-mentioned factor, language impairment is caused by other diseases such as developmental disabilities (autism, Down syndrome, cerebral palsy, Spinal cord injury, Rett syndrome), acquired neurogenic disorders (stroke, brain injury, various neurological conditions), degenerative neurological conditions (ALS, progressive primary aphasia) (Mcnaughton & Light, 2013). Many of these disabling conditions are also associated with motor issues.

Disorders and communication difficulties usually range from mild, such as occasional misarticulation of words and stuttering, to complete inability to use language and speech for communication and are considered a main cause for worsening the people's quality of life and limit children to fully live their childhood. Several studies have reported that children with multiple and complex disabilities often face barriers that hinder their interpersonal interactions and their participation in meaningful daily activities, such as caring for themselves, playing, hobbies, teaching, etc. By participating in meaningful activities, children could develop certain skills, learn to self-express, and are better engaged in social activities (Chantry and Dunford, 2010). Disabled children are therefore less involved in activities than their peers and activities are often confined within the home with little possibility of social interaction (Law et al 2004, Majnemer et al 2008). These restrictions are all as severe as the impairment's severity (Beckung and Hagberg 2002, Kerr et al 2006).

Individuals presenting such disabilities must necessarily lay on others to satisfy their essential needs (Fleming et al, 2010). The communication difficulties occur During the interaction with parents, but it is especially accentuated while interfacing with strangers (Borgestig et al, 2016(a)). The possibility to inform other individuals regarding their needs and preferences is fundamental for establishing solid social relations (Fleming et al, 2010). On the other hand, poor language skills, health problems, psychological disorders and trauma that limit a person's ability to speak or move could put the patient at high risk of receiving extra doses of medicines that could be potentially harmful or lethal (Wolk, 2019). In order to maintain an acceptable social life, have decision-making abilities and the capability to indicate needs and willingness, an effective communication method is necessary, so Augmented and Alternative Communication (AAC) has become an essential part of intervention programs for those persons who have difficulties utilizing common communication channels (Flores et al, 2012).

The possibility of independent and effective access to technology makes it possible to remove some of these barriers (Davies et al, 2010). Langone (Langone, 2000) argued that although the computer cannot offer a cure to the disabled or make his disability less real, the advancement of technology can act as an equalizer, or to be an enabling factor which gives the disabled child the opportunity to engage in certain activities with the same success as his peers. For people with severe disabilities, without words and with severe physical impairment it is impossible, for example, to work on the computer because they cannot use traditional inputs such as mouse, keyboard, joystick, etc. So, assistive technologies have been developed with the aim of allowing disabled people to access the computer in an alternative way compared to the standard ones, Computer Access Technology (CAT) (Dhas et al, 2014): the Human Computer Interface (HCI) standard, such as mouse or keyboard, are suitably modified; alternatively, special devices have been developed, which are, however, typically expensive and designed ad hoc for the needs of the individual (Chen et al, 2006).

2.2.1 Assistive Technologies (AT)

Many non-verbal children with severe motor impairments need to rely on facial expressions to interact with others (Clarke & Price, 2012) Some children are using low-tech devices such as tables or books containing images and, by indicating with fingers or pointing with eyes, it is possible to interpret their intention. However, if children involved are presenting motor impairments as well, it gets more complicated. A possibility is to understand where the child is looking, but more frequently parents are interacting with simple “yes or no questions”, on which children are Able to respond, for example, by showing different facial expressions or by orienting their gaze up and down (Borgestig et al, 2016 (a)).

Neurodegenerative disorders such as ALS or lesions in the brain caused by stroke can lead to a locked-in syndrome (LIS), a term that indicates the state in which a person is aware of the environment and shows cognitive abilities, but is severely paralyzed (tetraparesis or tetraplegia) and is unable to speak (aphonia or severe dysphonia). People in locked-in state necessarily require a technological solution that replicates the word (Kathner et al, 2015).

Hence, the use of devices able of detect these features automatically is necessary. Even though, AT technologies may offer a treatment for the patient or at least reduce its disability, it may act as an equalizer, by being a factor that offers to a disabled child the opportunity to be dedicated to activities while having the same success as peers children without disorders

(Chantry e Dunford, 2010). With support of computers, children develop a new awareness toward the importance of using a communication code (Besio and Salminen, 2004). Computer ATs could in fact support clinicians, educationalists and parents to improve children's participation into diverse childhood occupations and to develop their own occupational role (Chantry e Dunford, 2010). In literature, various studies reported that technology have the potential to "free" children from their disability and to enable them to show their real potential (Hasselbring and Williams Glaser, 2000). The most frequently reported benefits of the examined studies are that these technologies provide an opportunity for disabled children to engage in activities and explore environments that they would otherwise not be able to do and provide a safe environment for children to develop, exercise and learn skills through trials and errors, without the risk of potentially harmful or negative consequences that could occur in the real world (Lannen et al, 2002). The parents reported that through the use of computers they had seen their children engage in playful activities that they had never been able to perform before (Lindstrand, 2002; Brodin & Linstrand, 2004) and had learned new ways to interact with others (Reid, 2004; Brodin, 2000).

On the other hand, it was found that children tended to use Computer Augmented Communication on demand rather than on their own initiative (Salminen et al, 2004). Advances in mobile technologies have provided new tools for communication, whose wide distribution is changing the way of working, learning, socially interacting and spending free time (Mcnaughton & Light, 2013) and therefore can ensure greater social integration even for individuals with communication problems. Recently, interest in the use of portable media players and smartphones as speech-generating devices has increased. In general, these new technologies are smaller and more financially affordable in comparison with traditional AAC devices (McNaughton & Light, 2013). These mobile technologies offer several benefits, including:

- increased awareness and social acceptance of the AAC
- increased consumer responsibilities in access to AAC solutions
- increased adoption of AAC technologies

For example, tablet utility has been already proved in this field which resulted as more favorable compared to traditional techniques that utilize *picture cards*, and these types of devices offer advantages in terms of the amount of work since it does not require cards preparation, which overcome the problem of having to find a place and a suitable way to keep them always handy (Flores et al, 2012).

Most HCIs are based on a selection operation consisting of two steps (Chin et al, 2006):

1) *Pointing*: Place the cursor on the appropriate screen position
2) *Clicking*: Running the Up/Down function of the mouse interpreted by the computer operating system as an indicator to complete the selection of the element associated with the icon in the cursor position of the screen.

Individuals with severe physical impairment are not able to use targeting devices in an appropriate manner, so the ability to communicate and learn through the computer decreases dramatically (Flores et al, 2012). To match users with needs, alternative Human Computer Interfaces have been adopted. Several studies used gesture recognition techniques, capable of automatically recognizing some specific hand gestures and translating it into vocal outputs (Matetelki et al, 2014). However, this technology has some Limitations: Technological, i.e. requires special equipment (such as use of a camera or a glove); Statistical, because the algorithms of gesture recognition are based on an error prone Statistical model; physical, requires accurate hands and fingers movements of the user (Wolk et al, 2017).

Other studies used as an input a bio-signal registration. For example, muscle electrical activity signals (Surface Electromyography) (e.g. (Chin et al, 2006)) is used to detect specific contractions of the facial muscles to move the cursor on the screen; or brain-computer interface (BCI), most of which are based on electroencephalogram signal (e.g., (Cincotti et al, 2008)) without the need for motor input. In relation to EMG-based systems, BCI doesn't require any motor input, but requires a long preparation time (Pasqualotto et al, 2015). In some cases, the conditions are of such severity that for individuals with severe physical disabilities and with poor (if not absent) speech functionality, an infrared sensor able to convert the movement of the eyes into "the control of a cursor on a display" appears to be the only solution (Majaranta & Donegan, 2011). Eye-gaze technology could provide a mean to access AAC electronic systems in a fast, reliable, and more independent way (van Niekerk and Tonsing, 2015). Eye-gaze interfaces can be an efficient input because eye-gaze is natural, fast and involved muscles are subjected to little effort (Ball et al, 2010). So, this technology can improve patients' quality of life and provide a hope for a child's future inclusion in society.

2.2.2 Gaze-based AT

Already in the last decade of the past century, many researchers started to assess the possibility to support individuals affected by both language and motor impairments with employments of gaze-based AT (Angelo et al, 1991; Evans et al, 2000; Chen et al, 2006; Lancioni et al, 2007). Several ways could be used to interface eye-gaze systems with computers or an AAC technology, some are surface electrodes around eyes (electrooculogram), remote video imaging to measure eye's movement, gaze-tracking or eye-tracking to measure the line of gaze view (Ball et al, 2010).

A device that integrates gaze-tracking, a screen showing a keyboard or an image and a text-to-speech (TTS) technology allows to communicate by blinking or winking, or by dwelling the gaze on the element for a time at least equal than a prefixed time period (*dwelling time*) (Majaranta and Raiha, 2002). To date, there are three types of *gaze-control systems* (Majaranta & Donegan, 2012):

- *all-in-one systems*: provides everything the user asks in a single device
- *dedicated modular systems*: communication devices that support a range of input methods in addition to *gaze-control*, which the user can choose which to use
- *add-on system*: enables each computer to be used as an *eye-tracking*.

Previous researches have just reported positive results regarding the usage of gaze-based AT by people with serious motor impairment to carry out activities of daily living (e.g., (Calvo et al, 2008). A previous study engaging amyotrophic lateral sclerosis patients have demonstrated that subjects who used eye-gaze devices were less depressed and showed an improved quality of life in comparison to whom were using a phonetic board (Hwang et al, 2014). The introduction of eye-gaze controlled computers at home and school could enhance children's communication skills, allowing them to express their desires and to carry out recreative activities (Hornof and Cavender, 2005), as well as improving their social activities (for example, choosing their game mate or which song to be listen at school (Van Niekerk and Tonsing, 2015) and furthermore express pain and where pain is located (Rytterström et al, 2016).

We have developed a communication AR-based system for children affected by language and motor disabilities, to be implemented for a head-mounted display (HMD). Throughout the HMD, an *all-in-one system* that can be used at any time and wherever you are, users can select the icons shown on the display, by pointing his/her gaze for more than a programmable period, so that it activates the related function, like how to read a sentence out loud.

2.3 Covid-19

In December 2019, the city of Wuhan, the capital of Hubei Province in China, became the center of a pneumonia epidemic of unknown origin, which caused concern among health officials at the end of December 2019. On 31 December, a notice was issued by the Wuhan Municipal Health Commission, a team was sent to Wuhan by the Chinese Center for Disease Control and Prevention (China CDC) and a notification was sent to the WHO (WHO, 2020 (a)). The epidemiological investigation involved the wholesale market of Huanan fishery products in Wuhan, which was closed and disinfected, an active research case was launched and vigorously pursued (Zhu et al, 2020). Although it is likely that the epidemic began with a zoonotic transmission event associated with a large fish market that also traded wild alive animals, it soon became clear that efficient person-to-person transmission was also taking place.

On 7th January 2020, the pathogen was isolated and identified as a new coronavirus, which followed the genomic characterization and development of the test method (Chan et al, 2020). The International Committee on Taxonomy of Viruses announced "severe acute respiratory coronavirus syndrome 2 (SARS-Cov-2)" as the name of the new virus on 11 February 2020. This name was chosen because the virus is genetically related to the coronavirus responsible for the 2003 SARS epidemic. Although related, the two viruses are different. Following the guidelines previously developed with the World Organization for Animal Health and the United Nations Food and Agriculture Organization, on 11 February 2020 the WHO announced "COVID-19" as the name of this new disease. The clinical spectrum of SARS-Cov-2 infection appears to be broad, including asymptomatic infection, mild upper respiratory disease, and severe viral pneumonia with respiratory failure and even death, with many patients hospitalized for pneumonia in Wuhan (Zhou et al, 2020).

On January 20th, China's "National Infectious Disease Law" was amended to make new coronavirus diseases of 2019 (COVID-19) a Class B notifiable disease and its "Law on Health and Frontier Quarantine" has been modified to support the response effort to the COVID-19 epidemic. Then, on 23 January, the Chinese government began to restrict the movement of people in and out of Wuhan and two days later announced its highest commitment level and mobilized all sectors to respond to the epidemic and prevent the further spread of COVID-19. (CCDC, 2020). Despite the intervention of China, the spread of severe acute respiratory coronavirus syndrome 2 (SARS-Cov-2) has expanded in other regions of China and especially has begun to take on an intercontinental dimension, having quickly infected more than 100000 people globally (Callaway, 2020), such that on March 11 the WHO declared the state of pandemic. The spread of the SARS-Cov-2 virus is causing high mortality rates and putting a strain on health systems. The most worrying factor is the proportion of cases requiring intensive care support, about 5% and patient management is complicated by the requirements for the use of personal protective equipment and to engage in complex decontamination procedures. Preventing further transmissions is a priority (Ferretti et al, 2020). Today's society has reached a level of global interconnection that makes an epidemic a very problematic event to contain with traditional quarantine measures. This has meant that a highly contagious disease, such as COVID-19, creates an unprecedented international health crisis.

2.3.1 How to limit COVID-19 diffusion

For the first time in history, the global human community is experiencing a pandemic in real-time with awareness of the event that affected it and its dynamics. The global spread of Coronavirus disease 2019 (COVID-19), caused by SARS-Cov-2, has already caused millions of patients and hundreds of thousands of deaths; numbers that continue to grow, while health services and researchers from all over the world are involved in the search for therapies and in the development of vaccines, being able to count on huge economic resources, coming from both national and international institutions and from private subjects, and especially on an extraordinary scientific and technological background (ISS Bioethics Working Group COVID-19, 2020).

The biological details of Beta-Coronaviruses transmission (family to which belongs the SARS-Cov-2) are known in general terms: these viruses can be transmitted from one individual to another through exhaled droplets, aerosol, contamination of surfaces, and possibly fecal-oral contamination (Ferretti et al, 2020). Considering the case of an epidemic that mainly spreads among people by close contact, through respiratory droplets from coughing and sneezing or through direct contact, the ideal procedure is to immediately identify the "zero patient" and then quarantine all those with whom he came in contact, so as to limit the spread. The recent outbreak of COVID-19 has shown, however, that this approach is difficult to pursue and becomes unsustainable especially since the incubation period is long due to the high number of interactions and the lack of strategies to effectively warn all people who have come into contact with the infected (Faggian et al, 2020). To date, however, there are many knowledge gaps of the pathogen and a high uncertainty on the contagiousness mechanisms of the disease. Furthermore, it is not yet defined in which terms can we speak of immunity for those who have been affected by SARS-Cov-2 and we are not able to assess whether we will manage to promptly vaccine the population. We must therefore be prepared to live with this virus indefinitely, waiting for solutions that scientific research will be able to offer us: Economic and social recovery around the world depends on how good we will be able to contain the contagion without resorting to prolonged confinement of the population (ISS Bioethics Working Group COVID-19, 2020).

Coronavirus infection spreads in clusters and therefore can early identification of these clusters is crucial to slow down the virus spread (Rossman et al, 2020). Containment is an effective mean of slowing the spread, giving health systems the ability to treat infected people. On the other hand, mass quarantine (lockdown) can also disrupt the productivity of the population, distort markets (restricting the transport and exchange of goods) and introduce fear and social isolation for those who are not yet infected or who have recovered from an infection. The absence of an effective method to track the spread of the epidemic results in an exponential growth of cases and this, in return, can lead to a difficult situation to contain the spread without serious restrictions on personal freedom (Faggian et al, 2020).

The approaches that we currently have available to stop the epidemic are classical epidemic control, physical distances and hygienic measures, such as case isolation, decontamination of the places visited by the infected individual, tracing and isolation of contacts (***contact tracing***) (Ferretti et al, 2020).

An alternative approach is that of **wastewater-based epidemiology**. The presence of a virus in urban wastewater is an "indicator", an alarm bell that can indicate early a possible circulation of a virus (early warning), thus allowing it to recognize and circumscribe more quickly any new epidemic outbreaks. Environmental surveillance may also be used for the study of the genetic variability of viruses circulating in the population, for the study of emerging viruses or also to highlight trends in case of epidemics.

2.3.2 Contact tracing

Contact research (or Contact Tracing, CT) is a key public health tool for the prevention and control of communicable diseases spread from person to person, which is used daily to control various infectious diseases such as tuberculosis, measles, and certain sexually transmitted diseases (e.g. syphilis, HIV infections). According to WHO (https://www.who.int/westernpacific/news/q-a-detail/contact-tracing) "People in close contact with someone who is infected with a virus, [...], are at higher risk of becoming infected themselves, and of potentially further infecting others .Closely watching these contacts after exposure to an infected person will help the contacts to get care and treatment, and will prevent further transmission of the virus".

CT is defined as the identification and follow-up of persons who may have encounter an infected person. The objective of CT is to quickly identify people exposed to existing cases as potential secondary cases and to prevent further transmission of the infection. The CT can be quickly implemented at the first warnings of an epidemic, but it continues to be effective when there are recurrence problems of the disease. After an initial epidemic peak, CT can be an effective tool to contribute to the decline of the disease and avoid multiple peaks (epidemic waves) and reappearance of the disease (Barbar et al, 2020).

The three essential activities of CT are:

1) *Contact identification*: identify, from confirmed cases, those who the infected patient came into contact with (according to the mode of transmission of the pathogen).
2) *Contact listing*: record possible contacts of infected patients and contact such persons
3) *Contact follow-up*

The traditional CT, so far widely practiced by the Prevention Departments through the interview of cases and contacts, allows to have very detailed information about the positive subject and his contacts, but on the other hand it is an activity that requires high resources, both in terms of time and in terms of specialized staff, is susceptible to memory errors and fraught, as easily guessed given the sensitivity of the data being processed, privacy problems (Barbar et al, 2020). On the one hand, health professionals have a social and ethical duty to alert an individual in relation to his exposure, supported by legal devices that allow him to act to contain a communicable disease; on the other hand, infected persons nevertheless have a recognized right to general and medical confidentiality. Health professionals, following the indications of the GDPR (General Data Protection Regulation, EU Regulation 2016/679), must detect the minimum amount of information required to achieve the objectives of CT (ISS Bioethics Working Group COVID-19, 2020).

The emergency situation has pushed all the affected countries to an analysis of the opportunities offered by current technology with the aim of adapting to the complex dynamics of our societies and local communities an apparently simple strategy, isolation, which to date is the most effective way of containing the spread of contagion. The international reflection and comparison have developed around the possible technological supports to the traditional CT, on the tracing of contacts through special Apps installed on mobile devices. The structure of the software can vary a lot: they can just repeat something very similar to what is already done manually and personally by health workers when they go back to the transmission chains, but it could also be transformed into means of controlling the population, tracing in detail the personal behavior of each citizen. There are, of course, possible intermediate situations between the two just described, with enormous consequences in terms of individual and collective freedom, public health and individual health, and therefore crucial ethical principles and constitutional rights, such as the dignity of the person, freedom, equality, solidarity and democracy (Giansanti et al, 2020).

With the recent almost ubiquitous availability of smartphones, many people carry a tool that can be used to quickly identify the contacts of an infected person during an epidemic, such as the current COVID-19 crisis (Ferretti et al, 2020). Apps installed on commonly used mobile devices, such as tablets and smartphones, or on wearable media such as smartwatches or smart wristbands, provide a solution for CT in an automatic manner, since by means of proximity detection technologies (focused on Bluetooth) and position detection (GPS), are able to assess the risk of virus transmission through monitoring of the number, duration and type of contacts. This surveillance facilitaty measures by making them faster and more effective. A CT App that builds a memory of proximity contacts and immediately sends a notification to positive case contacts could, if used by a sufficient number of people, offer the advantage of more effective surveillance and thus, potentially help to identify contacts more quickly (reducing the risk of transmission) to limit the spread of infection among the population (Giansanti et al, 2020).

Such technologies potentially have a high rate of penetration and invasiveness towards the very sphere of personal freedoms that its use would like to safeguard. While it is true that with an efficient and early identification of potentially infected people it is possible to address the recommendations only to those who are at risk, avoiding mass quarantine that is harmful to society (Ferretti et al, 2020), generalized confinement and physical distance measures, and therefore the suspension of many social and economic activities; on the other hand, these objectives can be achieved by accepting forms of control over one's own movements and personal contacts, with the risk of going beyond the strict needs and epidemiological contingencies. To this problem, we add the problems related to the security of the management of the collected data, that is, the fact that for system errors, unforeseen situations or malicious external interventions, the personal data may be made available to individuals and/or organizations outside the user and institutional authorities involved in territorial surveillance, or that are used for purposes deviating from their original purposes. In addition, it should be considered that such technologies, introduced under emergency conditions, could become of common use, especially if the pandemic continues. Paradoxically, their epidemiological success could push towards an acceptance of even less respectful forms of personal freedoms, in the name of greater physical freedom of movement, and/or to increase their security (ISS Bioethics Working Group COVID-19, 2020).

The risk that the coronavirus epidemic will result in unpopular choices or limitations of civil rights - is tangible, not only in countries governed by authoritarian regimes. In a recent document (Amnesty International, 2020), a number of international organizations call on governments to show their leadership in addressing the pandemic in a way that ensures that the use of digital technologies to track and monitor individuals and populations is carried out with respect for rights of the individual himself. The above-mentioned document asks governments not to use surveillance strategies to respond to the COVID-19 pandemic if they do not meet the following conditions:

1) Surveillance measures adopted to address the pandemic must be lawful, necessary, and proportionate. They must be provided for by law and must be justified by legitimate public health objectives, as determined by the appropriate public health authorities, and be proportionate to those needs. Governments must be transparent about the measures they are taking so that they can be scrutinized and if appropriate later modified, retracted, or overturned. We cannot allow the COVID-19 pandemic to serve as an excuse for indiscriminate mass surveillance.
2) If governments expand monitoring and surveillance powers then such powers must be time-bound, and only continue for as long as necessary to address the current pandemic. We cannot allow the COVID-19 pandemic to serve as an excuse for indefinite surveillance.
3) States must ensure that increased collection, retention, and aggregation of personal data, including health data, is only used for the purposes of responding to the COVID-19 pandemic. Data collected, retained, and aggregated to respond to the pandemic must be limited in scope, time-bound in relation to the pandemic and must not be used for commercial or any other purposes. We cannot allow

the COVID-19 pandemic to serve as an excuse to gut an individual's right to privacy.

4) Governments must take every effort to protect people's data, including ensuring sufficient security of any personal data collected and of any devices, applications, networks, or services involved in collection, transmission, processing, and storage. Any claims that data is anonymous must be based on evidence and supported with sufficient information regarding how it has been anonymized. We cannot allow attempts to respond to this pandemic to be used as justification for compromising people's digital safety.
5) Any use of digital surveillance technologies in responding to COVID-19, including big data and artificial intelligence systems, must address the risk that these tools will facilitate discrimination and other rights abuses against racial minorities, people living in poverty, and other marginalized populations, whose needs and lived realities may be obscured or misrepresented in large datasets. We cannot allow the COVID-19 pandemic to further increase the gap in the enjoyment of human rights between different groups in society.
6) If governments enter into data sharing agreements with other public or private sector entities, they must be based on law, and the existence of these agreements and information necessary to assess their impact on privacy and human rights must be publicly disclosed – in writing, with sunset clauses, public oversight and other safeguards by default. Businesses involved in efforts by governments to tackle COVID-19 must undertake due diligence to ensure they respect human rights, and ensure any intervention is firewalled from other business and commercial interests. We cannot allow the COVID-19 pandemic to serve as an excuse for keeping people in the dark about what information their governments are gathering and sharing with third parties.
7) Any response must incorporate accountability protections and safeguards against abuse. Increased surveillance efforts related to COVID-19 should not fall under the domain of security or intelligence agencies and must be subject to effective oversight by appropriate independent bodies. Further, individuals must be given the opportunity to know about and challenge any COVID-19 related measures to collect, aggregate, and retain, and use data. Individuals who have been subjected to surveillance must have access to effective remedies.

8) COVID-19 related responses that include data collection efforts should include means for free, active, and meaningful participation of relevant stakeholders, in particular experts in the public health sector and the most marginalized population groups.

The development of App for CT has spread in many countries, with significant differences also at local and sub-regional level. A comparison is decidedly difficult, due to both the multiplicity of political, cultural and health contexts in which each app must be inserted, and to the lack of uniformity in the literature data on the results obtained.

2.3.2.1 Solution implemented by foreign countries

Although the WHO has issued recommendations on health policies, many politicians in different countries have chosen and implemented different strategies to contain the epidemic. These strategies depend on many factors, including the local diffusion of COVID-19, health system resources, economic and political factors, public adherence, and their perception of the situation (Rossman et al, 2020).

In the eastern countries, where the COVID-19 epidemic occurred earlier than in other continents, there has been an attempt to contain it through approaches characterized by a strong use of technologies associated with very different containment measures. China, Singapore, and South Korea have adopted coercive and restrictive control measures through Apps, platforms, and information systems, with the triple purpose of:

1) Population control: to force positive persons to stay at home and prevent citizens in general from violating the measures (for example, using drones).
2) Tracking the movements of positives (with ad hoc app, cellular network data, etc.) to identify the people with whom they came into contact and isolate them consequently.
3) Draw up a positive map for the benefit of the population and the civil protection, to avoid travel to areas with higher risk of infection.

The main factor contributing to the containment of the virus in China was the aggressive use of quarantines. It is estimated that in the Hubei area up to 57 million people have been placed in strict quarantine, with a very strict "red zone". In addition to these very vigorously implemented restrictive measures, the virus has become a catalyst in China for further expansion of surveillance technologies. The Chinese government has opted to expand and improve a control system based on technology, big data, artificial intelligence, which was already ready, and whose effects, were until then not visible to the population, have come to light. Much of the population uses two commercial apps, WeChat (used pervasively by citizens like our WhatsApp) and Alipay (a payment system). The strategy of the Chinese government was not to create an additional App, but to integrate a tool, which took the name of Alipay Health, with the two most downloaded Apps, so that the government can know information about the location and movements of users, with whom they met for a certain period, etc. The tool specifically created by the Chinese government for the control of contagion is the system called Alipay Health Code. This tool has been integrated with several sensors, such as facial recognition systems to detect high body temperatures in the crowd or individuals who do not use personal protection devices, or license plate trackers. In addition, for greater control of the population, the App Health Code has been implemented which automatically assigns to each citizen one of the three color codes (green, yellow and red) in relation to their state of exposure to the pandemic (travel history, time spent in epidemic hotspots and exposure to potential virus carriers) and on the basis of which it is established the possible status of quarantine or freedom of movement (for example, use a public transport or access to a restaurant) (Giansanti et al, 2020).

For Singapore, the situation could have become a catastrophe. Singapore is a country of 23 million inhabitants, where three different cultures coexist, Western, Chinese, and Indian, it is considered the Eastern Swiss. The island's territory is closely interconnected with mainland China, with direct flights to Wuhan, the center of the epidemic. The National Centre for Infectious Diseases (NCID) was established in the Republic of Singapore, which has been affected by previous outbreaks of avian flu and H1N1, an institution that over the years has been able to build on the experience using the most advanced technologies and keep the control and alert systems vigilant. Because unlike Wuhan, many individuals were linked to an identified symptomatic source, Health authorities in Singapore have decided to test all cases of flu and pneumonia, quarantine those affected and monitor them remotely via an application. As it is necessary to track down the affected persons as soon as possible, a real hunt has begun for every possible contact of the infected persons, through a process that operates 24 hours a day, 7 days out of 7, based on interviews with patients and which also involved the police (who makes use of surveillance cameras), the posting of leaflets and a test developed locally for antibodies (Zunino, 2020). Once the individual was identified, it was reported to the centralized system on the NCID server and automatically placed on the *Trace Together* App (https://www.tracetogether.gov.sg/) within a Digital Contact List. The people on the list were called daily (even several times a day, at any time) and were obliged to share the location of their smartphone.

Singapore’s rapid mobilization is in clear contrast to South Korea and Japan, which are also close to China and have advanced health systems, due to increased political weakness and ambiguous communications. On the other hand, in South Korea the development of the epidemic was particular: The center of the epidemic was Shadowy Church in the district of Daegu where a religious cult practiced the secrecy of infected people and performed a ceremonial with the purpose of self-infecting and healing on the basis of the "will of God". This event specifically circumscribed the cluster of contagion, obtaining the competitive advantage of the “patient zero”, that is to have almost the perfect full spread tracing who have had contact with the members of the cult. The South Korean government has opted for localized blockages, focusing its energies on testing large numbers of people to identify "hotspots" of infections. As Koreans are young and highly digitized people who constantly work in the field of product innovation, numerous Apps to inform the population about the proximity or risk of frequenting places frequented by those who are positive or suspicious, Apps have been made available (by both the government and the private). In particular, the most popular was the App Corona 100m, developed by the Government, in which you can not only find all the statistics on infections, deaths, healed, and of course all the hygiene advice, but also useful information from CT, user reports and in some cases information on the movements, even too detailed, of infected people (for example, the App triggers a real alarm on the smartphone when you are close, or in the area of 100m, near to a positive) (Zunino, 2020). These systems, with the more or less voluntary participation of citizens, have allowed to slow the spread of the virus (Giansanti et al, 2020). The CT led to the identification of many new cases, often before the onset of symptoms, and substantially reduced the time from the onset of symptoms to isolation, thus reducing the likelihood of transmission. Although evidence suggests that the traceability of contacts in several Asian countries has been effective in containing the virus, it is difficult to quantify the actual effect of CT, as this system has been accompanied by other strict control measures adopted at Community and individual level (Zunino, 2020).

At a European level, the challenge is to isolate confirmed cases and their contacts while respecting the fundamental rights and freedoms of European democracies. Despite the many objections initially raised against the effectiveness of CT the latest scientific research on the epidemic COVID-19 shows that diagnostic testing alone is not sufficient to reduce the infection transmission because the time needed for case recognition delays other prevention actions. In fact, clinical manifestations of COVID-19 may be absent or could take a few days to express themselves, delaying the recognition of cases with infection. To this is added the time needed to receive the results of diagnostic tests. This latency is reflected in the timeliness of isolation measures for the infected. Scientific research shows that the disease is asymptomatic up to 55% of transmissions with a very short generation period (3-5 days). The reconstruction of the transmission chain of the virus from the mere outcome of the diagnostic tests is therefore insufficient and delayed. It has been shown that even at very high levels of success in the isolation of positive cases, a rapid and extensive identification and quarantine of at least the first level contacts are needed to bring the epidemic under control (Ferretti et al, 2020). The manual activity of reconstructing the contacts of a COVID-19 patient is proving to be a slow and cumbersome activity. The Big Data Institute in Oxford has proposed a reference workflow for the development of technological solutions specifically aimed at contact tracing for COVID-19. The model outlines the instantaneous traceability scheme of first-degree contacts: a smartphone alerting system is able to inform users, based on their contact matrix and possibly their geographical location, compared to when they can move safely, when they must seek medical assistance, when they must avoid vulnerable people. In line with the above-mentioned considerations and evidence, the indications provided by the WHO appeared clear and explicit, stating: "Find, isolate, test and treat every case and trace every contact". Therefore, to limit the expansion of the transmission chains it is essential to use processes and technologies that have the objective of tracing infections in a rapid and as automatic as possible manner.

2.3.2.2 European Model

Many countries of the European Union (EU), including Italy, have chosen the road of the lockdown of activities to flatten the curve of the pandemic. In the EU, the virus has spread rapidly and knows no geographical or political boundaries, so to try to keep the situation under control we must act in a single way, involving speed of intervention and international cooperation. In response to the rapidly growing number of cases and the danger of overloading health systems, many countries have imposed travel restrictions or adopted economic and social blockages to slow the spread of the coronavirus. As a long-term blockade is not economically and socially sustainable, a number of European public and private subjects have worked to develop a joint response that, through interoperable CT technological solutions, protects the health of citizens without risking the collapse of the health system.

On 15 April 2020, the European Commission published guidelines for the implementation of infection tracing applications (Mobile applications to support contact tracing in the EU's fight against COVID-19 - Common EU Toolbox for Member States) which states that "mobile apps have the potential to strengthen personal contact tracing strategies, which are necessary to contain and reverse the spread of Covid-19", by adding the following "EU Member States are converging on effective solutions, based on apps that minimize the processing of personal data; also recognize that interoperability between these apps can not only help national health services but also facilitate the reopening of the EU's internal borders". The selection of the reference technological solution at European level was proposed by the international consortium "Pan-European Privacy-Preserving Proximity Tracing (PEPP-PT)" and is geared towards full compliance with European laws and principles on privacy and data protection. The mechanisms and technical standards sought are therefore geared to protecting privacy, transparency, and security in the management of data, exploiting the possibilities of digital technology to maximize the speed and real-time capacity in response to the pandemic. The solutions proposed in the European model should not collect on an ordinary basis personal data, nor other data that allow the identification of the mobile device owner, for which include proven proximity tracking technologies, secure and encrypted anonymization of data, reliable mechanisms to allow contact between the user and health officials in a data protection compliant environment, digital data exchange interfaces (APIs) providing anonymized contact chains and risk assessment to other applications. The solution must keep track of only the number, duration, and type of close contacts with other devices in which the same solution is active, through which the probability of infection is calculated.

Using Small Area Network-oriented data transmission methods such as, for example, Bluetooth, Bluetooth Low Energy and Wi-Fi Peer-to-Peer based on the sensor available on the device and crossing (where possible and always under explicit authorization of the user) location data from GPS and Network Position (triangulation based on phone cells), the phone acquires a unique and encrypted ID of all smartphones in the vicinity (about 1-2 meters) and retains the duration and estimated distance of such close contact. The scan takes place at programmable periods of a few seconds, even with the App in the background the selected technologies must be able to track contacts near the potentially infected subject with a very high precision, in the order of a few tens of centimeters. The user is not necessarily geo-localized (although this may be technically possible, if it is specifically and consciously chosen by the user), nor is it made recognizable, unless you explicitly accept these options, where applicable and available. However, it should be noted that, based on the current technological constraints on certain types of devices, in particular those based on iOS operating system, Bluetooth proximity tracing alone may not maximize the likelihood of identifying all contacts, as it may fail to intercept signals from devices where Bluetooth functionality does not operate consistently for the purposes of the application. It is therefore considered appropriate not to exclude a priori the possibility that, under the condition of informed consent, the technological solution to be implemented may handle some precise and limited geolocalized information, not oriented to reconstruct the paths but limited to specific places of potential contagion, especially if high density and frequency of contacts, as not all possible contacts may have devices (due to a lower penetration of smartphones, especially among the elderly population) or installed apps (lower adoption/compliance by the population). In case of contagion, the information, stored only on the user's device, is shared with health authorities. The acquired data and the calculated risk can be made accessible anonymously to health authorities, who can read the risk data and update the status of a person (negative or positive to the test). Citizens can be informed in real time and can spontaneously take precautionary measures (voluntary isolation) against those closest to them. Local health authorities can thus have an important tool for concentrating tests on people who have had contacts at risk of contagion.

To converge with the digital contact tracing model proposed by the European consortium PEPP-PT, the desired operation of the contact tracing solution can be summarized in the following points (Senate Studies Service, 2020):

1. *Sending an anonymous identification code*: each enabled device transmits a temporarily valid, authenticated, and anonymous identifier that is not connected to either a user or a phone number. The proximity between phones of other system users is estimated by measuring the radio signals emitted by the device (Bluetooth, etc.) using tested and calibrated algorithms.
2. *Recording proximity history*: when the device "A" is in epidemiologically relevant proximity to the device "B" for an epidemiologically sufficient period of time, as determined by empirical measurements and medical heuristics, The anonymous ID of phone B is recorded in the encrypted proximity history stored locally on phone "A" (and vice versa). In the model proposed by PEPP-PT, no geo-location, no personal information, no telephone number, or other data are recorded, so that in no way allows the identification of the user. This anonymous proximity contact history cannot be viewed by anyone, not even the user of the

"A" phone. Events in proximity history are progressively eliminated when they become epidemiologically unimportant (for example, after 21 days)

3. *Usage of proximity history*: when it is confirmed that the user "A" phone is SARS-Cov-2 positive, health authorities will contact user "A" and provide the user with a special encrypted key, with which the user can voluntarily provide information to the national health service that allows the notification of apps recorded in the history of proximity and therefore potentially infected. Since history contains anonymous identifiers, neither person can be aware of the identity of the other.
4. *Country and/or region-dependent health service operation*: anonymous IDs contain cryptographic mechanisms to identify the country and/or region of each App using the system. Using this information, anonymous Ids are managed country specific.
5. *Healthcare Processing*: the process of how to inform and manage the exposed contacts can be defined country by country, to ensure the interoperability of the processes between the different local health authorities.
6. *Information and infrastructure*: all procedures, mechanisms, standards, and system codes must be constantly monitored by the security team. At the same time, national IT security agencies and national data protection agencies regularly monitor and validate all lines of code from a cybersecurity point of view. Everything released to the public is controlled to prevent unwanted effects in procedures or code.

2.3.2.3 COVID-19 in Italy

In the COVID-19 Pandemic, Italy was hit very hard. At the time I am writing, March 2021, the number of documented cases has exceeded 3.3 million with over 100 thousand documented deaths linked to coronavirus infection (SARS-Cov-2) from severe acute respiratory syndrome. Such high numbers of cases and deaths cannot be simply explained by the fact that Italy was one of the first countries (probably the first in the Western world) to be affected by the epidemic. On the other hand, it is true that Italy has the oldest population in Europe and the second oldest population in the world after Japan and has a high percentage of patients with smoking history and high rates of chronic obstructive pulmonary disease and ischemic heart disease. The most affected population by SARS-Cov-2 is the oldest (in Italy the average age of the deceased is 80 years and that of those in need of critical care of 67 years) and the morbidity and mortality of COVID-19 are highly dependent on the presence of serious concurrent diseases (Boccia et al, 2020).

A second set of factors in Italy is the increased load of cases that have occurred in the healthcare system. On 20 February 2020, a 30-year-old patient was admitted to the intensive care unit (ICU) of the Codogno Hospital (Lodi, Lombardy, Italy) for an atypical pneumonia that did not respond to treatment but was not considered at risk of infection with COVID-19. The positive result of the test for SARS-Cov-2 was immediately reported to the Lombardy health system and government offices. Over the next 24 hours, the number of reported positive cases rose to 36, resulting in a situation of enormous severity for several reasons: the patient (called "patient 1") was healthy and young; in less than 24 hours, 36 additional cases were identified, without links to patient 1 or positive cases previously identified in the country; it was not possible to identify with certainty the transmission source to patient 1 at that time; and, since patient 1 was in intensive care and there were already 36 cases by day 2, it was likely that there was a cluster of unknown size that would with great probability create an additional spread (Grasselli et al, 2020). A second cluster has been identified in the municipality of Vò, in the province of Padua (Veneto). Veneto entities carried out aggressive tests, swabbing all residents (about 3300 citizens) on the day the first case was detected (in the third week of February) identifying 3% as infected and thus managing to extinguish the epidemic. However, elsewhere in Italy, the prevalence of infection was likely to be several times higher in the absence of effective public health intervention. For example, it is likely that in Bergamo health system was overwhelmed by the massive viral transmission during the Champions League match of 19 February 2020 (Atalanta vs Valencia), in which a third of the Bergamo population have participated, to which were added other people in festivities that continued at night. A third set of factors concerns the standard capacity of the health system and the decisions taken during the hospital management of the presented cases (Boccia et al, 2020). Italy has a highly competent state health system but has only a small number of beds in intensive care and very few beds for sub intensive care. In total, in Italy there are 5090 beds in intensive care (8.4 per 100,000 inhabitants) and 2601 beds in coronary care units (4.3 per 100,000 inhabitants). Given the little experience in dealing with the new virus, it is inevitable that some strategic mistakes have been made regarding patients to be admitted. In winter, hospitals tend to operate close to full capacity, with 87% of average employment in Italy during the flu season. Apparently, many patients with relatively modest symptoms were admitted; when more patients with severe symptoms began to arrive, the reserves were limited. Hospital overcrowding can also explain the high infection rate of medical personnel. By 30 March 2020, 8920 medical personnel had been found infected in Italy, leading to a further loss of hospital response capacity. In addition, early infection of medical personnel has led to the spread of the infection to other patients within hospitals (Istituto Superiore di Sanità, 2020).

In the first decade of March 2020, the percentage of patients in intensive care reported daily in Italy was constantly between 9% and 11% of patients actively infected (occupying 1028 beds of intensive care, about 5200 in total on the national territory). As the contagion was assuming an exponential trend, forecasts indicated that by mid-April 2020 almost all beds in intensive care units would be occupied, with the additional risk that the number of patients who would have been in the emergency room would have become much higher than what the system is able to cope with. In addition, it should be noted that the prevalence of patients with COVID-19 was mainly concentrated in some regions (especially in northern Italy) where the situation was much more serious than that of regions of Central-South Italy. Lombardy, for example, was responding to the lack of beds for COVID-19 patients by sending patients who need intensive care but are not infected with COVID-19 in hospitals outside the region to contain the virus but if uncontrollable clusters emerged in these regions, the national health system would have collapsed. Under the strong pressure of medical personnel, on 8 March 2020 the Italian government implemented extraordinary measures to limit viral transmission, including the restriction of movements in the Lombardy region, aimed at minimizing the likelihood of non-infected persons coming into contact with infected persons (Remuzzi and Remuzzi, 2020). Despite the prompt response of the local and regional intensive care network, health authorities and the government to try to contain the initial group, the increase in patients in need of admission to intensive care was overwhelming. In addition, forecasts show that increasing the capacity of intensive care is not enough. In practice, health system cannot support an uncontrolled epidemic and the only option has been to implement stronger containment measures. Thus, since 10 March, Italy has been placed in mass quarantine (lockdown) and the government has established stronger containment measures, including strict self-isolation measures, to slow the transmission of the virus (Grasselli et al, 2020). If the Italian epidemic had followed a trend similar to that of the province of Hubei, in China, the number of new infected patients should have started to decrease within 3-4 days, moving away from the exponential trend (Remuzzi and Remuzzi, 2020). In Italy, however, the contagion curve has been slow to descend. This could be due to the decentralization of Italian health care in favor of regions that may have hindered preparation and containment. In addition, there are socio-political reasons: Italian life is famous for its socialization and frequent congregations and groupings and it is also possible that in the early stages there was not much adoption of standard hygienic measures and instructions to stay at home proved to be difficult to accept, with many complaints registered to the police (Ministry of the Interior, 2020).

2.3.2.4 Contact Tracing in Italy

The Decree Law on 9th March for the strengthening of the National Health Service does not expressly authorize the traceability of smartphones or geolocation as means of monitoring citizens in quarantine or positive results to the virus for which it is imposed "the absolute prohibition" to leave the house. In the debate also the Privacy Guarantor Antonello Soro made his voice heard, who, in an interview dated 17 March, recalled how rights can, in emergency contexts, be subject to restrictions even incisive, admissible as long it is proportional to the specific needs and only if they are limited in time (Bolco and Di Giulio, 2020). Provision must therefore be made for mechanisms that are proportionate, that correspond to needs that are genuinely necessary and appropriate to the risk, with measures that are the least invasive as possible, in compliance with the principles of purpose and minimization of data, of which it will also be necessary to ensure safety. It will also be important that any choice is decided to be made with regard to controls or tracings is not irreversible but necessarily limited in time, being able to be 'defused' when the purpose of containment of the epidemic has ended. Art. 14 of the decree foresees, exceptionally, for the duration of the COVID-19 emergency, a certain derogation from the GDPR for the processing and communication by qualified persons of health data of citizens affected by coronavirus. In view of the changing nature of the scenarios arising in relation to the evolution of the virus, it is to this standard, as a special provision, that someone looks at, wondering if it cannot represent a window for the introduction of contact tracing forms similar to Chinese, in derogation from the general rule of the Privacy Code, art. 132, which provides for the processing of traffic data (cell phones or geo-referencing) only in exceptional cases and in compliance with a specific procedure (Mischitelli, 2020).

With timeliness respect to other countries and the European Commission, on March 21, 2020, the Minister of Health held a videoconference with technicians of the Ministry, representatives of the Italian National Institute of Health and the World Health Organization, the Minister for Technological Innovation and Digitization as well as technicians and experts of the Department of the Presidency of the Council for Digital Transformation to define essential features of an action line for the introduction of a digital CT system (Senate Studies Service, 2020). Italy has evaluated among several CT candidate apps, many of which respect privacy in a new way compared to the Apps used by Eastern countries, using sensors such as:

GPS, more invasive, only in order to have aggregated data useful to identify new outbreaks and, at the most, to study the respect of the measures by the general population; Bluetooth to trace people in a more identified way, but with techniques of pseudonymization and encryption, so as to protect its identity (which may also remain unknown to the Government) (Mischitelli, 2020). A fast call for contribution has been launched as part of the initiative “Innova per l'Italia: technology, research and innovation on field against Covid-19 emergency” (a public call for tenders to collect contributions from companies, universities, research centers and civil society in the area of devices for the prevention, diagnosis and monitoring of the containment and control of the coronavirus spread, promoted by the Ministers of Economic Development, University and Research and Technological Innovation and Digitalization) with the aim of identifying the best digital solutions available on telemedicine applications and home care of patients as well as technologies and strategies based on technologies for "active" monitoring of the contagion risk to which over 300 technological solutions for monitoring have been presented. On 31th March, the work of the working group set up by the Minister for Technological Innovation and Digitization in agreement with the Ministry of Health to evaluate and propose technological solutions based on data analysis and to address the sanitary emergency, socially and economically linked to the spread of the SARS-Cov-2 virus in Italy. The working group is composed of a multidisciplinary group of 74 experts, selected in collaboration with the Ministry of Health, the Italian National Institute of Health, and the World Health Organization. In view of their respective autonomy, the Italian Competition guarantor Authority and the market, guarantor authority for Communications and the protection of personal data do not participate directly in the work and provide opinions on issues related to their competences (Senate Studies Service, 2020). The working group identified the best and most appropriate solutions, basing its assessments and opinions on the following points:

a) the entire integrated CT system must be entirely managed by one or more public entities and its code must be open and subject to review by any independent subject who wishes to study it;
b) the data processed for the purposes of operating the system are "made sufficiently anonymous to prevent identification of the data subject" [cf. Recital 26 GDPR] taking into account the set of objective factors, including costs, available technologies and the value of reidentification at least under normal conditions and subject to the occurrence of pathological events or, at least, pseudo-anonymous following the adoption of appropriate measures to limit the identification risk of data subjects;

c) The decision to use technological solution is freely taken by individual citizens.
d) Once reached the purpose pursued by all data wherever and in whatever form it is stored, with the exception of aggregated and fully anonymous data for research or statistical purposes, these data are deleted with a consequent absolute guarantee for all citizens to meet, before public and private entities, under the same conditions to the one before the use of the solution;
e) The solution adopted - in its technological and non-technological components - can be considered, at least in a prognostic dimension, effectively effective from the epidemiological point of view, since, in default, it would become difficult to justify any, although modest and possible solution, that restricts fundamental rights and freedoms.

Based on the above-mentioned evaluations, with the official confirmation of the emergency commissioner Domenico Arcuri, Italy has chosen the Immuni App, formulated by Bending Spoon (one of the leading mobile developers in the world), Jakala, Geouniq and Centro Medico Santagostino. The team has joined and actively collaborates with the European Consortium PEPP-PT, a positive factor regarding the ability to work at a pan-European level and with a view toward implementing a shared European solution in a short time. Like all Apps screened in major European countries, Immuni makes use of Bluetooth technology; respects privacy because data is stored only on the device in an encrypted way protecting anonymity; the use is on a voluntary basis (Zunino, 2020). The application also allows the data storage on the personal device of family/cohabiting in relation to which - until the implementation of wearable devices - only the function of "clinical diary" can be activated with the same guarantees of data minimization implemented for the main user of the App (Senate Studies Service, 2020). The acquisition of geolocation data and metadata associated with the information shall not be provided, except for health condition of the user diagnosed by health care provider by virtue of temperature measurements entered by the same user. The working team stated that, should GPS technology be deemed necessary, it could be easily integrated to acquire information in aggregate form to trace possible new outbreaks (Zunino, 2020).

Let's briefly see how Immuni works (https://www.immuni.italia.it). When logging in, each user is assigned a pseudo-randomly generated code that does not allow them to identify the user of the specific device. Bluetooth Low Energy (BLE) technology is used to recognize device interactions. Immuni stores locally, or only on each user's device, all the Bluetooth codes of other devices with which it comes into contact (based on proximity and duration of contact), equipped with the same App (be these smartphones, smartwatches or standalone devices like bracelets) in encrypted mode. Functionality is triggered when a citizen is found positive after a coronavirus test. Before completing the analog questionnaire, health care provider asks the patient whether he has installed Immuni App and whether he will give his consent to the processing of data stored on his mobile phone, allowing - only in that case - to rebuild his network of contacts in the previous days. The operator then generates, with a different specific App for health professionals, a code with which the citizen can upload to a server the list of Bluetooth codes with which the subject has been in contact, for each of which the risk of infection is calculated and sent, also via the App, a notification to users devices potentially at risk without the operator being aware of any personal data of the recipients. The notification has a message decided by health authorities and asks to follow a protocol (isolation, contact emergency numbers for swabs). It is therefore easy to understand that, in order for this solution to be effective to reduce the spread of the virus, it is necessary that Immuni is implemented by citizens: it has been calculated that the App should be used by at least 60-70% of the population for the system to work. To date (16 December 2020), the number of downloads is 10,029,517, with 6584 users who have uploaded their keys and 81586 notifications of possible exposure to risk generated by the application.

Our working group (Giansanti et al, 2020), strongly supported by the director of the National Center for Innovative Technologies in Public Health as well as external tutor during my doctoral course, engineer Mauro Grigioni, was immediately activated to contribute to the research of possible technologies for contact tracing that met the requirements set in the fast call for contribution. The solution we propose is not an alternative to Immuni, but rather it integrates it functions to create a more robust cluster identification and monitoring system. By means of a GIS system and an App that can be downloaded to your device, each citizen can, in a completely voluntary way, fill out an anonymous questionnaire at any time by providing personal information that integrates into a database that can only be analyzed by health authorities (General Practitioners and Territorial Structure). In addition, with the consent of the user, the system allows you to share sensitive data with your General Practitioner to create a direct, safe, and secure communication network between patients and General Practitioner.

2.3.3 Wastewater-based epidemiology

The research of pathogens in urban wastewater dates to the second half of the '40s, when the first studies on the presence of enterovirus polio and non-polium were published (Sinclair et al, 2008). The WHO, as part of the global polio eradication program (Global Polio Eradication Initiative) recommends the implementation of surveillance systems for the maintenance of "polio-free" status which provide both active surveillance of acute flaccid paralysis and environmental surveillance of urban wastewater for the search for polio- and non-poly enterovirus. The enormous usefulness of this type of approach is evident in the representation of the so-called "pyramid of surveillance": compared to people who have contracted infection, only a part seeks health professionals, while most may be asymptomatic or paucisymptomatic with spontaneous resolution of symptoms; one party needs to address the SSN and only hospitalized or notified cases to the surveillance system are highlighted in statistics. In this context, if clinical surveillance targets the tip of the pyramid, environmental surveillance targets its base, identifying all the infections within the population, including asymptomatic or paucisymptomatic infections.

Wastewater-based epidemiology (Wbe) has been an established science for years now that analyses not only pathogens, but also drugs and substances from human metabolic residues in urban wastewater. The rationale of environmental surveillance is based on the principle that viruses are excreted, mainly by feces, by subjects with infection (symptomatic, paucisymptomatic, asymptomatic) and reach treatment and purification plants through the sewage system. Urban wastewater, in fact, collects the human metabolic residues of the entire population connected to a sewage collector and then to a city sewage treatment plant. Viruses circulating in each community (for example, metropolitan areas, city districts) are thus intercepted by analysis of urban wastewater collected at the entrance of a sewage treatment plant or on certain nodes of the sewage system. This approach uses urban wastewater as a source of dynamic observation of pathogen circulation in the population. A single urban wastewater sample represents a pool of many individuals, varying according to the size of the sewage treatment plant (equivalent inhabitants served). As specified by the WHO in the guidelines for the environmental surveillance of poliovirus, it is possible through the analysis of urban wastewater to intercept an infected individual among 10,000 healthy individuals (La Rosa et al, 2020(a)).

Recent studies have shown that SARS-Cov-2 can be responsible for gastroenteric symptoms (nausea, diarrhea, abdominal pain) and can therefore be isolated from the feces of patients with infection, both symptomatic and asymptomatic. It is known that gastrointestinal symptoms are observed in patients with COVID-19 and that about 50% of patients with COVID-19 have detectable viruses in the feces (Ouali et al, 2020). The viral load in the feces of COVID-19 patients has been estimated at between 102 and 106 genomic copies per liter of wastewater (g.c./L), depending on the course of infection (Foladori et al, 2020). Such evidence has led some authors to question the possibility of fecal-oral transmission of the virus, but to date, there is no evidence of water transmission of Sars-Cov-2 and the virus has never been detected in drinking water. Based on this evidence, research groups from various countries undertook SARS-CoV-2 research in wastewater, analyzing historical wastewater samples for past circulation testing of SARS-Cov-2 (WHO, 2020(b)). Detection of non-infectious RNA fragments of SARS-Cov-2 in untreated wastewater and/or sludge has been reported in several contexts, such as Spain, France, the Netherlands, the United States of America, Australia, and Pakistan. In addition, researchers in the Netherlands, France and the United States of America have shown a correlation between SARS-Cov-2 RNA concentrations in wastewater and COVID-19 clinical cases, suggesting that RNA concentrations may give 4-7 days warning before the confirmed data of COVID-19 cases (WHO, 2020(b)). Therefore, the possibility to carry out an environmental surveillance for SARS-Cov-2 through the analysis of urban waste water can be a useful tool to supplement the epidemiological surveillance, in order to monitor the circulation, also in asymptomatic form, of the virus in the population and to detect at an early stage a possible appearance/reappearance of the virus, allowing to recognize and circumscribe more quickly any new epidemic outbreaks. The monitoring of urban waste water, was carried out in a systematized form and in connection with territorial health surveillance networks, can also be used as early warning, that is, it can be an early warning system in relation to the possibility of outbreaks in the population. According to press sources, Wbe systems are being planned or implemented as national initiatives in Spain (Baraniuk, 2020), Australia, (https://www.abc.net.au/news/2020-04-17/australia-to-test-sewage-for-coronairus-as-testing-net-widens/12156858) and Great Britain (https://metro.co.uk/2020/05/11/boris-suggests-sewage-will-monitored-coronavirus-12687732/). However, there is not yet sufficient evidence for environmental surveillance to be recommended as a standard approach for COVID-19 surveillance (WHO, 2020(b)).

In Italy, the presence of SARS-Cov-2 RNA in wastewater was first detected in a study by the Istituto Superiore di Sanità (ISS) in urban wastewater samples from the cities of Rome and Milan collected between February and April 2020. Of particular significance, was the positivity found in the wastewater of Milan dating back to samples collected on 24 and 28 February 2020, when the cases notified in Italy were still few (La Rosa et al, 2020(c)). This result highlighted the importance and sensitivity of environmental surveillance in detecting the presence and circulation of the virus in the population by shifting the focus from the individual to the community. The positivity detected in the purification plant in Rome, however, dates back to the end of March-early April 2020, in the middle of the epidemic period in which over 3,000 cases were confirmed in the Lazio region, 2,000 of which in the metropolitan area of Rome. These results led to the analysis of 40 samples of archive waste water collected in northern Italy in the pre-epidemic period (between October 2019 and February 2020), from which it emerged that in Italy (or at least in northern Italy) COVID-19 is disseminated well before the identification of what has been called “patient 1” (21 February 2020): 15 of the 40 samples were positive to the test and the presence of SARS-CoV-2 RNA was detected in samples taken in December 2019 in Milan and Turin, while in January 2020 in Bologna (In most positive samples was found an amount of RNA of the order of 102-103 g.c./L). In all samples before December 2020, as well as the "blank" samples taken between September 2018 and June 2019 (before the Emergence of SARS-Cov-2 as a human pathogen), no traces of SARS-Cov-2 RNA were detected. The results therefore confirmed the usefulness of this type of analysis as well as evidence of early detection about the spread of the virus among the population (La Rosa et al, 2020 (b)).

In view of this evidence, the ISS, which with Ordinance No. 640 of 27 February 2020 was charged with coordinating a surveillance system that integrates microbiological and epidemiological data provided by Regions and Autonomous Provinces (APs) and the National Reference Laboratory for SARS-Cov-2 of the ISS and strong of the fact of having within it the Department of Health and Environment that since 2007 collects urban wastewater for the research of enteric viruses within different projects, decided to integrate environmental surveillance with epidemiological surveillance methods in order to have a more complete understanding of trends in community transmission. The ISS, which in 2011 established a permanent sentinel system for enteric and non-enteric viruses in Italy, added SARS-Cov-2 to the surveillance list in March 2020. In the recent document of the Ministry of Health "Prevention and response to COVID-19: evolution of strategy and planning in the transition phase for the autumn-winter period" (https://www.iss.it/documenti-in-rilievo/-/asset_publisher/btw1J82wtYzH/content/prevention-and-response-to-covid-19-evolution-of-strategy-and-planning-in-the-transition-phase-for-the-autumn-winter-season.-english-version), the environmental surveillance of SARS-Cov-2 through urban wastewater is recommended in order to gain insight into epidemic trends and contribute to the development of an early warning system, in line with recent European preparedness recommendations to address the COVID-19 outbreaks(https://ec.europa.eu/info/sites/info/files/communication__short-term_eu_health_preparedness.pdf).

The development of a system for the research of Sars-Cov-2 RNA in urban wastewater (La Rosa et al, 2020a, La Rosa et al 2020b), and the availability of many health and environmental control facilities, allowed to propose to the Ministry of Health, in summer 2020, an epidemiological surveillance project of SARS-COV-2 through urban wastewater (Environmental Wastewater Surveillance in Italy, SARI) coordinated by ISS, which, through the Interregional Coordination of Prevention, Health Commission, Conference of Regions and Autonomous Provinces of the State-Regions Conference, proposes an environmental surveillance activity for SARS-Cov-2, modelled on the Wbe. In order not to lose valuable information during summer months, it was started on 30/6/2020 with a dedicated webinar organized by ISS, a first pilot phase lasting about 3 months (July-September), through the voluntary participation of Regional Environmental Protection Agencies (ARPA), Local Health Authority (ASL), Experimental Zooprophylactic Institute (IZS), Universities and Hydro-potable Managers, for SARS-Cov-2 research of in urban waste water, with the most ambitious objective of building a structured national surveillance network to integrate the clinical instruments of control on the territory (screening with buffers and serological tests) with the environmental control (La Rosa et al, 2020(a)). A national surveillance activity may be able to provide important information in different areas during the epidemic and post-epidemic period. During the **epidemic period** it will be able to provide information on the spatial and temporal circulation of the virus in the population that can give important indications on the evolution of the epidemic trend (growth phase, steady phase, degrowth phase, exhaustion). The production of qualitative data (virus presence/absence and gene sequencing of positive samples) shall be accompanied by quantitative information (virus concentration data in the effluent, expressed as genomic copies per waste volume, c.g./L) by which it is possible to calculate indirect estimates of the number of individuals excreting the virus. Already several studies on enteric viruses have shown that it is possible to correlate the amount of viral RNA with the number of infected individuals by special algorithms that take into account a number of factors (virus concentration in the feces of infected patients, volume of feces eliminated per day, number of persons connected to the sewage treatment plant, flow rate to the sewage treatment plant, etc.). Sequencing data are also very useful for monitoring possible mutations in the viral genome and for subsequent phylogenetic studies. A stable and active surveillance network during the **post-epidemic period**, is, otherwise, a real early warning system (on the model of environmental surveillance poliovirus) allowing, in the eventual presence of viruses in urban waste water, not only to detect the appearance, but also, in combination with appropriate management actions, to recognize and circumscribe more quickly any new epidemic outbreaks (La Rosa et al, 2020(a)).

As part of the SARI project, as the National Centre for Innovative Technologies for Public Health, our working group was involved with the aim of developing a system based on GIS technology for the centralized collection of data produced by regional authorities, the creation of dashboards for real-time data visualization and for the study of a correlation between environmental data and clinical data for the purpose of providing meaningful information, which may be used to support decisions on more or less restrictive measures, as well as the assessment of the effectiveness of the ongoing control measures.

3 CHAPTER 3 – Materials and Methods

3.1 AR to improve quality of life of elderly people with cognitive impairment

Due to the inevitable decline in cognitive and sensory functions due to age, older people tend to use mental representations to improve memory, particularly short-term memory, to reduce cognitive load. An excessive cognitive burden has a negative influence on decision-making processes as well as on performance.

Augmented reality can be a useful tool to counter the cognitive decline of the elderly. Several studies have suggested that the cognitive load can be reduced by the augmented reality interface (Lee et al, 2005; Quintana and J. Favela, 2012; Wood and Mccrindle, 2013; Boletsis and Mccallum, 2016; Chang et al, 2016; Chandrasekera et al, 2017) precisely because of the characteristics of this technology to improve the perception of the surrounding real world through the overlapping of digital elements (Augmented Object, AO) in real time, without isolating the user from the surrounding physical environment. In addition, an AR system provides the ability to show hidden objects (for example, room behind a door or hidden objects from a door), to warn the user that contact with an object may be harmful (stove, oven, etc.), or to give instructions on how to run a certain task.

So, we developed CogAR, a home-made marker-based Augmented Reality App designed for HMDs for augmented reality (also called **smart glasses**), to monitor and support people who are affected by both mild age-related cognitive decline and sensory impairment in an unobtrusive manner (Rossi et al, 2020a; Rossi et al, 2020b). The proposed instrument is mainly aimed at individuals living alone (about one third of all people with dementia live in their own homes), who are considered to be a particularly vulnerable group, most in need of social care, environmental, psychological and medical. CogAR presents itself as a useful tool to provide more independence to older patients during actual ADL and in navigating their home - but also away from home - notifying users of useful information or potentially dangerous situations through appropriate cues in real time, with the aim of restoring, albeit partially, autonomy and independence to the elderly, so as to provide an opportunity for such individuals to continue their life at home for as long as possible before they need to move to a reception facility.

3.1.1 Experimental set-up

In recent years, efforts to develop software and hardware for AR have increased considerably, so much that today there are many devices for this technology. Some of them are already well developed, others are still under development and need more time to reach their more mature stage. A first big division sees these augmented reality devices divided into two macro-categories: wearable devices (headsets; smart glasses; helmets and in the future also contact lenses) and non-wearable devices (smartphones, tablets, PCs). A further subdivision is based directly on the device type used. The augmented reality experience can be done on devices specially designed for this purpose, or on other types of devices not specifically designed for this purpose (in this category we find more non-wearable devices). Smart glasses are perhaps the most popular type of device for augmented reality, as they allow the visualization of the digital information projection before our eyes, without losing the communicative contact with the surrounding environment. For this reason, we have chosen smart glasses as a hardware device for our purpose.

3.1.1.1 Hardware

Among the products available on the market, we selected the Epson Moverio BT-300 (Fig. 1) mainly for the lightness of the device (about 70 grams), compatibility with the latest standards of wireless connectivity (Bluetooth, Wi-Fi and Miracast), the possibility of being worn with eyeglasses thanks to nose pads and flexible rods and the accessible cost to a large part of the population (the price is around 1000 euros).

Fig. 1 – Epson Moverio BT-300: selected hardware for the study.

Moverio BT-300 smart glasses use Epson’s innovative silicon-based OLED (Organic Light Emitting Diode) digital display technology, which makes it the lightest OLED-enabled binocular viewer on the market (compared to data reported on the websites of competing companies that offer devices with similar characteristics). HD display (720p) and high brightness ensure crisp images and bright colors.

The front camera (Fig. 2 and Fig. 3) offers a first-person view, while the binocular view provides a more natural view and a better field of view of the surrounding environment.

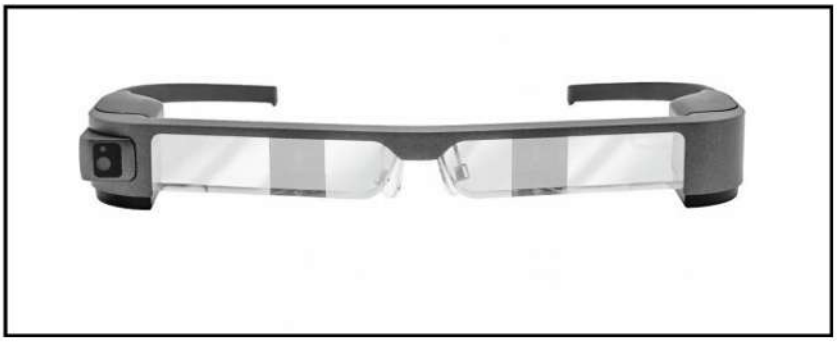


Fig. 2 – Epson Moverio BT-300: frontal view of the headset.

Fig. 3 – Epson Moverio BT-300: back view of the headset.

The controller has an input function (Fig. 4) and contains a 2950mAh lithium polymer battery with a power consumption of less than 20 Watts/hour that guarantees a range of up to 6-8 hours and can therefore be used for extended periods of time.

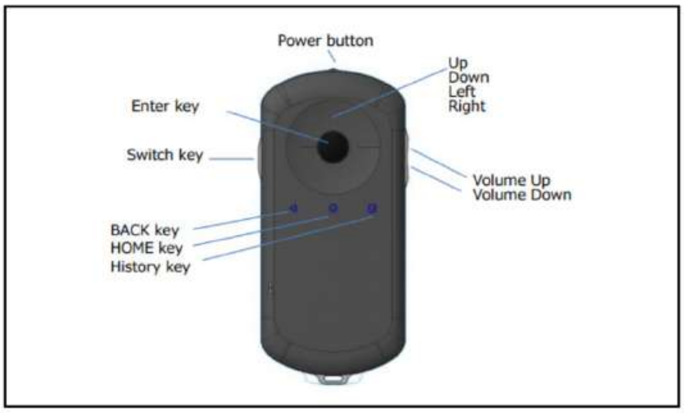


Fig 4 – Epson Moverio BT-300: The controller.

Finally, the Moverio BT-300 is equipped with numerous sensors integrated into the headset and/or controller, including GPS, accelerometer, gyroscope, and geomagnetic sensors (Fig. 5).

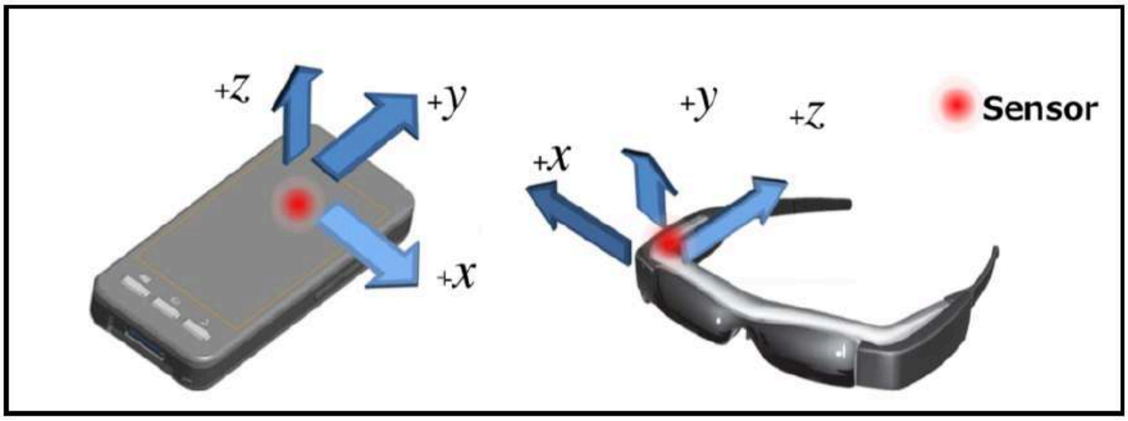


Fig 5 – Position and axes of inertial sensor

3.1.1.2 Software

Moverio BT-300 adopted Android as its software system. It is therefore possible to develop Apps for the BT-300 in the same environment as for Android smartphone apps. However, since it applies its own functions, it is necessary to control via the EPSON Application Programming Interface. In some cases, the Android or App emulator that works with Android smartphones may not be executable on the BT-300.

For the software development of the configured Apps for the BT-300 we used Unity, a complete development environment, even in its free version, for all those vital aspects of an App (graphic rendering, light effects, physical simulations, audio implementation, network functionality and a scripting system) which offers the ability to export apps to many platforms, including all desktop operating systems, almost all mobile ones (iOS, Android, Blackberry) and for the main gaming consoles (Wii, PS3, Xbox). The creation of an account, also free, will allow access to the Asset Store, or an online market where you can buy (or download for free) scripts, characters, 3-D models, sound effects, materials and more to use in the App. Together with Unity, MonoDevelop is also installed, which is a useful software used to create and edit scripts to be connected to the objects in the scene in order to manage their behavior and interaction with and between them aiming to add interactivity components. The programming language is C# (Csharp), an object-oriented language developed by Microsoft.

In addition, the "Moverio BT-300 Unity Plugin" package is available free of charge in the Unity Asset Store, which is very useful in creating the AR App for Epson Moverio BT-300

Smart Glasses. The plugin allows developers to choose and upload specific 2-D images or 3-D models that will act as markers. Through Unity it is possible to associate each of these markers with an AO, positioned close to the marker, which can be represented by a customizable image, text or multimedia content (audio or video).

3.1.2 CogAR: an AR App to support elderly people during ADL

CogAR is a marker-based AR App designed for smart glasses to improve the quality of life of people who are affected by mild cognitive impairment and mild sensory disabilities. To run it, requires only an Android device equipped with a camera and an audio output, the Moverio BT-300 in our studio, and markers, to which, during programming, have been associated with the Augmented Objects.

During the development of CogAR we thought of solutions to make the home a safer environment, following the indications of the National Institute on Aging (USA) (NIA, 2017), for a better management of the behavior of fragile subjects, such as the loss, wandering and agitation, which cannot be managed medically. To make the domestic environment safer, they suggest different measures depending on the stage of the cognitive decline of each individual. In general, the following solutions are recommended:

- Place the phone number of the caregiver and emergency near all the phones.
- Use brightly colored signs or evocative images to label the various rooms in the house.
- Place signs next to the taps, indicating that of cold water and especially hot water, and household appliances that overheat (oven, toaster, etc.).
- Remove cabinet and sideboard doors and chests of drawers, replacing them with transparent doors.

When the user wears the glasses and runs CogAR, he can experience the surrounding real-world environment through the projection on the device display of the images captured by the camera, always active while the application is running, and processed via software (Fig. 6). As illustrated in Figure 6, in the upper part of the display we have placed the essential contacts for the user (police telephone numbers, ambulance and caregiver), so that they are always at hand and well visible in case of need.

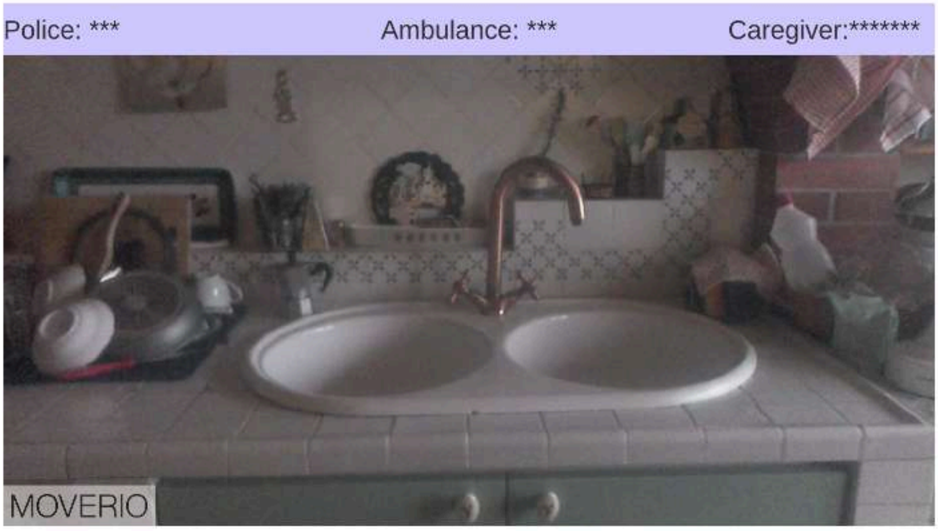


Fig. 6 - The view by the smart-glasses. The picture is a screenshot of the smart glasses display.

Thanks to the GPS technology, integrated in the device, the user can share with the caregiver information about his location in real time. In addition, by means of a free-available screen mirroring App on Play store "Wi-Fi-Display (miracast) sink" you can share the user's field of view on another Android device, thus enabling the caregiver or therapist to monitor the activity that the user is performing and above all having the possibility to monitor it remotely, giving the ability to check patient's activity at any time from his/her smartphone and therefore being able to quickly identify potentially dangerous situations. These functions are essential to reduce the wandering problems associated with patients with cognitive decline, who very often suffer from hypertension and therefore feel an irresistible need to walk away from their home but soon losing orientation (Sposaro et al, 2010). In addition, it is possible to set timed messages (similar to the Smartphone Clock App) in the form of text, image and/or audio files, customizable according to user's needs with the purpose of remembering, for example, the intake of a drug or if the user remembered to perform a certain activity.

For the augmented reality part of CogAR, we have prepared a set of images, to be placed near the physical object to which each refers, that act as a marker. Each image has been associated with one or more AO, programmed based on the needs of the individual who will use it. In the following figure (Fig. 7) are represented some CogAR programmed markers. It is noticeable that, in some of the cases, we have chosen images as markers that make it easy to intuit the object on which they must be placed and the nature of the message of the AO.

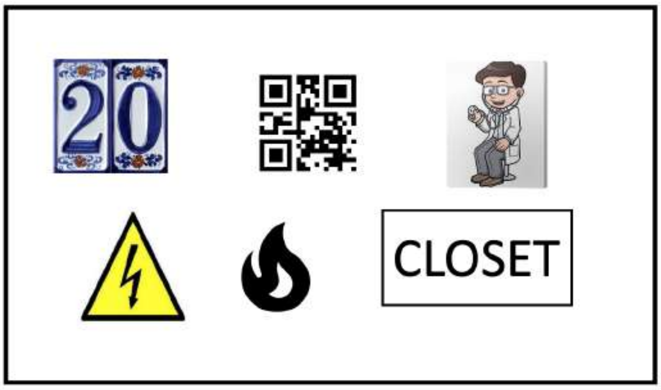


Fig. 7 - Examples of 2D images that represent the markers used in CogAR.

With the App running, the user can perform without any hindrance the daily activities as he is used to do. The augmented information is presented only when a marker enters the device cameras' field of view. When the camera recognizes an image, the AO associated with it is shown to the user in such a way to not obstruct the entire field of view. To notify the presence of an AO, simultaneously with the presentation of text and digital images, the controller also provides tactile feedback and an audio message is played. So, in case the smart glasses identify or receives messages of potentially dangerous situations, the controller starts to vibrate, and the smart glasses speaks a related text loudly. As Represented in figure 8 the smart glasses say: "Alert" followed by the type of danger.

Fig. 8 - Thanks to the headset audio output you can send voice messages to the user.

Let us now look at some explanatory examples of how CogAR works.

In this first example, the marker is an image that represents a house number, to be placed on the user's door. As long as the marker is out of the camera's field of view, the user perceives only the information of the physical reality (as if he was not wearing the smart glasses) (Fig. 9). When the marker is recognized, around it is shown the AO defined in the programming phase with the aim of providing support to the user in recognizing their home door. The AO (Fig. 10) in fact has the objective to bring back to the user's memory the information about their home, such as the image of their living room, their pet and an explicit written message, as well as the reproduction of an audio file.

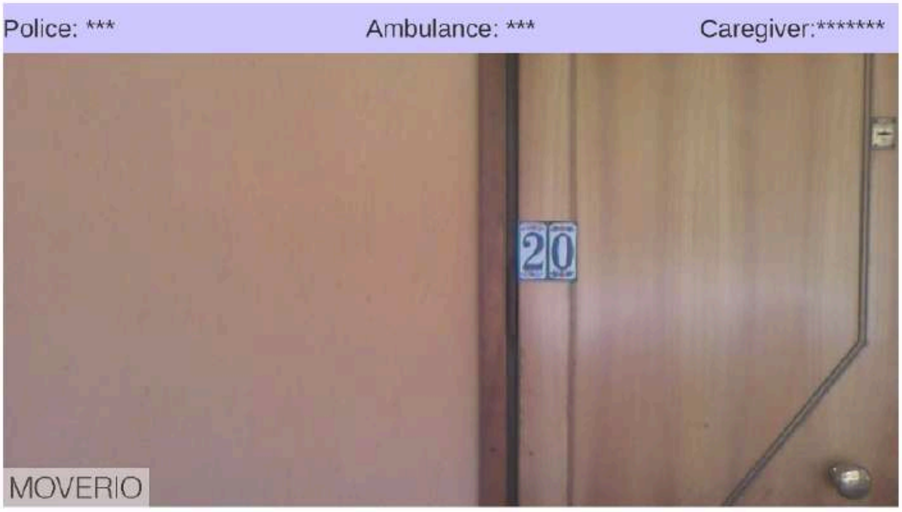


Fig. 9 - The image shows the vision through the transparent lenses of Moverio BT-300 when the marker is too far to be recognized.

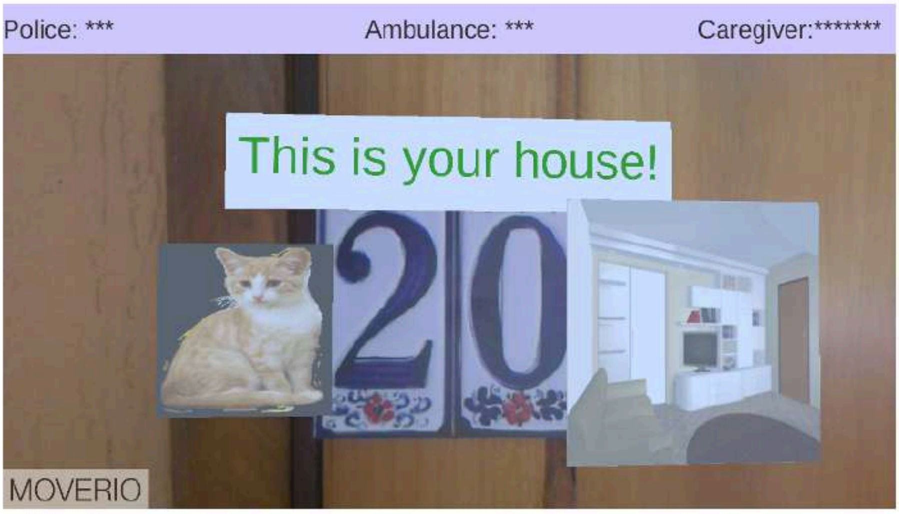


Fig. 10 - When the user looks at the marker, through Moverio BT-300, information that recalls his/her own home is shown.

In this case the marker is represented by the image of a doctor, designed to be applied on a drawer of the nightstand used as a medicine cabinet and in which the user retains what concerns his health. So, when the marker enters the camera's field of view, the AO such as for example recipes and medicines are triggered and the contents of the drawer is presented to the user without having to open it.

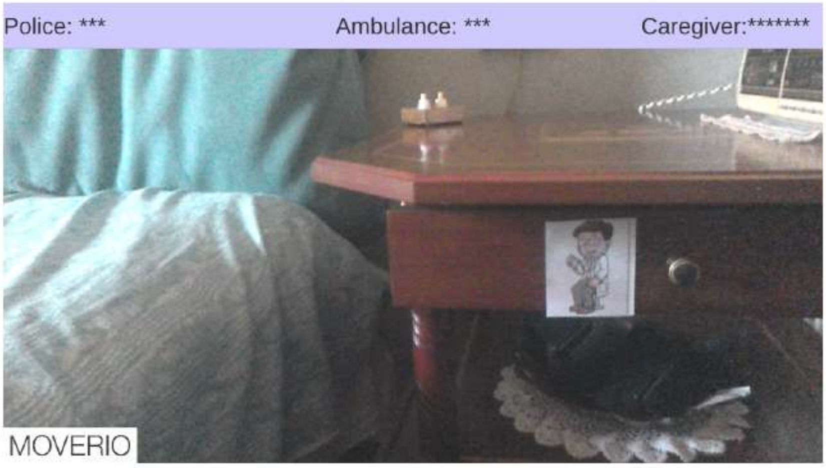


Fig. 11 – The marker is applied on the bedside table where the user keeps the medicines.

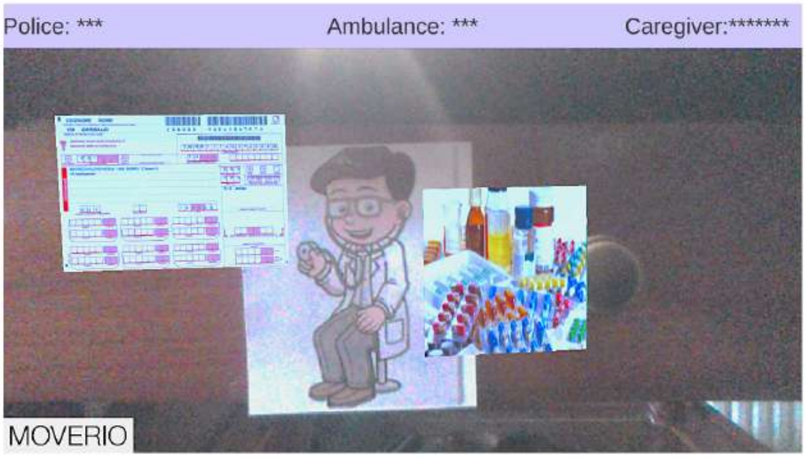


Fig. 12 – The view through the HMD when the user looks at the marker that shows the contents of the drawer.

Here are two additional examples on the use of markers with the aim of making the home safer by limiting the number of non-necessary activities to complete a certain action, showing what is hidden behind a door (Fig. 13) or the contents of the cabinet (Fig. 14).

Fig. 13 - On the left we have the marker (the label with a written closet) placed on the cabinet door; on the right is illustrated the Augmented Object associated with it.

Fig. 14 - On the left image the marker is represented; in the right image, the augmented object shows the room behind the closed door.

Within CogAR, it is also possible to develop Serious Games with the dual purpose of the so-called, intelligent entertainment and at the same time, test and solicit the cognitive functions of the individual. For example, we have implemented a game that consists of a first phase of learning/reviewing some general culture information during which, on the Moverio BT-300 display are presented to the user 10 researcher-discovery pairs in sequence. In the second step the user must answer 10 questions in which an element of a pair is presented with three answers, among which the user must select the correct one. This second phase can be chosen between two types depending on the skills of each individual user:

1. Purely cognitive exercise: in this case an image is shown on the display and the user must select the correct answer.
2. Cognitive + physical exercise: in this case the user must move in the surrounding environment to locate one of the images of the 10 pairs that act as a marker. When the camera recognizes the marker, 3 Augmented Objects are shown representing three answers options among which there is obviously the right choice (Fig. 15).

After the second phase of the game, on the display of the glasses appears a screen with the score obtained by the user, calculated according to the number of correct answers and the time taken to complete phase 2. In this way it is possible to draw up a ranking of the scores in which users can challenge themselves or other users in order to increase engagement and it is also possible for the caregiver or the therapist to analyze the performance over time in order to identify trends associated with the course of the disease.

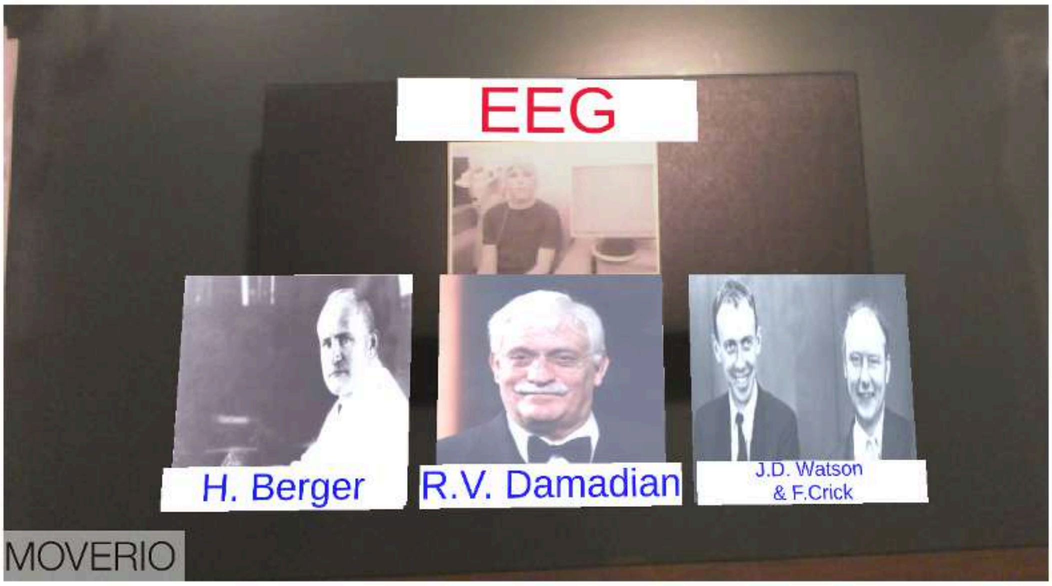


Fig. 15 - The marker is represented by an image illustrating a recording of brain activity (EEG). The three augmented objects show three researchers, among whom the user must indicate who invented the electroencephalogram.

3.2 A MR application for people with both verbal and motor disabilities

People with speech disorders must use technologies that can replicate the word, such as speech synthesizers, to communicate. If motor disabilities are added to such disturbs, for the subjects, the traditional instruments of input do not turn out effective and it is therefore necessary to adopt/to adapt existing technologies or to develop new ones on the basis of each particular necessity. For these patients, the only solution is often the use of Assistive Technologies that use as an input an eye tracking technology tool associated with text-to-speech (TTS) technologies.

Most of these systems require the placement of a screen between the two interlocutors, which reduces, if not eliminates, the non-verbal component of communication. This barrier can be overcome with Augmented Reality and Mixed Reality (MR) technology, thanks to the ability to display information on Head-Mounted Display (HMD) see-through holographic lenses, only partially reducing the view of the surrounding physical environment (e.g. Wolk, 2019).

We have therefore developed a system of Augmentative and Alternative Communication (AAC), designed for children, able to detect the user's gaze and translate it into an input for a HMD of Mixed Reality with the aim of allowing the user to carry out activities that he alone could not accomplish, in particular a conversation (Rossi et al, 2020c).

Specifically, the App provides for the interaction of the user's gaze with a digital table containing several selectable elements projected on the HMD display. Thanks to text-to-speech (TTS) technology, the user selection is transduced to an audio output.

3.2.1 Experimental set-up

3.2.1.1 Hardware

For the AAC system we have selected HoloLens, a wearable and autonomous device designed and developed by Microsoft, which uses the latest and most advanced technology of Mixed Reality (MR).

HoloLens (Fig. 16) is a head-mounted display unit equipped with transparent holographic lenses that use an advanced optical projection system to generate colored multidimensional holograms (Augmented Object, AO) with a very low latency that are completely immersed in the environment and belonging to the real world.

Fig. 16 - Microsoft HoloLens: the hardware of the AAC system proposed.

HoloLens works exactly like a computer, except it's a holographic computer. Once logged in, a main menu is projected on the HMD lenses, from which you can launch the photo or video camera, access the menu with all the Apps and run the chosen one, etc. The device can be worn by all, thanks to an adjustment wheel placed on the back of the headband, which allows you to tighten or widen the circumference; it is rechargeable via a microUSB port, and can also be used during the charging period; the declared weight is 579 grams.

Analyzing the technical details, HoloLens is an extremely powerful device: it does not need wires nor an always connected computer, so it is a totally independent device; the operating system is Windows 10; it is equipped with a 16.5Wh battery, CPU and GPU, 2GB of RAM and 64GB of memory; Wi-Fi and Bluetooth technologies to connect to the internet and with any device respectively; Bluetooth Low Energy technology to connect to the *clicker* (Fig. 17), a button-shaped accessory provided by Microsoft to facilitate the selection, scrolling and moving of interactive elements.

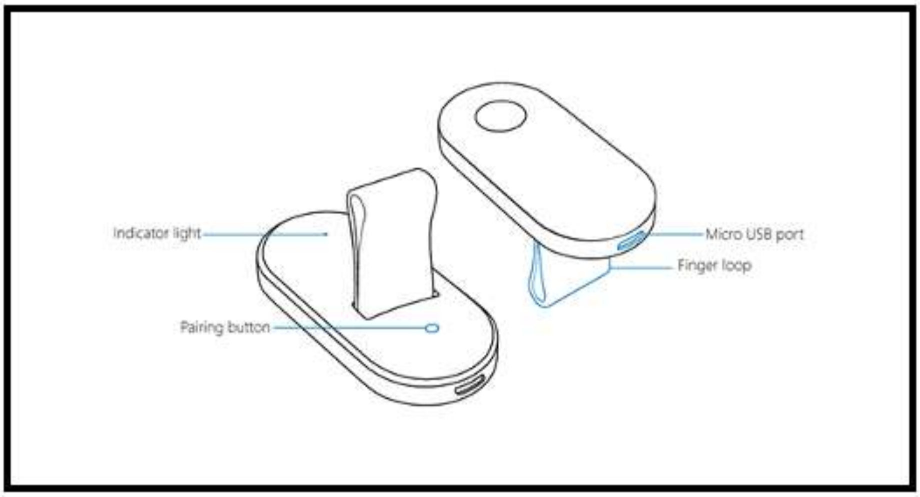


Fig. 17 -The clicker: a kind of input device for HoloLens.

One of the strengths of HoloLens consists in the ability to analyze the world that surrounds it (Fig. 18): using spatial mapping techniques is able to acquire information about the real space around the user and to identify plans (tables, floors, walls and ceiling) and/or any obstacles. Information about the physical world is captured at any time continuously by the device, making a real mapping of space. In this way a completely realistic rendering of the surrounding environment can be obtained within which interactive holograms representing real objects or interactive digital contents of another kind can be placed. To perform this function Microsoft has integrated in HoloLens several sensors (Fig. 19): an Inertial Measurement Unit (IMU), consisting of an accelerometer, a gyroscope and a magnetometer; four cameras, two on each side, which act as sensors "understanding the environment"; an energy-efficient depth camera with a 120° inch x 120° inch angle of view; a 2.4-megapixel photographic video camera; an ambient light sensor; an array of four microphones; two speakers (one per side) at ear height (Microsoft, 2017).

Thanks to the integrated sensors in HoloLens, a user can place the AOs in the surrounding environment. Such holograms can be fixed in a determined position of the space (*pinning*) or can be placed in relation to the position of the user so that they can follow him during his displacements. Thanks to the techniques of spatial sound synthesis, the user can hear the sound effects associated via software holograms.

Fig. 18 - Example of mapping of the surrounding environment performed by HoloLens.

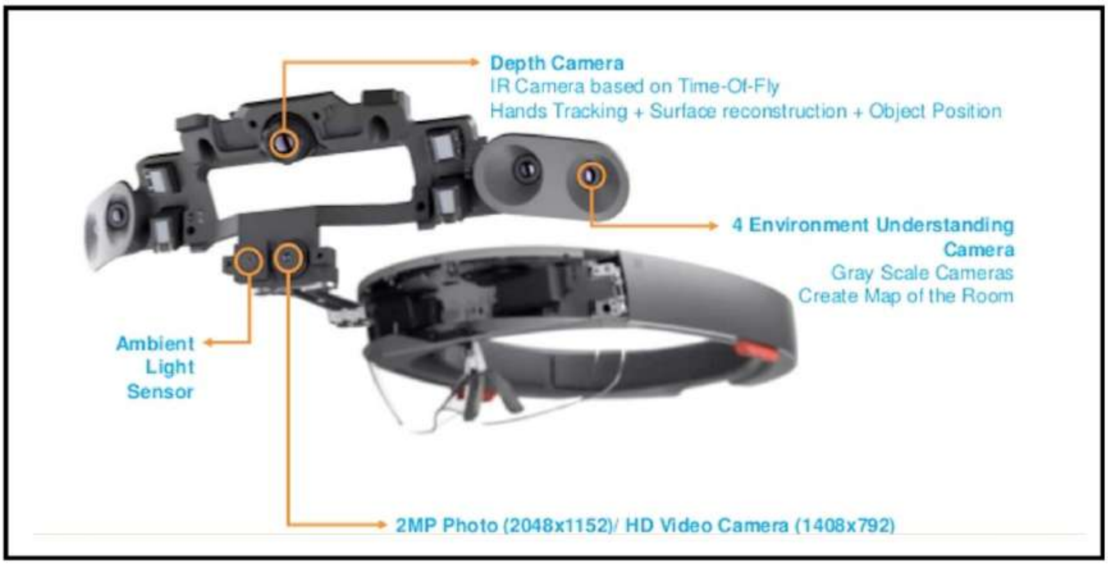


Fig. 19 - HoloLens: built in sensors.

The user's interaction with the AO must be as natural as possible, so HoloLens allows four different types of interaction. In fact, holograms respond to *clickers*, voice commands, hand gestures and gaze direction (https://docs.microsoft.com/en-us/windows/mixed-reality/design/design).

- ***Clicker***: A physical button-shaped controller connected via Bluetooth can be used to select and move AOs.
- ***Voice commands:*** it is possible to program voice commands with the purpose of giving instructions to the application and interact with the AO.

- ***Hand gestures***: some hand movements executed according to a precise sequence are recognized by the sensors of the device and then processed to perform the action associated with them during development. To date, HoloLens recognizes two movements: the first "ready state" in which the hand is closed with fist turned forward (Fig. 20(a)); the second is defined "pressed state" and is given by the hand closed to fist, with the index lowered forward (Fig. 20(b)). The combination of these two movements allows you to perform various actions, including *clicking*.

- ***Gaze direction***: Eye tracking is crucial in the use of HoloLens since it acts as a *pointer*.
  Technically, the integrated sensors only trace the orientation and movements of the head (meaning there is no trace of the eye), so based on the position and movements of the head detected by the helmet, it will change the identified direction and then the position of the cursor. To identify the user's gaze, a ray casting is performed, that is, an imaginary line is drawn in the direction specified by the person (just like a laser beam). The cursor is fixed and clearly visible so that the user is able at any time to clearly recognize the object identified by the gaze on which the actions will be carried out.

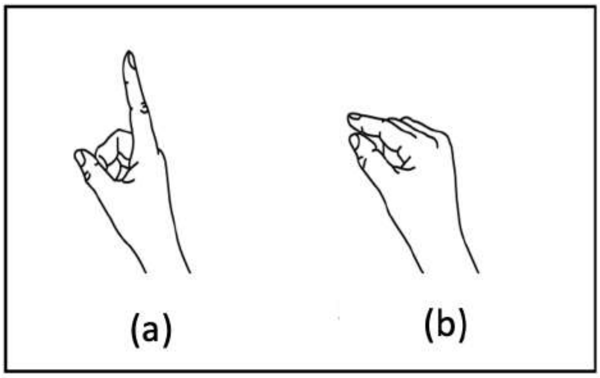


Fig. 20 - On the left (a), the position of the hand in the "ready state"; on the right (b), the hand is in the "pressed state" position.

3.2.1.2 Software

At the time of its introduction into the market (2016), HoloLens boasted of being a wearable computer, thanks to the computing power that made it perform at the level of a Windows 10 computer. Before starting to talk about development, it is important to point out that Microsoft provides a number of web resources that present an overview of the technology, including a page to download the software needed to develop Apps for HoloLens (Visual Studio, the Mixed Reality Toolkit, etc.) (https://docs.microsoft.com/it-it/windows/mixed-reality/develop/install-the-tools?tabs=unity). Particularly useful was the distribution of the Windows SDK together with Mixed Reality Academy (https://docs.microsoft.com/it-it/windows/mixed-reality/develop/unity/tutorials), a set of detailed online tutorials with corresponding project files to approach and familiarize with the features of Mixed Reality, and the deployment of an emulator to test some features of the MR Apps even in the absence of a physical HoloLens device.

In order to develop a Mixed Reality App for HoloLens a machine with the following system requirements is needed:

- Windows 10 Pro, Enterprise, or Education Edition
- 64-bit CPU
- CPU with 4 cores (or multiple CPUs with a total of 4 cores)
- 8GB of RAM or more
- Hyper-V support to run virtual machines in Windows
- Visual Studio Community Edition, a free and fully featured integrated development environment, integrated with full Windows capabilities to write code, and run debugging, testing and deployment.

Any application supported by the Universal Windows Platform (UWP) can be run on HoloLens (or on the emulator). An application for HoloLens is a holographic representation of the contents that exploits all the basic principles of the technologies integrated in the device, that is dealing with space management, actions to be carried out when a gesture is recognized and to keep track of the position and direction of the gaze.

Thanks to an agreement between Microsoft and Unity, a dedicated plugin "Mixed Reality Toolkit" (MRTK) was made available, which allows to manage the features of HoloLens, without the need for extra SDK in a way consistent with other Unity APIs. MRTK provides support for setting up a Mixed Reality Unity project and a set of features to accelerate your development process:

- Provides the multi-platform input system and the elements constituting the user interface and interactions.
- Allows rapid prototyping through simulation in the editor which allows to immediately see the effect of changes.

- It works as an extensible framework that gives developers the ability to replace the main components and modify their features through scripting.

Through Unity and MRTK it is possible to develop Apps in which augmented objects, or holograms, can also be characters available for free in the Unity Asset Store. Thanks to Visual Studio it is possible to modify the behaviors and functions of the AO through scripting, using the programming language C#.

3.2.2 A MR App to communicate through the gaze

Most systems that make use of eye focus to produce text (*eye-typing*) are implemented to show the user an on-screen keyboard (Majaranta & Rih, 2002). A valid alternative may be to provide the user with preset sentences rather than having to compose a sentence letter by letter. This choice reduces the time needed to construct a sentence of complete meaning, even if on the other hand it limits communication. For people with disabilities, especially children or people with diseases developed in the childhood, the use of pictograms and/or ideograms (symbolic images that express a concept through a graphic resemblance to a physical object) has a higher potential (Borgestig et al, 2016(b); Wolk et al, 2017). For these reasons and because the App is designed primarily to be used by children, we opted for the implementation of a solution that uses pictograms and ideograms.

The system we have proposed (Rossi et al, 2020c) is an App developed for HoloLens that, by using eye tracking technology and TTS technology, it acts as a communication tool. The developed system allows users to have face-to-face conversations, improve social relations and express their personal potential only by choosing specific digital elements that use eye-gaze only.

Fig. 21 shows the screen projected on the HoloLens display when the App is executed and acts as Home Page. Thanks to the "pinning" function and the HoloLens sensors that detect the user’s position, the board always remains in the user’s field of view following his head movements.

(a) (b)

Fig. 21 – (a) The figure shows the user view when the App is running. (b) The home page of the App: on the top right an icon (lock) is displayed that blocks the App; the four central icons allow to open the related sub-menus; The bottom two icon (Yes or No) give the specific vocal answer.

The white point visible in the center of the image in Fig. 21 (b) is the pointer, that is the projection of the position in which the user is looking. At any moment, then the user has feedback on where he is focusing his gaze thanks to the always present pointer on the display.

The table presented to the user contains 7 elements with which he can interact by focusing his gaze on one of them and then activating the function assigned to each one respectively in the programming phase:

- The icon representing the lock (on the right of the written word MENU) has the function to block the selection, that is deactivating the interactivity of the elements, in order to avoid false detection at the moment in which the user does not need/desire to communicate;
- The two icons at the bottom (representing the thumb upwards and the thumb towards, left and right respectively) have the function of activating the speech synthesizer and respond in an affirmative or negative way.
- The icon on the top left shows the communication between two individuals and has the function of opening a submenu in which there are new icons to each of which is associated with a preset phrase that, once activated, it will be read by TTS technology allowing to have a conversation (Fig. 22);
- The icon with the image of the kitchen, as guessable allows the access to a submenu containing phrases related to food needs (Fig. 23).

- In the case of the icon representing the bathroom, the associated submenu contains phrases associated with the needs related to the bathroom and cleaning (Fig. 24).
- The icon with the bell has the function of calling for attention. When activated, the device emits a sound and a submenu with phrases is opened which is related to discomfort the user needs to communicate at that given time (Fig. 25).

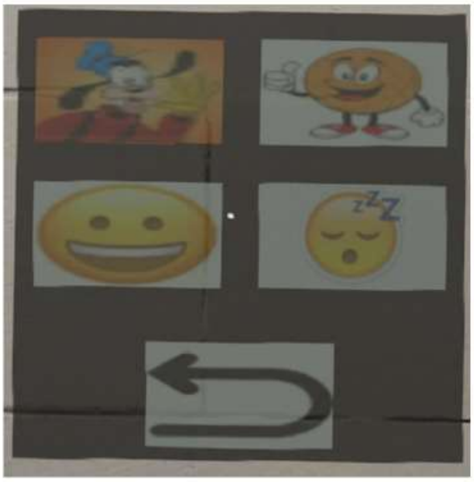


Fig. 22 - The figure shows the submenu that opens when the communication icon is selected. Starting from left to right, from top to bottom true: (a) when activated, HoloLens pronounces a presentation phrase; (b) the triggering phrase is "I am fine thanks. And you?"; (c) the related phrase is "Today I feel good"; (c) "I am tired, I need to rest". The bottom button returns the user to the Menu screen

Fig. 23 - The figure shows the submenu that opens when the communication icon is selected. Starting from left to right, from top to bottom true: (a) when activated, HoloLens pronounces "I am hungry"; (b) the triggering phrase is "I am thirsty"; (c) the related phrase is "Can I have pizza?"; (c) "I would like some juice". The bottom button returns the user to the Menu screen

Fig. 24 – The figure shows the submenu that opens when the communication icon is selected. Starting from left to right: (a) when activated, HoloLens speak aloud "I need to go to the toilette"; (b) the triggering phrase is "Excuse me, where is the toilette?". The bottom button returns the user to the Menu screen

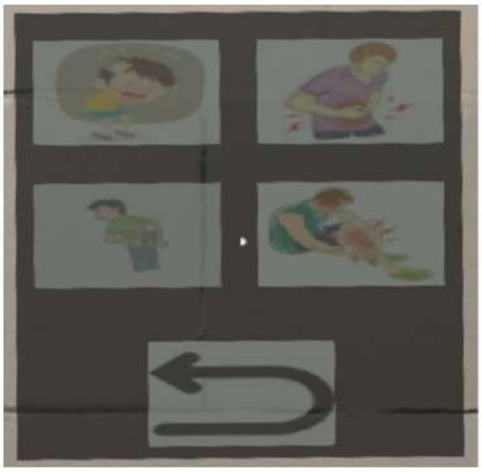


Fig. 25 – The figure shows the submenu associated with the bell of the main screen. Each icon allows to indicate in which part of the body the subject is feeling discomfort/pain: whether to the head (a), stomach (b), back (c) or legs (d).

The selection of an element can take place in two different ways based on the input used established according to the residual motor skills of each individual subject. If the user has enough motor skills to use the *clicker*, the selection goes through two steps: looking at the element so that the pointer overlaps; pressing the *clicker* button to activate the relative function. If otherwise the user does not have the possibility to use the *clicker*, the direction of the look will have the double function and the selection of the element will go through three phases, designed to minimize false selections:

1. When the cursor crosses an element, a visual feedback is automatically given, represented by the appearance of a word at the element describing its function (Fig. 26 on the left).

2. If the cursor remains on the element, that is the duration of the permanence of the look (dwell time), for more than 1 second another visual feedback is given to the user (the color of the word superimposed on the element changes from white to green) (Fig. 26 to right).
3. If the look remains for 1 second from the moment the word has become green, the element is considered selected and the associated function is performed.

Fig. 26 – The figure shows a comparison between the icons previous the selection. On the left, white word, is displayed on the icon for cursor pointing for less than 1 second; on the right, green word, for cursor pointing between 1 and 2 seconds from the instant which the cursor and the icon are overlapped.

The choice of dwell time durations fell on the 1 second period because we believed it can be a good trade-off between communication speed and selection errors. The dwelling time has been fixed starting from the consideration that usually when an element attracts our attention, the look remains fixed for a short time (200-600 ms) (Majaranta et al, 2006). If on the one hand fixing a long-time interval allows to prevent false selections, on the other, it becomes uncomfortable for users and it sets an upper limit to the typing speed (Stampe and Reigold, 1995).

The lack of feedback to the user on the detection of a certain event can generate errors, such as repeating the same function several times or causing the selection of an unwanted element, especially because the technology is designed for disabled individuals, who very often have never had full control of anything (Majaranta & Raiha, 2002). In addition, interaction with graphical user interfaces improves if sound feedback is provided (Gaver, 1989). To try to minimize the number of errors and make the system as comfortable as possible, we chose a combination of visual feedback (the appearance of a word that subsequently changes color) in addition to a feedback sound (each selection is associated with a certain phrase that thanks to the speech synthesizer is read aloud).

3.3 GIS systems to monitor situation during pandemic period

During an epidemic, it is essential to have an overview of the situation in order to analyze the situation. For the monitoring of the temporal and spatial evolution of the diffusion of a certain pathogen, a technology that can integrate information of various kinds with information of geographic nature is fundamental: Geographic Information System (GIS). The integration of geographic data with other types of data and their organization in information/visualization layer using Maps, provides real-time operational awareness helping to improve the efficiency and safety of workers and citizens (ESRI, 2020).

3.3.1 Geographic Information System (GIS): Esri

A GIS system reveals insights on data by returning schematics, reports, and graphs that help users make decisions. In particular, it allows:

- Identify problems
- Monitor changes and understand trends
- Managing and responding to events
- Forecast
- Prioritize

The reference company in Italy for geospatial solutions, geolocation and GIS is Esri Italia, an integral part of the Esri One Company system that has over 80 international companies operating in networks in over 200 countries (https://www.esriitalia.it). Esri uses a WebGIS system that allows to manage and organize all aspects of an organization. The default accuracy levels of most location collection technologies today create datasets that fall under privacy and compliance regulations. Esri values the privacy of its customers, distributors, and partners, as it is a principal component of establishing trust. Esri has created a general company Privacy Statement (https://www.esri.com/en-us/privacy/privacy-statements/privacy-statement) and a separate Products & Services Privacy Statement Supplement (https://www.esri.com/en-us/privacy/privacy-statements/privacy-supplement) to ensure that customers receive the level of privacy they deserve and expect. These privacy statements describe how Esri collects data and uses information provided to us and are independently validated. Esri complies with the

EU-US Privacy Shield Framework (https://www.privacyshield.gov/Program-Overview) as set forth by the US Department of Commerce regarding the collection, use, and retention of personal information transferred from the European Union, Switzerland, and the United Kingdom to the United States. Esri's location tracking software and services allow customers to comply and fulfill the regulatory requirements of the General Data Protection Regulation and California Consumer Privacy Act (https://www.caprivacy.org). Esri has a Data Processing Addendum (DPA) available for signing that sets the conditions related to privacy, confidentiality, and security of personal data associated with online services and maintenance that we provide to customers under a master agreement. A major benefit of location tracking services and applications provided by Esri is that customers fully own their data being collected and Esri does not sell or share the data to third parties (ESRI, 2020).

The GIS produced by Esri for the use of geographic data and for their visualization and sharing is ArcGIS Online, the world's largest online geographic resource container that includes maps and data on over 1000 topics, provided as a SaaS (Software-as-a-Service) solution, and therefore accessible anywhere from any device at any time. It is built on open, scalable technology that automatically adjusts to meet peak demand periods. ArcGIS Online is Federal Risk and Authorization Management Program (FedRAMP) Tailored Low SaaS, authorized by the United States government for sharing information with the public. The Privacy Shield certification meets the EU adequacy requirements (ESRI, 2020). GDPR roles for ArcGIS Online are as follows:

- The customer utilizing ArcGIS Online is the data controller.
- The individual to whom personal data relates is the data subject.
- Esri operates as a data processor;
- The cloud services providers are data sub-processors.

3.3.2 ArcGIS Online

Through an ArcGIS Online subscription, organizations can manage all geographic content in a secure Esri cloud-based environment. The ArcGIS Online Platform allows to create, integrate, and share maps, applications, and data, to coordinate the work of people within an organization bringing technological innovation and greatly improving decision-making processes. Administrators of an organization can configure their home page on the platform, set security and content sharing policies, add members to which they assign privileges (users are classified into two macro categories, Creators or Viewers) based on the work they have to do on ArcGIS and also integrate the company's single access system. Members of the organization, depending on their privileges, can use maps to browse data, create and share Maps, Dashboards and Apps from any networked device, as well as publish data as a hosted Web layer. The platform also allows to integrate user's geographical data with those provided by Esri and with those of other users of ArcGIS, whether belonging to the organization or not. The contents (App, Layer, Web Map and Dashboard) can be kept private, shared with other users or in public form depending on the sensitivity of the data treated. In fact, private groups can be configured and only by invitation or public groups open to all.

Let's now look in detail at some of the tools made available by ArcGIS Online used for our purposes, which is the Field App (Survey123), the data collection and data sharing tool (feature layer), the Web Maps for the visualization of the geographic data and the Dashboards for the visualization and the analysis of the results.

3.3.2.1 Survey123

For data collection, ArcGIS provides the *Survey123* service, a simple and intuitive solution for data collection through the compilation of forms. Survey123 for ArcGIS simplifies and streamlines field data collection by replacing paper-based data collection with a more reliable digital solution, available at any time and from any networked device (but also offline) adapting to the needs of field personnel. The strong point of Survey123 is the complete integration with ArcGIS: it takes advantage of the security and information model of ArcGIS and integrates with other Apps.

ArcGIS Survey123 is a complete, form-centric solution for creating, sharing, and analyzing surveys. It is a simple yet powerful field data collection solution that makes it possible to create, share and analyze surveys in three simple steps:

1 - *Ask questions*: Create and publish intelligent modules that support a wide variety of questions from the basic ones: text, date, integer numbers, decimal numbers, single and multiple choices questions, signatures, time, notes, repetitions, photos, barcodes and much more. It is possible to acquire the geographic information of the user: the connection to the device GPS allows to detect the current position of the user, or to select an address or a location, or associate a default location to each user's account. Smart modules also allow to incorporate

advanced logic to control user input: they support calculations and default settings, in which user's own expressions and formulas can be entered; constraints for answers based on previous questions and hide or show questions based on their relevance. The creation of custom modules is possible through the App Survey123 Connect for ArcGIS, it is possible to take advantage of the XLSForm power to create surveys using spreadsheets.

2 - *Get answers*: the Survey123 ArcGIS App is available in Google Play, iTunes, and Windows stores. Once installed on the device, surveys can be downloaded and shared with the user as well as capturing data both online and offline. It is also possible to participate in public surveys by accessing through the web browser.

3 - *Make the best decision*: Survey123 includes ready-to-use reporting tools so it can quickly find out how much data is being acquired, where, when and by whom. Reports also include summaries of the answers to user's questions to make it possible to understand the trends in the data.

3.3.2.2 Feature Layer

When a new survey is published on Survey123 Connect, a *hosted Feature Layer* is automatically generated in ArcGIS Online, meaning a logical collection of geographic data sent by the App field that can be used to create 3D Maps and Scenes. Hosted Feature Layers support query, display, and edit operations on vector features and are suitable for displaying overlaid data on base maps. Feature layers are the basic element of ArcGIS Apps.

Depending on the level of sharing selected for the survey, the collected data may be collected anonymously by the public or only by some users, and consequently shared and usable on other Apps (Map, Dashboard, etc.) by other users.

3.3.2.3 Web Map Application

ArcGIS Web Map is a dynamics and interactive graphical representation of geographic information that can provide information and answer questions. Interactive maps are communication tools: they create engaging experiences, tell stories, share ideas, and stimulate people to ask questions about the situation under observation.

ArcGIS Online provides Map Viewer, an App containing all the elements that make a Map appealing. The main features of Map Viewer are briefly described below. This tool allows to choose the Basemap (from a wide range of types provided by ArcGIS Online) based on the type of data and it includes all the options to view the information on the map in order to integrate several Layer features shared through ArcGIS Online and allow to manage the legend of individual layers. It offers the possibility to navigate the map, that is by zoom in/out to view a more or less extensive area, the function “Find personal position” to locate the current position and a search box to locate points of interest. It is also possible to manage refresh intervals in order to define the refresh rate of the operating layer and through a time slider to run the animation to display changes over time.

Another strength of the ArcGIS Online platform is the ability to share Web Map Applications through different channels:

- Integrate the map into a website, a blog, and social networks.
- Share the map in various ready-to-use apps (Application Builder, Story Map, etc.).
- Create and share Apps using App generators or APIs.
- Include maps in Operations Dashboard for real-time viewing. In particular, we chose this tool for sharing and displaying data in the systems we proposed.

The selection of the visibility level of the Web Map Application determines the visibility of the Apps in which it is integrated.

3.3.2.4 ArcGIS Dashboard

Dashboard for ArcGIS is a tool that allows to design on a single screen a view of data and geographical information.

There are several reasons to design Dashboard:

- Condense all the data needed to be communicated or to make decisions on a screen.
- Monitor information on daily operations in real time.
- Connect colleagues to ensure that the focus is on the same objective through the display and use of the same information.

- Monitor the status of a company, a product, an organizational team, or a campaign.
- Create a custom view of a larger set of data to show all the most interesting metrics.

The type of dashboard is designed on both the basis of the recipient and the type of information to be transmitted. Some dashboards are operational in nature, meaning they must tell what is happening in real time and match the evolution of certain events and activities. Some are more analytical and are used to identify and show data trends or other interesting data characteristics. Finally, some are simply informative and are used to tell a story through data.

A dashboard is composed of one or more elements that can be rearranged in numerous ways, designed to always occupy 100 percent of user's browser window. In fact, when the user resizes the browser, the elements resize to fit. In addition to geographical information, obtained by integrating a Web Map Application, several elements can be inserted for the design of an effective Dashboard:

- *Indicator*: to show numerical attributes of single characteristics, or display a count, a sum, an average, a statistic summary.
- *Serial chart and Pie chart*: it is possible to introduce different types of charts, such as pie charts, bar charts, line charts or smooth lines.
- *Gauge*: useful to display a single metric within a quantitative context defined by minimum and maximum values.
- *List and Details*: to show items or lines from a feature layer.
- *Embedded content*: for embedding documents, images, videos, or other web contents into the dashboard.

In addition, the ArcGIS dashboards offer robust filter capabilities, allowing to present data in a refined manner. These filters can be applied at the design stage by the dashboard author or at the execution stage by users by usage of selectors and by means of interaction with an element that determines the configuration of the other elements (for example, zooming in a certain area of the Map will show only information related to the framed area).

3.3.3 A system to monitor Italian situation through daily reports of the citizens

During a viral epidemic that is transmitted from person to person through close contact with an infected patient (close contact is defined as face-to-face contact at a distance of less than 2 meters and contact time of at least 15 minutes in an enclosed environment in the absence of suitable personal protective equipment) it is essential to be able to detect the contagion chain in a prompt manner so as to circumscribe clusters and limit its spread. Day-to-day population surveys assessing the development of symptoms caused by the virus and related to geographical information are a valuable and strategic tool to identify such clusters and to inform epidemiologists, public health officials and policymakers with the aim of taking measures related to containing the spread of the virus.

In Italy, the transmission of information between the various competent structures is far from fluid, mainly because of the number of structures involved and the tools used for the data communication between them. The chain is, in fact, long: the information passes from the structures through the Territorial Directions, then to the Regional Direction and from there to the Direction of Emergencies (Fig. 27). Each structure uses its own system which is often not compatible with that used by other structures, and this, in a situation of continuous variability, involves a high risk of information loss, partial or incorrect communications.

The tool we propose takes advantage of the ArcGIS platform for the collection and analysis of data in real time: a simple system to use as it does not require specific training, accessible from any device connected to the network and extensible on a national scale (Fig. 28). The system allows:

- Rapid detection of diffusion zones; a snapshot of the number of people in each area having developed symptoms.
- Forecasts of future circulation areas several days before an outbreak occurs.
- The effectiveness evaluation of the various social expulsion measures adopted and their contribution to the reduction of the number of symptomatic persons.

This information can provide a valuable tool for decision-makers to determine which areas need to be strengthened in social expulsion measures and which areas can be alleviated.

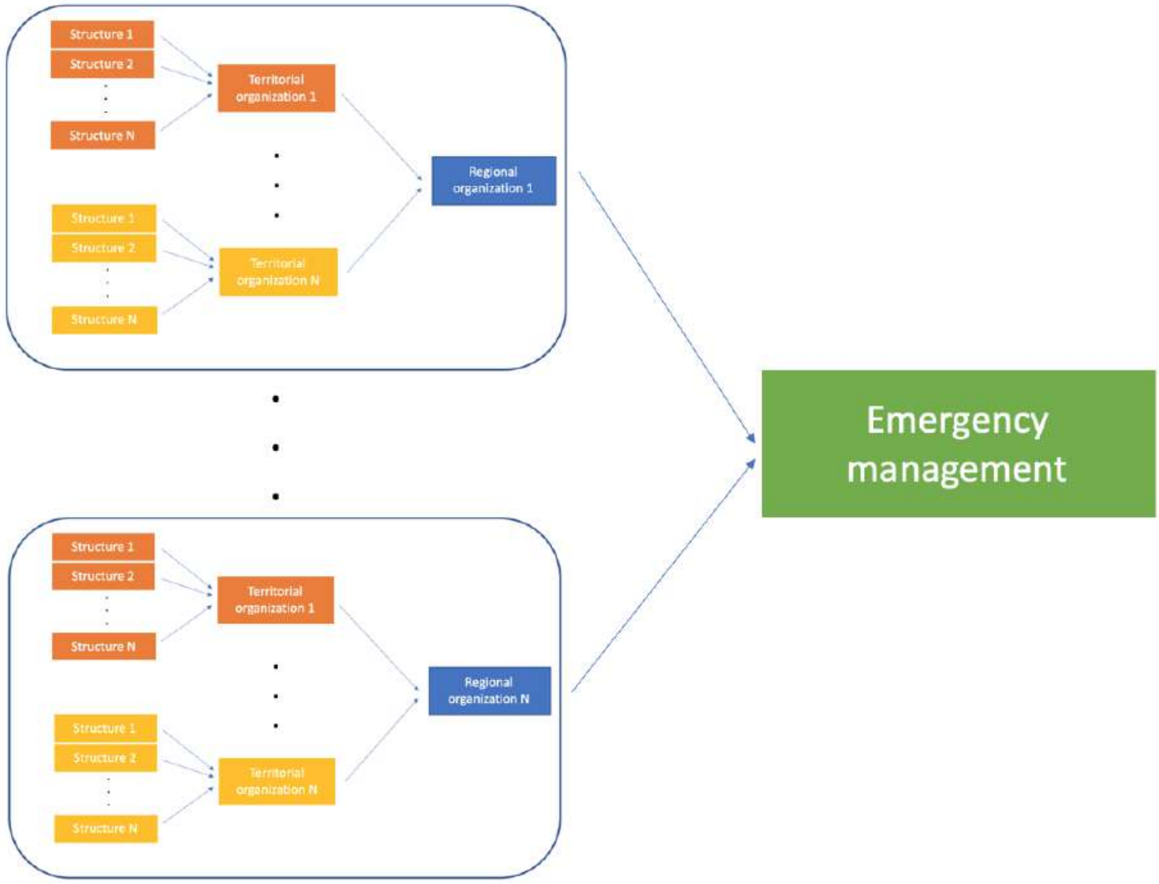


Fig. 27 - Schematization of the current flow of information between the various structures.

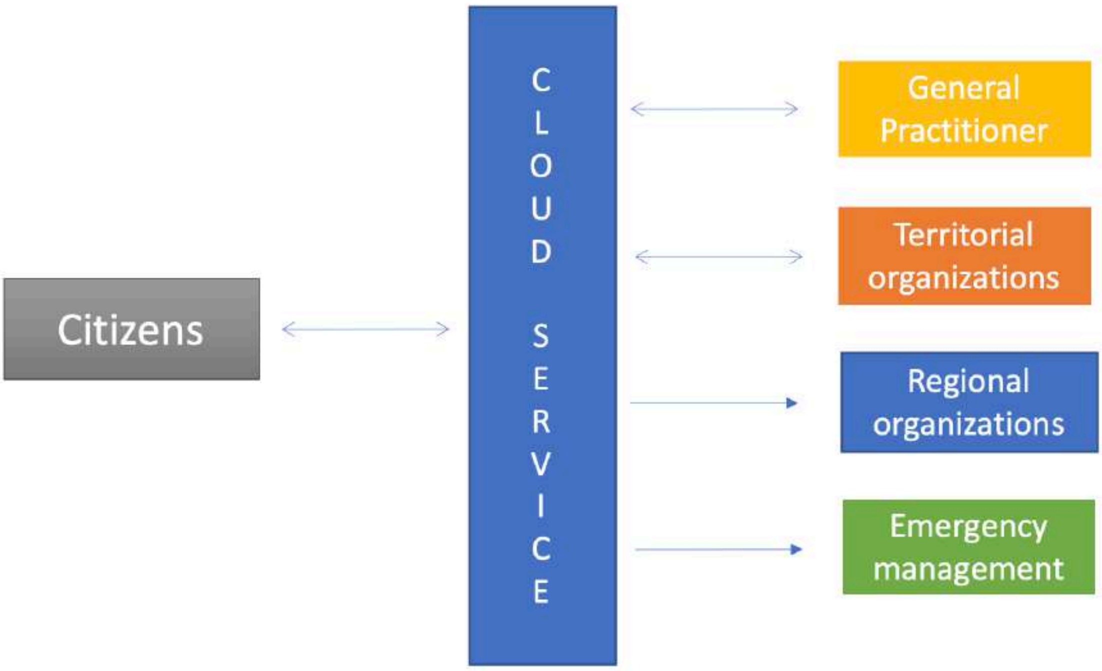


Fig. 28 - Schematization of the flow of information in the proposed system.

The system expects the collection of data from questionnaires that each citizen can fill out on a voluntary basis up to twice a day. The information is uploaded to a Cloud service accessible by the General Practitioner (GP), the territorial organization and the regional reference structure in order to create a direct communication network that maintains a patient connection, medical and territorial services as well as constantly updating the regional situation in real time.

Each citizen (or whom for him) can register in the system by downloading the App Survey123 from the Store on his personal device (smartphone, tablet, or PC) from which he can access the questionnaire. At the first access it is required to provide: the geographical information of your home, the generalities (name, surname, tax code, date of birth and gender), the territorial structure of membership and the GP reference, the number of partners, the type of work (whether or not it is a healthcare operator), possible vaccination status (Flu shot and/or Pneumococcal vaccine), previous and/or chronic pathologies (Diabetes mellitus, Hypertension, Cardiovascular disorders, Chronic lung disease, Chronic kidney disease, Malignant tumors, Immunodeficiency) and exemption code(s) (Fig. 29).

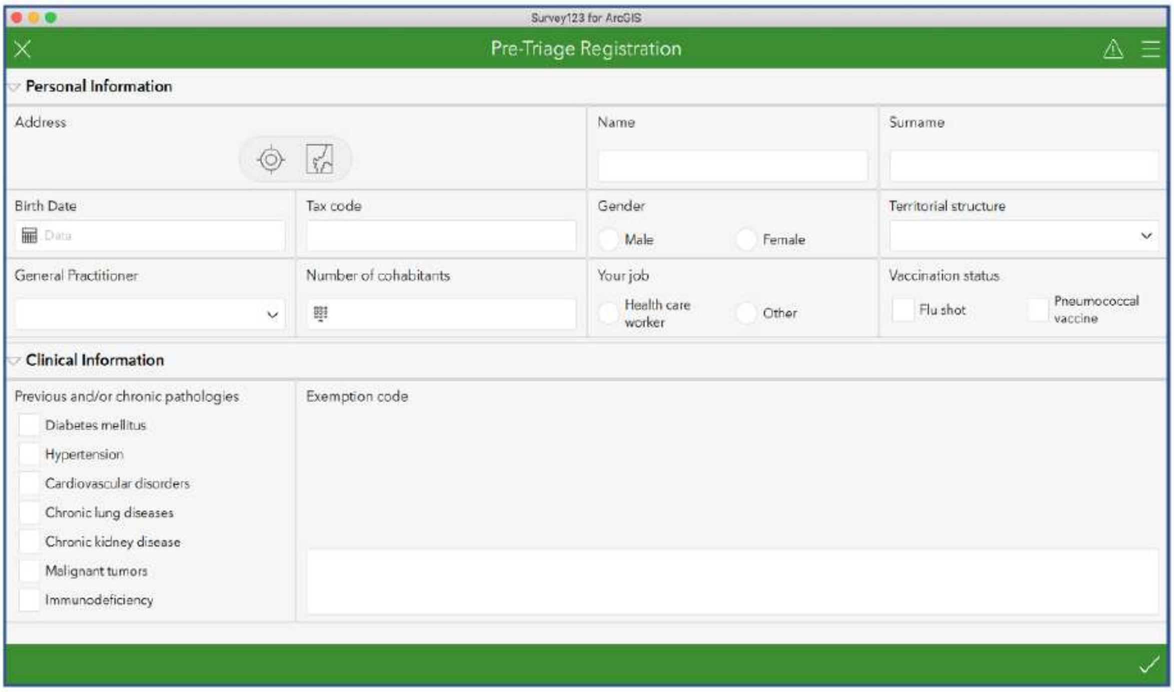


Fig. 29 – Platform interface for registration.

Once registered, the user has the possibility to install, from the Survey123 App, the questionnaire for the insertion of the current conditions, whose interface is represented in Figure 30. It consists of two buttons, the first (Collect) to access the questionnaire and the second (Inbox) where communications are received from the GP and ASL.

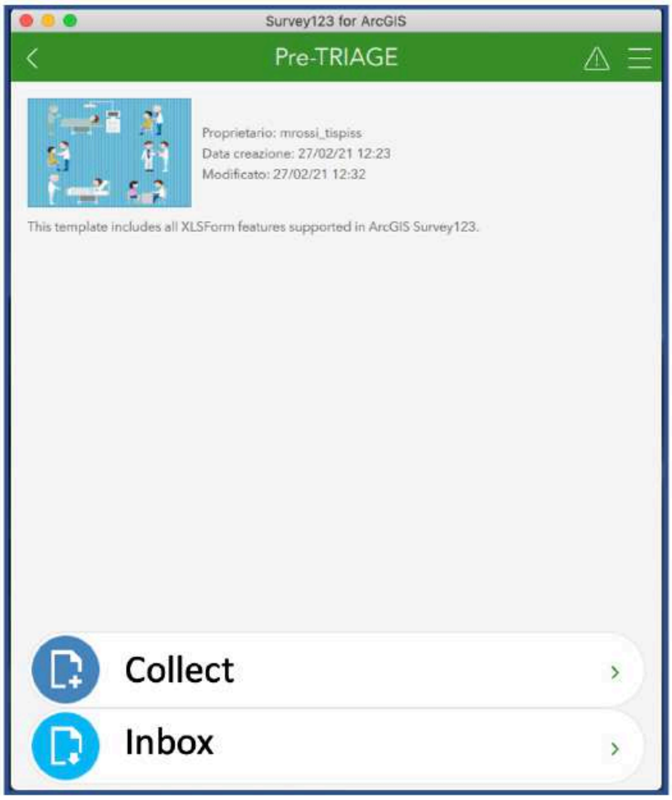


Fig 30 – User interface at the opening of the App: the "Collect" button allows users to log in to fill out a new questionnaire; in the "Inbox" section the user can view communications from the medic and ASL.

On a daily basis, users can fill out the questionnaire by pressing the “Collect” button to update their conditions. Insert date and time are automatically recorded when the questionnaire is sent. Taking the cue from the “GP evaluation sheet for respiratory infections suggestive risk SARS-Cov-2”, the following information is requested:

- The subject condition (Positive, contact with a person with Covid-19 and the presence of symptoms, contact with a person with Covid-19 and absence of symptoms, Healed or Other).
- The possible isolation status.
- Vitals parameters information: peripheral oxygen saturation (SpO_2), basal body temperature (BBT), blood pressure (BP) and heart rate (HR).
- The presence of more common symptoms related to SARS-Cov-2 infection: dry or wet Cough, Fatigue, Muscle pain, Shortness of breath, Rhinorrhea (Runny nose) and/or Nasal congestion, Diarrhea, Nausea and /or vomiting, loss of smell or taste.

Based on the information included in the questionnaire, two indices are automatically calculated for each patient: the *MEWS Score* (as established by the guidelines issued by the

Ministry of Health in the Circular on "Home Care of Patients with SARS-Cov-2 Infection") and the *Symptoms Ratio* (Rossman et al, 2020). Through the MEWS scale (Fig. 31), patients are stratified into the following risk groups:

- Low risk / stable (score 0-2).
- Medium/ unstable risk (score 3-4).is calculated as the number of symptoms manifested compared to the number of symptoms in the default list (cough, fatigue, muscle pain, shortness of breath, rhinorrhea and/or nasal congestion, diarrhea, nausea and /or vomiting, loss of smell or taste).
- High risk / critical (score 5+).

MEWS (Modified Early Warning System)							
	3	2	1	0	1	2	3
Respiratory Rate per minute		Less than 8		9-14	15-20	21-29	More than 30
Heart Rate per minute		Less than 40	40-50	51-100	101-110	111-129	More than 129
Systolic Blood Pressure	Less than 70	71-80	81-100	101-199		More than 200	
Conscious level (AVPU)	**U**nresponsive	Responds to **P**ain	Responds to **V**oice	**A**lert	New agitation Confusion		
Temperature (°c)		Less than 35.0	35.1-36	36.1-38	38.1-38.5	More than 38.6	
Hourly Urine For 2 hours	Less than 10mls / hr	Less than 30mls / hr	Less than 45mls / hr				

Fig. 31 - Modified Early Warning Score (MEWS).

The symptom ratio is calculated as the number of symptoms manifested compared to the number of symptoms in the default list (cough, fatigue, muscle pain, shortness of breath, rhinorrhea and/or nasal congestion, diarrhea, nausea and /or vomiting, loss of smell or taste).

$$Symptoms\ Ratio = \frac{\#\ reported\ symptoms}{\#\ symptoms\ in\ list}$$

To view patients' information each GP have two Dashboards: one with information about their patients in a global way and one that allows to evaluate the condition of each individual patient.

The first dashboard (Fig. 32) provides general information about patients who have joined the system, highlighting those whose condition deserves special attention. In particular, in the Dashboard the data have been organized in three distinct layers: one relative to the subject category according to what the user himself entered, one to the level of risk assigned by the medic and finally one to the result of the swab inserted by the territorial organization.

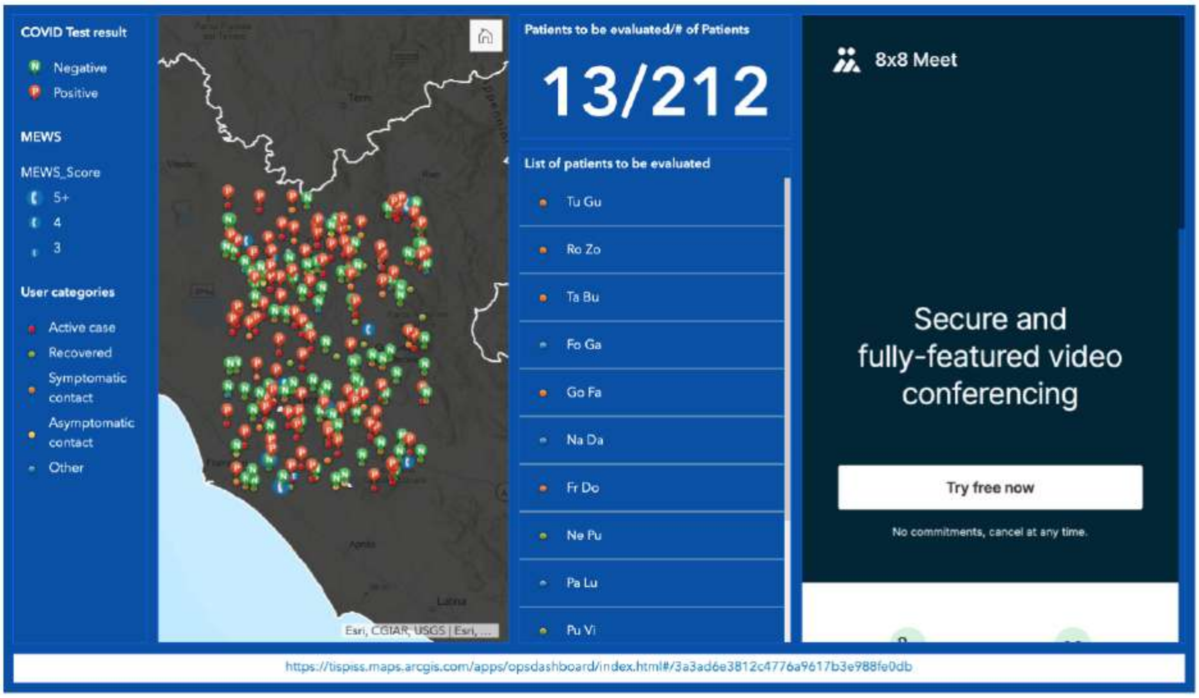


Fig. 32 - General Practitioner Dashboard: The Map provides an overview of the spatial distribution of individuals who have resulted positive for COVID-19; the indicator and list highlight the number and list of patients who need to be contacted by the doctor; 8x8 Meet allows to start a video call. The link below directs to a second Dashboard. The values shown in the figure are fictitious, resulting from a simulation.

This information is translated on the map as illustrated in the legend:

- The subject type is indicated with a color code (red = active case, orange = symptomatic contact, yellow = asymptomatic contact, green = recovered, blue = other) allowing to have a spatial view of the situation, represented by the presence of areas with the largest number of SARS-Cov-2 sufferers and therefore more affected by the epidemic.
- The risk level is indicated by the size of the phone icon, present for patients for whom the MEWS Score is greater than 2.
- For patients who have already been swabbed, the result is identified by a green or red icon, if the result is negative or positive respectively.

In the central part of the dashboard there is an indicator in which the number of patients at higher risk is reported (i.e. for whom the MEWS Score is greater than 2) compared to the total number of users, and in the box below the ordered list is showed according to the score of MEWS and the Symptoms Ratio. In the right part there is a screen containing 8x8 Video Meetings, available as a web application for browsers or as a native application for desktops and mobile devices, to make video calls. Finally, in the portion below there is a link that refers to a second Dashboard (Fig. 33).

Fig. 33 - The Dashboard allows, through special filters in the upper part, to visualize the evolution of the symptomatology of every single patient in a determined interval of time. The values shown in the figure are fictitious, resulting from a simulation.

This Dashboard is useful to monitor the evolution of the conditions for each individual patient. In the header bar there are two filters: the first one to select the patient according to the tax code and the second to select a certain time interval. General information about the patient is given in the two boxes on the left. On the right side, the list with the information inserted by each subject in all the completed questionnaires is shown from the least recent to the most recent. In the central portion, there are indices that support the doctor in the assessment of the patient and the graphs that show the temporal evolution of the main vital parameters (SpO_2, BBT, BP and HR). At the bottom, there is a link that refers to a Survey123 App through which the doctor, by entering the ID of the subject, can update the record by sending written communications to the patient (for example, which medicines to take) and above all, indicate to the territorial structure of competence the need for the patient to make an appointment for the swab.

Every territorial structure has access to a dashboard (Fig. 34) in which the information of all the patients belonging to it is shown, for which the GP have indicated the necessity for an appointment.

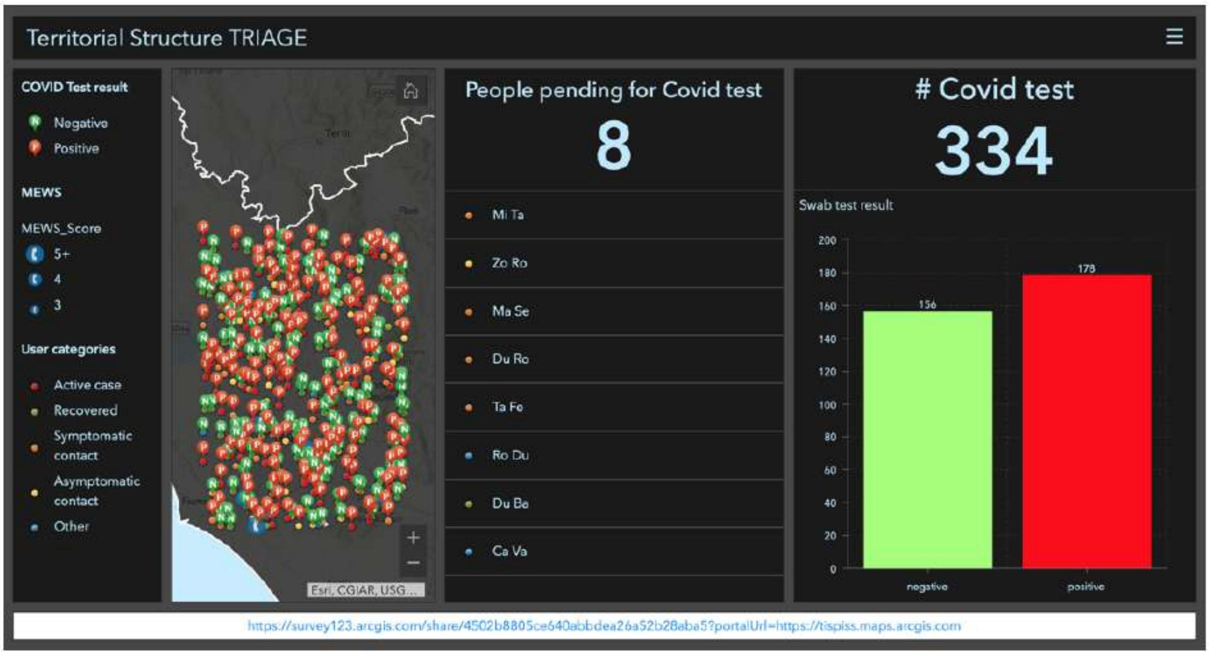


Fig. 34 - Dashboard for the territorial structure: the Map offers an overview of the spatial distribution of individuals' positive results to COVID-19 (red icon with the letter "P"), of individuals' negative results (green icon with the letter "N") and individuals who need an appointment for the test (icon with the phone); the indicator and the list highlights the number and list of patients who need to be tested and for whom the visit must be booked; on the right-hand side, the number of tests carried out is indicated, while the graph below shows the number of negative or positive tests. The values shown in the figure are fictitious, resulting from a simulation.

For consistency with the symbology used in the dashboard for physicians, the icons in the Map have an analogous meaning to what was attributed to them in the Map for physicians. Therefore, from the Map are easily identifiable information such as the need for the test, if the patient has already carried out the test and the associated result, if instead he came into contact with a positive subject and he presents symptoms, etc. On the right side of the map, the number of people for whom it is necessary to make an appointment with the relevant list is shown. The graph shows the statistics of the tests results. Finally, as for the doctor, even the territorial structure has the possibility to access the patient's record in order to indicate the date and time of the appointment and then the outcome of the swab by opening the link on the bottom of the dashboard.

The data related to patients who performed the test for Covid-19 of all territorial structures are collected in a Dashboard for the Region (Fig. 35). In this way, it is possible to visualize the regional framework in such a way to identify the most affected areas and therefore the structures mostly under pressure.

Fig. 35 - Dashboard for the Region: The Map gives an overview of the spatial distribution of the individuals that are tested positive for COVID-19 (in red) and the individuals that are tested negative (in green). The indicators provide information on the number of infected cases, in particular health workers; the number of current positives; statistics on the number of symptomatic and asymptomatic infected cases. The pie charts provide statistics on the distribution of infected cases by gender and age; the serial graph provides information on the number of symptomatic and asymptomatic contacts that are in fiduciary isolation. The values shown in the figure are fictitious, resulting from a simulation.

The Dashboard provides useful information for statistical purposes:

- The total number of infected cases, with reference to the number of health care workers who have contracted the virus.
- Distribution of infected cases by gender.
- Distribution of infected cases by age group: 18-30, 31-50, 51-65, over 65.
- The number of current positives.
- The number of symptomatic and asymptomatic cases.
- The graph with contact statistics (symptomatic and asymptomatic) in fiduciary isolation.

The elements are related to the view on the Map, so by zooming on a certain area the data reported on the various elements refers only to the area on which it has been zoomed on.

3.3.4 A system to monitor Italian situation through wastewater analysis

An epidemiological surveillance activity of SARS-COV-2 through the analysis of samples of urban waste water, based on the model of Wastewater-based epidemiology (Wbe) taken at the inlet of Waste Treatment Plant (WTP) on national territory allows to analyze trends of the virus spread to make indirect estimates on the number of individuals excreting the virus, providing useful information on epidemic trends and early warning of outbreaks, in addition to the clinical control instruments on the territory (*screening* with swabs and serological tests).

With the support of the technical-scientific expertise of the Department of Water Quality and Health (QAS), the Department of Health and Environment of the Italian National Institute of Health (ISS) and the technological capabilities of the National Center for Innovative Technologies in Public Health (TISP) a proposal for an action was drawn up entitled "Environmental Surveillance of SARS-CoV-2 through urban waste water in Italy: indications on epidemic trends and early warning (acronym: SARI)" by submitting it to the General Direction of Health Prevention of the Ministry of Health for the possible assessment that is in progress. The main objectives of this project are:

- Clearly define the objectives of the monitoring program.
- Develop and implement a common sampling protocol.
- Maximize collaboration, cooperation, and the exchange of acquired knowledge.

The first point to be addressed was to reduce research gaps in terms of the definition of sampling and analysis methodologies as well as the definition of predictive models. At present, there are several analytical methods (for both wastewater concentration and virus detection) none of which have been formally validated for SARS-Cov-2. Preliminary tests using the molecular tests recommended by WHO for the research of SARS-Cov-2 in clinical swabs, showed poor sensitivity for virus research in a complex matrix such as wastewater. For this reason, specific molecular tests (Nested RT PCR and Real time RT-PCR) were designed, evaluated for sensitivity and specificity on the urban waste matrix. ISS has therefore developed and characterized sampling methods (sampling and storage procedure), sample concentration, nucleic acid extraction of SARS-COV-2 for RNA detection evaluated for sensitivity and specificity on the urban waste matrix by retrospective investigations on archive samples. Sampling shall be carried out by appropriately trained personnel, typically operators within the facility who already sample for routine in-house analysis of the operator. The use of a standardized analytical protocol is necessary to avoid misinterpretation between different laboratories. The analyses carried out follow a shared protocol developed by ISS, towards which the data collected in the territory converge with harmonized methods; ISS is also responsible for carrying out in-depth analysis and data processing on the GIS platform for sharing data with central and regional health authorities.

In addition, it is essential to select the frequency and number of sampling sites in order to have appropriate temporal and spatial sampling that is representative of the population and to ensure close cooperation between environmental authorities (in most cases water supply facilities) and the health authorities which should guide the whole process. Recommended sampling sites are inputs to wastewater treatment plants. The ideal size of the original population for plants from which raw waste samples are taken, according to the WHO Guidelines (2003), is in the range of 100000-300000 equivalent inhabitants.

The project proposal is divided into two phases:

- The first phase, on a voluntary basis and self-financed by the project participants, focuses on a pilot network of priority sites with the aim of assessing the development of the epidemic, functional to possible prevention measures at local level and to the development of the management methods of the network extended on the national territory;
- The second phase, based on the available resources, provides an extensive surveillance network at national level, focused on urban aggregates, with the possibility of implementing flexible and widespread monitoring (e.g., city districts, airport purification sites), functional to the health prevention needs of different territorial areas, according to epidemiological scenarios.

Participation in the project on a voluntary basis - currently without cost coverage - of the Territorial Structures (STs) is subject to confirmation of the availability of each structure to conduct the experimental activities applying for one or more of the following 4 different levels, on the basis of specific availability, expertise and resources:

- ST-1 level: sampling, storage of raw waste sample and dispatch to the upper tier facility.
- ST-2 level: Virus concentration from sample, storage, and dispatch of concentrated sample to ST3.

- ST-3 level: extraction of nucleic acids, molecular screening, and data transmission to ST3R.
- Level ST-3R: regional reference structure that coordinates operations and sees the results of the Region.

In this context, participating structures are required to use the methods recommended by ISS for the purposes of the project. This does not, of course, prejudge any other possible research activities of a methodological, modelling or of other nature which, in any case, is ancillary to the SARI project.

The project was launched following a Kick-Off meeting on 30 June 2020, with the technical-scientific coordination of the ISS and with the support of the Interregional Coordination of Prevention, Health Commission, Conference of Regions and Autonomous Provinces. In order to implement the first phase of the project, preliminary adhesions were collected from the individual structures that will carry out the experimental activity with the aim of planning activities and workflows. For this purpose we have developed a questionnaire distributed by means of a Survey123 App (Fig. 36) (accessible through Browser, without the necessity of having to download any App) addressed mainly to ST as Regional Agencies Environmental Protection (ARPA), Local Health Agencies (ASL), Experimental Zooprophylactic Institutes (IZS), Universities, Research Centers and Integrated Water Service Managers.

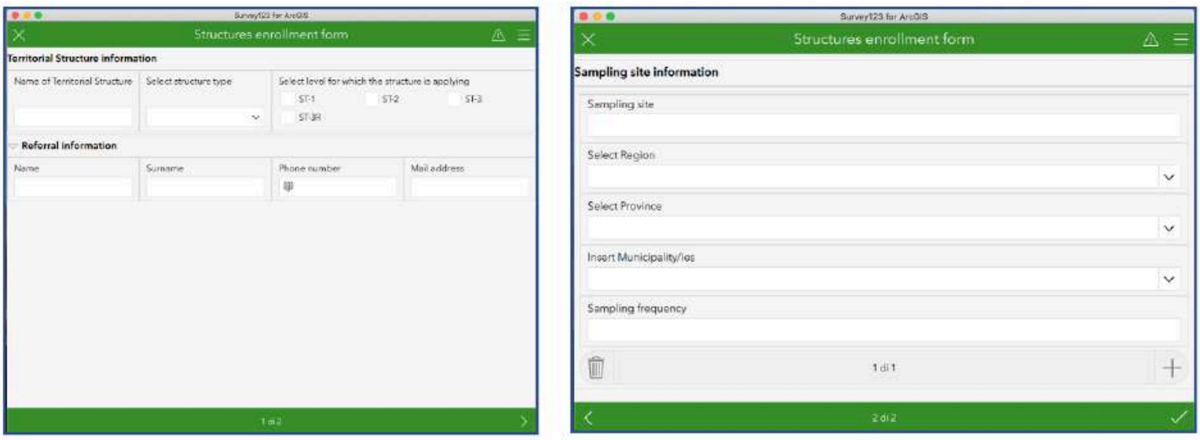


Fig. 36 - Interface of the questionnaire distributed publicly to collect adhesions from the single structures in function of the availability, the expertise, and the resources.

The results of the questionnaire were transmitted to each ST3R so that each Region could optimize the network structure. ST3R was therefore provided with a Form in which it was requested to indicate:

- Regional manager(s).

- ST3R name and referrals.
- ST3, ST2 Name and referrals.
- For each WTP:
    - ST1 name and referrals.
    - Name of WTP.
    - position (latitude and longitude).
    - Municipalities (or parts of it) covered.
    - Province/s.
    - Equivalent inhabitants.
    - Frequency of sampling shall be used.
    - Description of sample flow between structures.

The data received from regions that joined the project, in Excel format, were uploaded to the ArcGIS platform. For each Region it was therefore developed a Dashboard available for regional managers and ST3R referents (every user has access only to the Dashboard of its own Region, thanks to the creation of Groups on ArcGIS Online) containing the information collected through the Cards. In the following figure (Fig. 37) an example of regional Dashboard is illustrated, containing: the characteristics of every depurator, the description of the flow of the samples and the name, with annexed contact (address mail and telephone), of the ST1, ST2, ST3, ST3R referrals and regional leaders.

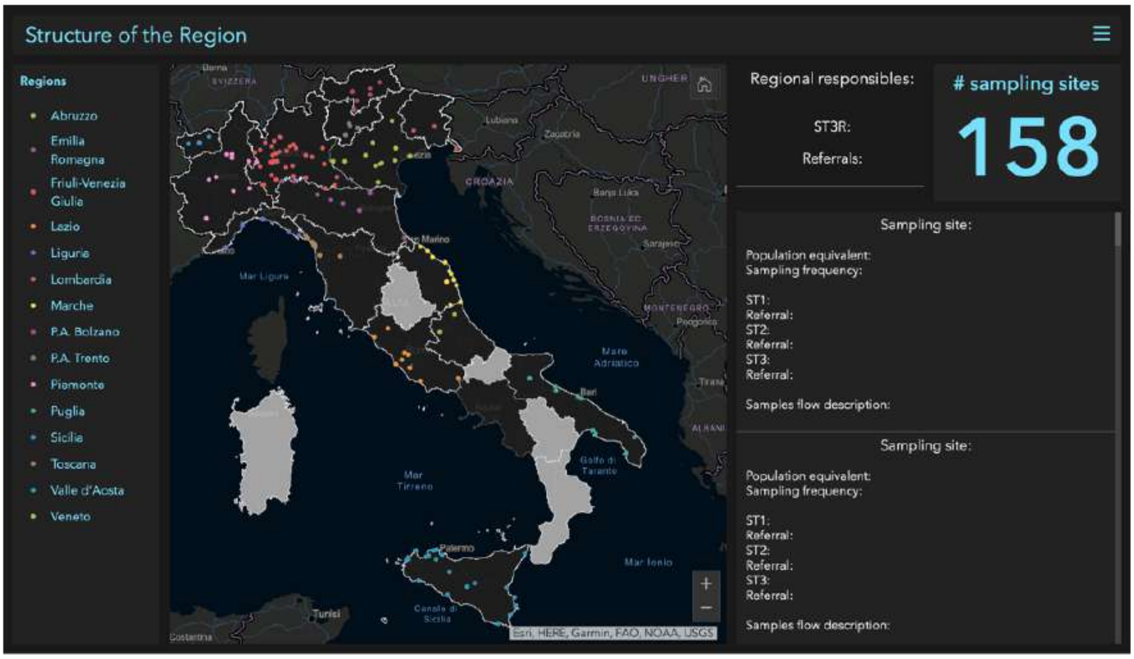


Fig. 37 - Dashboard Info WTPs. The map shows the geographical information on the location of the WTPs; the indicator above the map shows the number of WTPs enlisted in the SARI project for the Region; on the right is illustrated the list of those responsible for the various ST, the characteristics of each WTP and the description of the sample flow.

For the data collection, on ArcGIS Online, I have created a unique Feature Layer in which the data sent from the different structures of all the Regions that have joined the project are conveyed, in order to build a centralized database. For each structure ST1, ST2 and ST3 I have implemented an App with Survey123 that automatically loads the records on the Feature Layer, thus updating in real time the regional Dashboards.

The insertion of the sample in the database is charged to the structure of level ST1. When the user accesses the App with his credentials, the Home Page is shown (Fig. 38a) in which he has the possibility to insert a new sample by pressing the button "Collect" or to access the Inbox (useful as we will see soon to receive the sample code) (Fig. 38c). Clicking on "Collect" will open a short questionnaire (Fig. 38b).

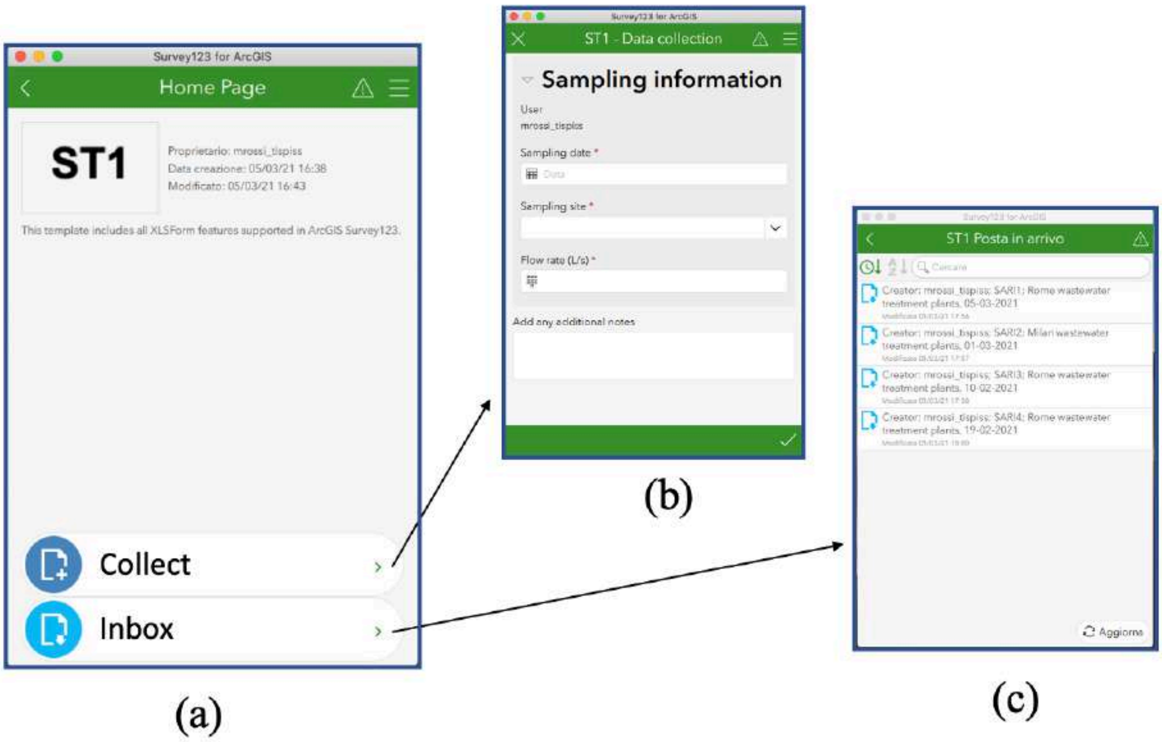


Fig. 38 - App for the ST1: user interface and illustration of operation.

Each account is associated with the WTPs, as defined by the Form compiled by the ST3R. The App is able to detect, from the device on which it is installed, the date and time, so if the ST1 operates only one WTPs, the user has to enter the value of the flow rate and press the Enter key (the flag at the bottom right in Fig. 38b). If, on the other hand, a ST1 manages more than one WTP, the operator must select the WTP from a drop-down list before sending the record.

When the record is sent, the central database also records the information associated with the WTP (Location, Municipality, Province, Region, Equivalent Inhabitants) and generates a unique code, which the user will receive in the Inbox section (Fig. 38c) so that it can be applied physically to the test piece.

Information about the sample entered by ST1 is transferred to the "Inbox" section of the ST2. From the Inbox, in which the ST2 will find the samples inserted by all the ST1 for which it acts as a reference, for each sample it will be able to enter the information related to sample preparation (Sample volume, Sample type, Storage temperature, Volume of the concentrated sample, Final volume of the concentrated sample) (Fig. 39). As soon as all fields are filled in, the record will go to ST3.

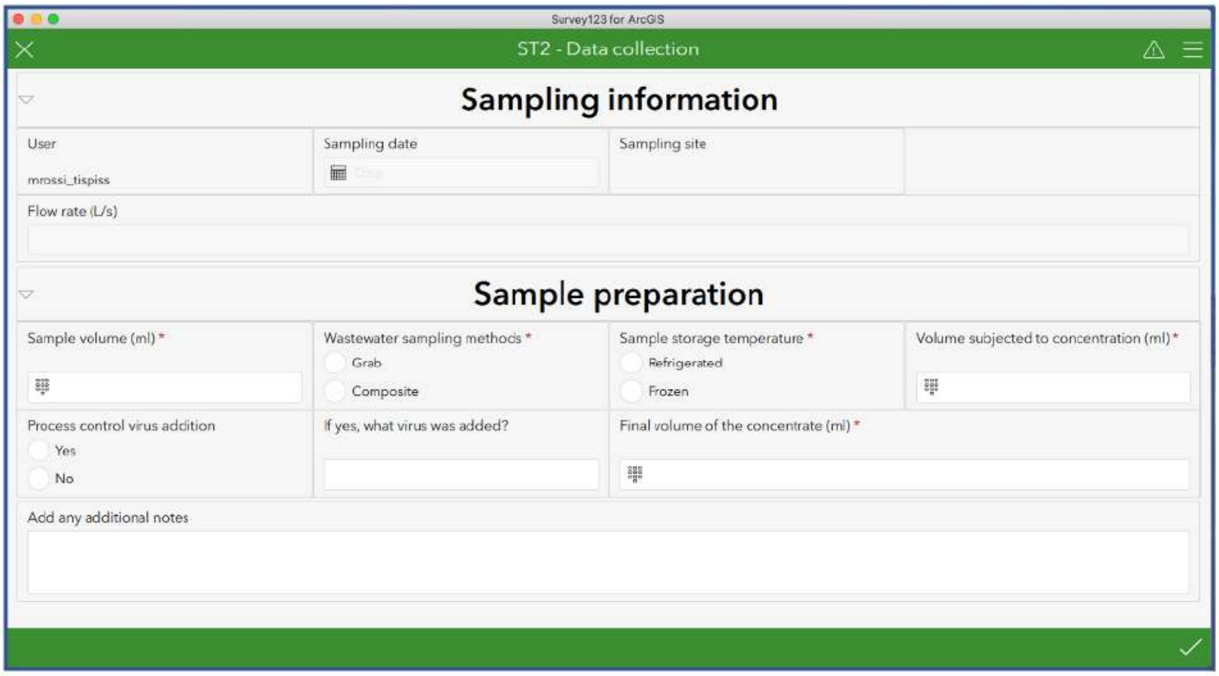


Fig. 39 – ST2 App: user interface.

Through the App, the ST2 has the possibility to create a new record, for example in case it was not already entered by the ST1 or simply for an organizational choice of the Region that indicated the ST2 as responsible for the inclusion of the sample in the database.

The ST3 App is completely analogous to those of the ST2 and the ST1 (Fig. 40). In the Inbox you will find the records of the samples created by ST1 (or ST2), updated with the information of ST2, which can in return, update with the information related to the extraction of nucleic acids and the analysis results of the molecular method (Real-time RT-PCR). The samples remain stored in the inbox until the answer to the question “Input finished”, set by default to the value “no”, passes to the value “yes”.

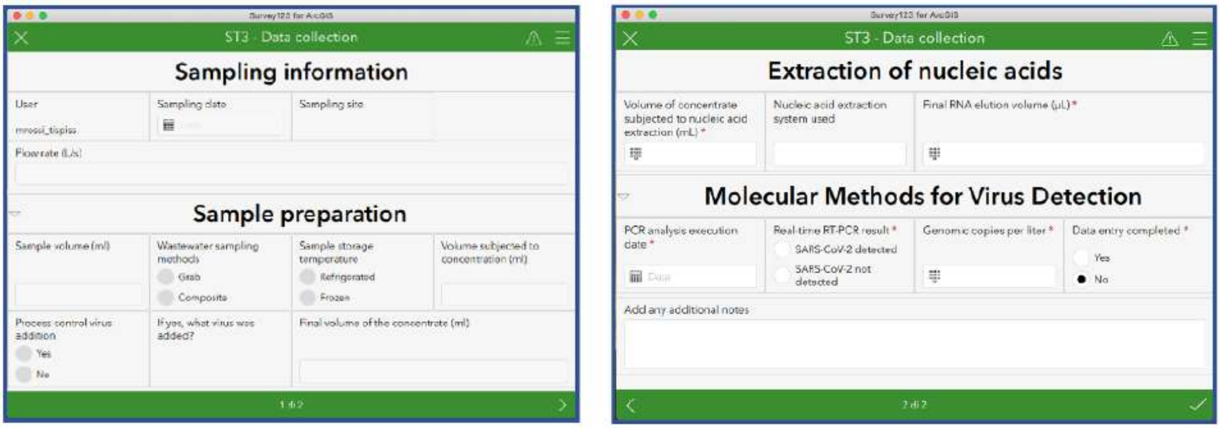


Fig. 40 – ST3 App: user interface.

As for ST2, ST3 also could create an ex novo sample using the "Collect" button.

The ST3R and the regional managers have access to a dashboard containing the results of the samples analyses collected by the WTPs on regional territory (Fig. 41).

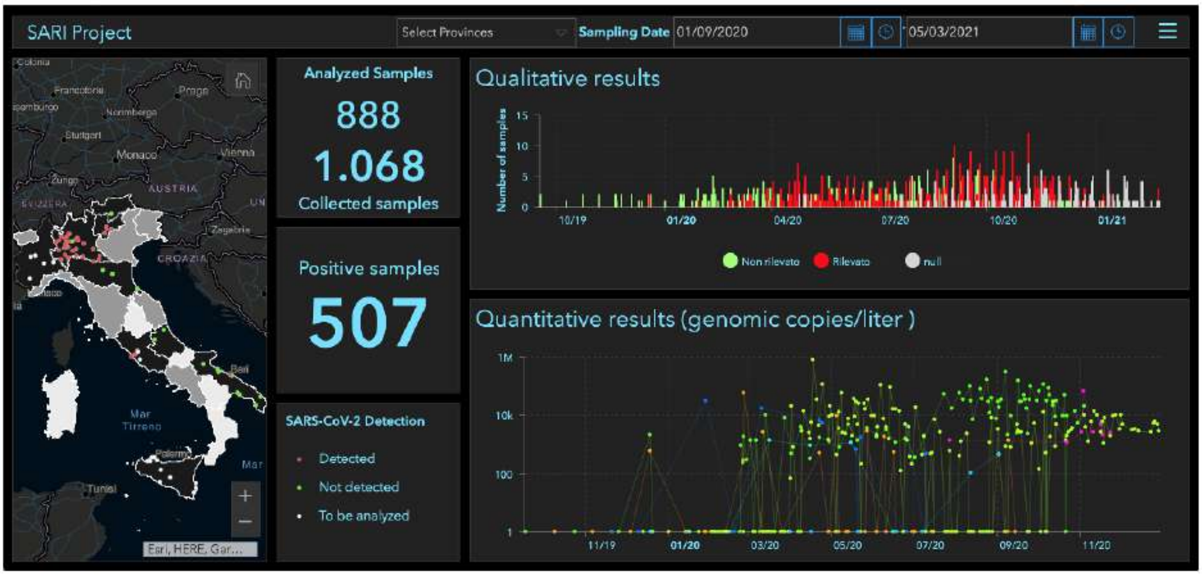


Fig. 41 - Dashboard Results. The dashboard allows to visualize the regional picture in terms of samples analyzed and samples taken, showing the temporal course of the results obtained with qualitative analysis (presence/absence) and quantitative (genomic copies/Liter of wastewater) from samples taken from WTPs in the region to which the user belongs.

In the header there are filters, which allow the user to view the samples results taken within a certain time interval or samples taken from WTPs that cover a certain province. In the Map the sampling sites are identified with a red icon, indicating the presence of SARS-Cov-2 in the analyzed sample, or with a green icon, in case the presence of SARS-Cov-2 was not detected. Indicators showing the number of samples analyzed, the number of samples taken, and the number of samples tested positive, or for which SARS-Cov-2 was found, are shown at the top. The two graphs on the right correlate the sampling date with the qualitative result (presence/absence) and the quantitative result (genomic copies/Liter of wastewater), in the upper and lower boxes respectively.

For each Region I have prepared a tutorial with step-by-step instructions for installing the Apps, necessary to create new records or to update existing records, to access the Dashboards, giving my availability for any clarification and to provide support in the first approach to this system.

The following chapter will illustrate the first results of the SARI project, updated to 16/03/2021.

4 CHAPTER 4 – SARI Project

In the document of the Ministry of Health "*Prevention and response to COVID-19: evolution of strategy and planning in the transition phase for the autumn-winter period*" (http://www.salute.gov.it/imgs/C_17_pageAree_5373_16_file.pdf), the environmental surveillance of SARS-Cov-2 through urban wastewater was recommended with the national project SARI (Environmental Wastewater Surveillance in Italy), according to the technical-scientific guidelines of ISS and through the Interregional Coordination of Prevention, Health Commission, Conference of the Regions and Autonomous Provinces of the State-Regions Conference, in order to acquire indications on epidemic trends and develop early warning, in line with recent European Health Preparedness recommendations to address the COVID-19 outbreaks. In July 2020, the Italian National Institute of Health (ISS), represented by the working groups of the Department of Health and Environment (DAMSA) and the National Center (NC) for Innovative Technologies in Public Health (TISP), with the support of Utilitalia (the Federation of Water, Environmental and Energy Enterprises), convened a meeting involving representatives of the Ministry of Health, regional health managers and territorial structures, such as ARPA, ASL, IZS, Universities, Research Centers and integrated water service managers with the aim of establishing a first environmental surveillance network for SARS-Cov-2, susceptible of further development in the following stages to share with the heads of the Regions the surveillance data obtained. In this first phase, the results are to be considered preliminary and do not, at present, constitute appropriate risk analysis elements for taking decisions in the management of the pandemic.

During the event it was illustrated:

- The sampling and analysis methods of the samples developed by the DAMSA, ensuring subsequent distance training activities for the correct execution of the methods with verification of the correct implementation before the monitoring starts. In addition, suitable reference materials and analyses methods will also be provided to the ST network during the surveillance, for the purpose of quality assurance of the analytical data.
- The data collection system and the tools for data entry and results visualization implemented by the NC TISP that will take care, for the entire duration of the project, of the management and maintenance of the software tools.

At the end of that meeting we sent to the individual participants, a link that refers to a public questionnaire with Survey123 for the voluntary adhesions collection of the structures on a centralized database managed by NC TISP, asking kindly to make it as widely spread as possible and confirming that in this first phase of the project, participation is on a voluntary basis without covering costs. The requirement to join the surveillance network is to use the methods recommended by ISS for the project purposes in order to make the database uniform and thus obtain comparable results on a national scale. This does not, of course, prejudge any other possible research activities of a methodological, modelling or of other nature which, at any rate, is ancillary to the SARI project. The initiation of analytical activities (or at least the collection of reflux samples to be frozen) is immediately recommended.

In the short questionnaire (Fig. 42) it was asked, for every structure, to insert at least one referent and to indicate the type and the level/s for which the structure is candidate (ST1 if collecting and storing the wastewater sample; ST2 if dealing with virus concentration from the wastewater sample; ST3 if dealing with nucleic acid extraction and molecular analysis; ST3R to coordinate operations). For each Waste Treatment Plant (WTP) already managed by the plant, it was requested to indicate its name, its geographical position (in terms of latitude and longitude), the province and the municipality, and the sampling frequency (it is strongly recommended to take at least one sample per week).

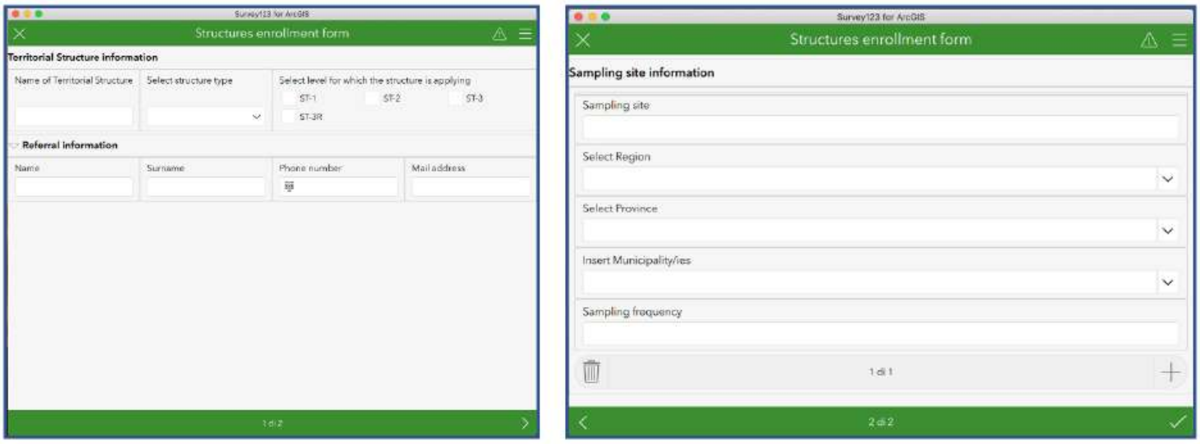


Fig. 42 - Overview of the questionnaire sent to the structures for the insertion of necessary information to create a regional network.

Despite the lack of funding to the structures belonging to the regions, the answer was prompt and positive (Fig. 43). Especially in areas where some of the major epidemic outbreaks occurred, water service operators and environmental protection agencies made themselves available for timely collection of wastewater and subsequent analysis according to the protocol defined in the project.

About 90 structures belonging to all the regions have expressed the will to take part in the unified network, for a total of 180 WTPs that cover a large part of the national soil. For most regions, at least one structure has become available for each level ST1, ST2, ST3, ST3R.

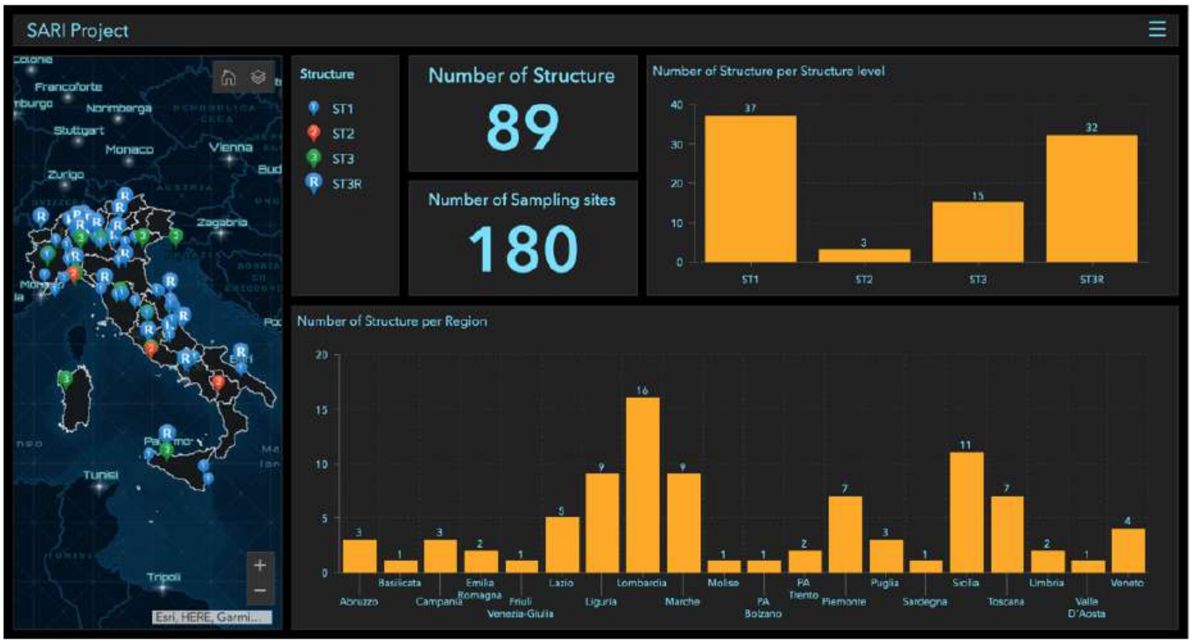
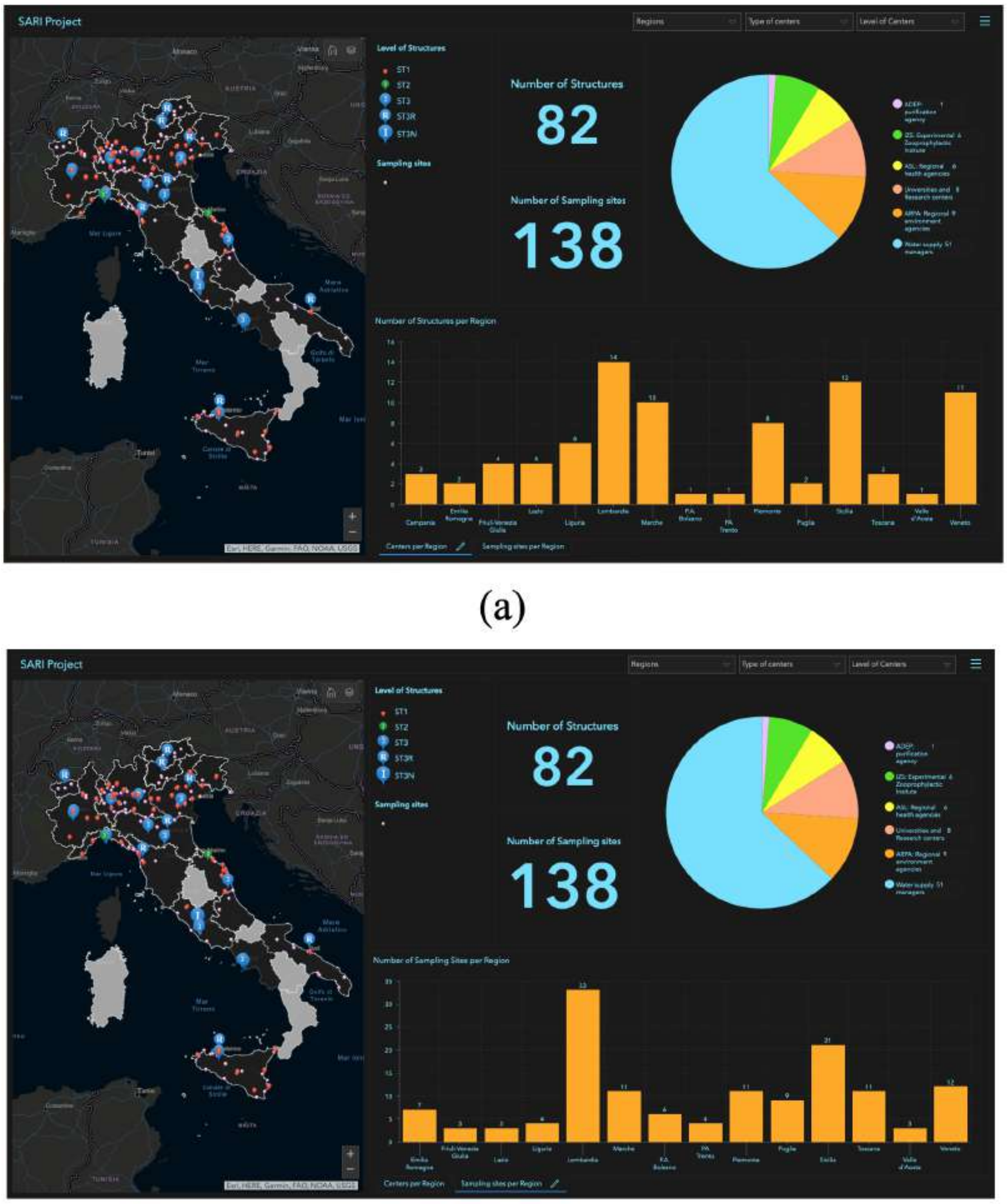


Fig. 43 - Dashboard for the visualization of the collected data by the questionnaires sent from the single structures.

The applications received through the ISS Central Information System have been shared in an aggregate form on a regional basis with the regional managers and with the ST3R contacts so that each Region/Autonomous Province (AP) had the possibility to define/update the specific monitoring program. Each regional representative and referral of the ST3R was sent an Excel card in which they had to indicate:

- Structures belonging to the regional network, with its relative role (ST1, ST2, ST3) and with the referral names.
- Information on purification plants (location, catchment area, equivalent inhabitants, sampling frequency, etc.).
- The flow of physical samples and digital information.
- User/s enabled to enter, transmit and read data.

Once we generated and provided access credentials to the ArcGIS platform, in November, following a series of meetings with each individual region, we organized an event, with the participation of the Ministry of Health, to which they have been invited all the organizations that have joined formally to the plan with the scope to update all the Regions on the state of the plan and to illustrate the obtained results (Fig. 44(a) and Fig. 44(b)).



(a)

(b)

Fig. 44 -Summary dashboard of the number of structures (a) and sampling sites (b) for each region that has joined the SARI project.

Thanks to the availability and the collaboration of all the structures that have taken part to the plan, the result has been remarkable: 15 between Regions/AP have been formally enlisted in the SARI plan (Abruzzo, Aosta Valley, Apulia, AP of Bolzano, AP of Trento, Emilia-Romagna, Friuli-Venezia Giulia, Lazio, Liguria, Lombardy, Marche, Piedmont, Sicily, Tuscany and Veneto). The participating structures are over 80 and manage 138 sampling sites covering most of the Italian provinces.

The great adhesion has made it possible to propose an Executive Project - CCM 2020 Program on "Epidemiology of wastewater: implementation of the surveillance system for the early identification of pathogens, with particular reference to SARS-Cov-2" that sees the ISS with the role of coordination of the activities and verification of the analyses quality and the results, the Lombardy region as a lead institution and the involvement of other 11 Regions (Abruzzo, Aosta Valley, Apulia, AP of Bolzano, Emilia-Romagna, Friuli-Venezia Giulia, Lazio, Liguria, Sicily, Tuscany and Veneto). The CCM program, which is currently awaiting a response, would make it possible to finance the regions with the possibility of further strengthening the surveillance network.

4.1 SARI situation

To date, 7 between Regions and Autonomous Provinces (Apulia, AP of Trento, Emilia-Romagna, Lazio, Lombardy, Piedmont and Sicily) have started the insertion of data related to archive samples, taken as part of other projects or collected in anticipation of subsequent analysis; For some weeks now, they have been updating information in real time as samples are taken and analyzed. The following figure (Fig. 45) shows the Dashboard that illustrates an overview of the current picture of the SARI Project.

Fig. 45 - Dashboard current situation of SARI project. The legend, the left part of the Map, illustrates the Regions that have started the insertion highlighted in black (Apulia, AP of Trento, Emilia-Romagna, Lazio, Lombardy, Piedmont and Sicily) and the Regions that are about to insert the results (Abruzzo, Aosta Valley, AP of Bolzano, Campania, Friuli Venezia Giulia, Liguria, Marche, Tuscany, Veneto). The indicators represent respectively, from left to right and from top to bottom, the number of samples taken, the number of samples subjected to qualitative analysis, the number of samples in which the presence of SARS-Cov-2 was detected and the number of positive samples for which quantitative analysis has already been carried out. In the graph on the right, the sum of the samples taken is shown, grouped monthly. Finally, the last entry dates and the sampling date of the last and most recent samples are given below.

At the time I am writing (16/03/2021), the last sample was entered on 15/03/2021 (last entry date) and the database counts 1082 samples taken between September 2019 (oldest sample 17/09/2019) and March 2021 (most recent sample 10/03/2021). Of the 1082 collected samples, 942 were analyzed using the SARI protocol methods and 56% of the samples detected traces of SARS-Cov-2 RNA. In addition, 420 samples of the 536 positive results were also subjected to quantitative analysis with the aim of detecting the amount of genomic copies per liter of wastewater. The graph in Fig. 45, shown in Fig. 46, shows the number of samples taken per sampling date, grouped on a monthly basis, for each Region. From the chart it can be seen how the sum number of samples entered monthly by each Region, starting from the month of July in which the SARI Project was started, has remained almost constant confirming the commitment and the availability of the various Regions while keeping in mind that at this stage they act on a voluntary basis and in absence of funding.

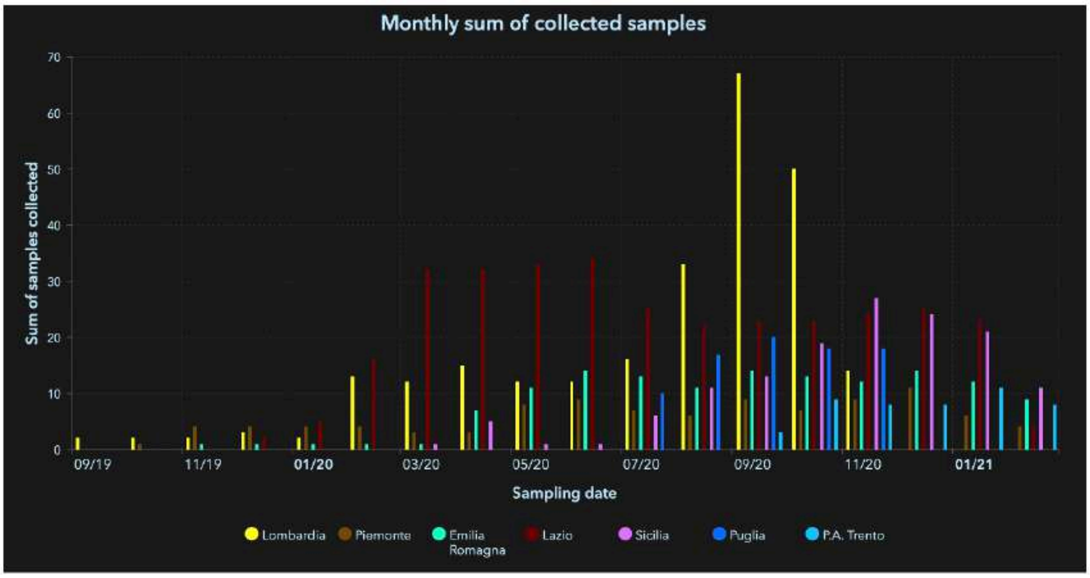


Fig. 46 - The figure shows the samples sum collected from each region from September 2019 until February 2021.

The results availability from regions of different areas of the Italian territory, thanks to the insertion of data by Southern, Central and Northern Italy, allows a preliminary analysis of the results at national level. Then, in the following paragraphs, the situation will be analyzed Region by Region.

In the following figure (Fig. 47) is represented the monthly sum of the samples number collected divided into 3 categories based on the qualitative analysis results with the Real-Time RT-PCR (presence/absence): *negative, positive or to be analyzed.* The data clearly shows the presence of positive samples previously compared to the first surveys of Covid-19 individuals in Italy. In particular, these samples are taken from a WTP in Milan (Lombardy) and a WTP in

Turin (Piedmont) in December 2019 and from a WTP in Bologna (Emilia-Romagna) in February 2020 (La Rosa et al, 2020(a)).

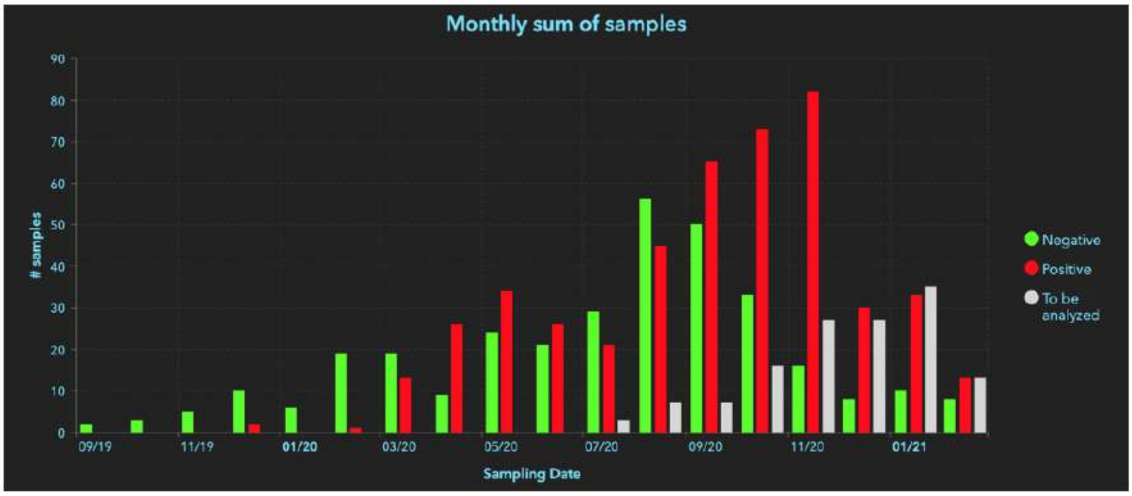


Fig. 47 - The figure shows the samples sum taken from September 2019 until February 2021 classified by qualitative analysis result: presence or absence of SARS-Cov-2 RNA or analysis to be performed.

Focusing only on samples submitted to Real-Time RT-PCR (942 out of 1082 collected samples), it is possible to analyze the temporal evolution of the monthly sum of positive and negative samples (Fig. 48).

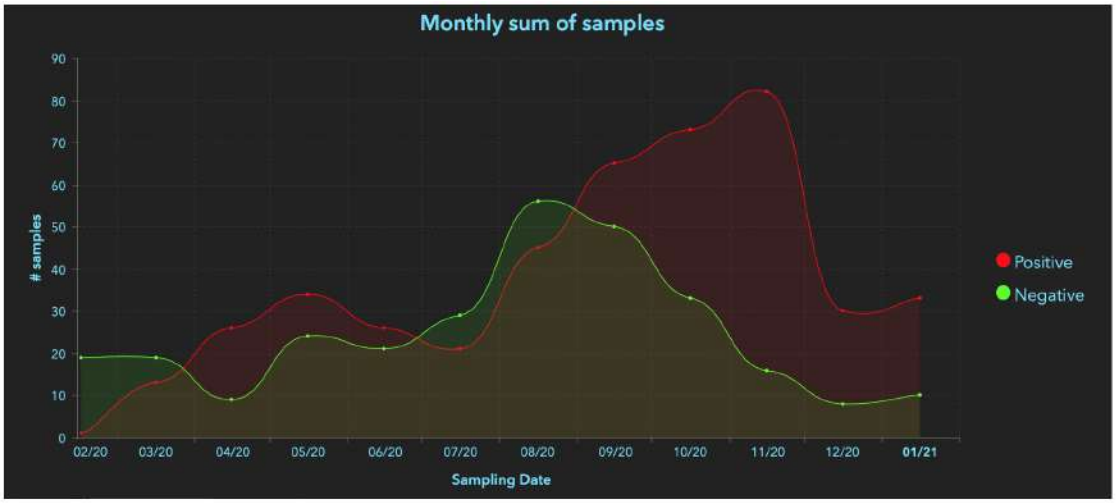


Fig. 48 - Temporal evolution of the sum of samples analyzed with Real-Time RT-PCR based on the obtained result, positive or negative.

By analyzing the temporal evolution of the monthly sum of the samples number in which SARS-Cov-2 was detected (positive samples) and those in which it was not detected (negative samples), it is clear that, the former, experienced a strong increase at the beginning of the epidemic (particularly between the months of March and May 2020) and a reversal in the early summer months, with a progressive decline until August. Since August, the number has started to grow again, although remaining below the sum of negative samples, reaching a peak in November, and then returning to decline. Samples in which SARS-COV-2 RNA was not detected show a completely opposite pattern.

More than the absolute value, it is interesting to observe the temporal evolution of the relationship between the number of positive and negative samples (Fig. 49).

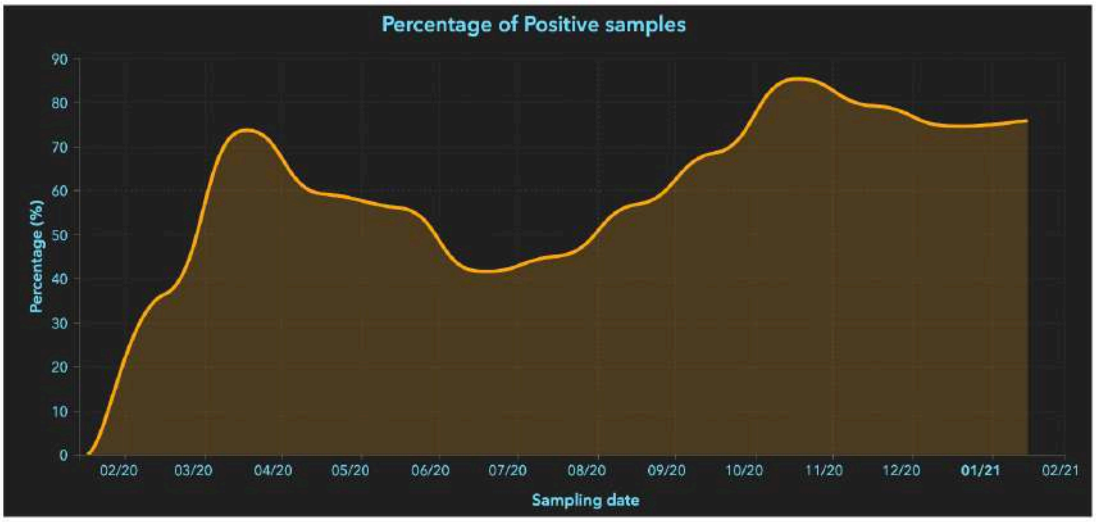


Fig. 49 - Temporal evolution of the percentage ratio between the number of positive samples and the number of samples taken, calculated on a monthly basis, between February 2020 and January 2021

The analysis to detect the presence of SARS-Cov-2 in wastewater samples therefore provides a picture of the situation which reflects fairly closely the evolution of epidemiological results obtained from the results of rhino pharyngeal swabs carried out on the Italian population. In the following picture (Fig. 50), the graphs show the data published by the Civil Protection on the Covid-19 situation in Italy through the bulletin issued daily (https://github.com/pcm-dpc/COVID-19) for a qualitative comparison with the data collected in the framework of the SARI project.

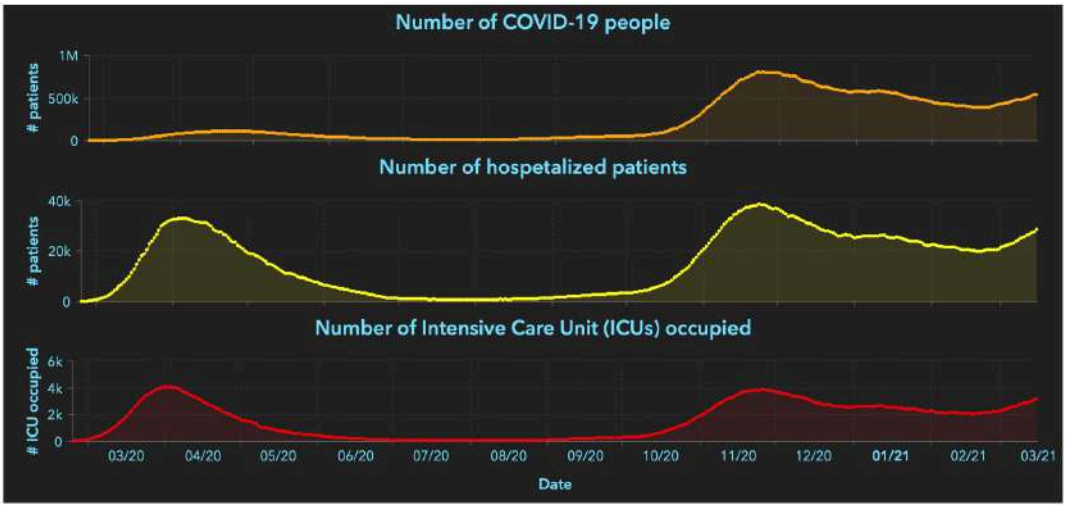


Fig. 50 - Temporal trend of the total number of individuals affected by Covid-19, of hospitalized patients and of occupied beds in intensive care units calculated daily. Data made public by the Civil Protection (https://github.com/pcm-dpc/COVID-19).

The temporal evolution of the subject's numbers currently affected by Covid-19, as well as that of the number of patients admitted and the number of beds occupied in the Intensive Care Units of Italian hospitals was reported. After a first peak between the months of March and April, the data have undergone a progressive decrease with a trend inversion starting from August and a second peak in November, exactly as we have seen just above for environmental data.

In the following paragraphs, the situation of individual regions will be analyzed in detail.

4.2 SARI – Lazio

Lazio region has joined the SARI project proposing 9 WTPs covering the provinces of Frosinone (1 WTP), Latina (2 WTPs), Rome (5 WTPs) and Viterbo (2 WTPs) for a total of 11 municipalities monitored (Fig. 51) and the involvement of about 3,430,000 equivalent inhabitants on a total of 5,879,082 residents according to Istat data updated on 1 January 2019 (http://www.datigis.info/scheda_dati_Depuratori/).

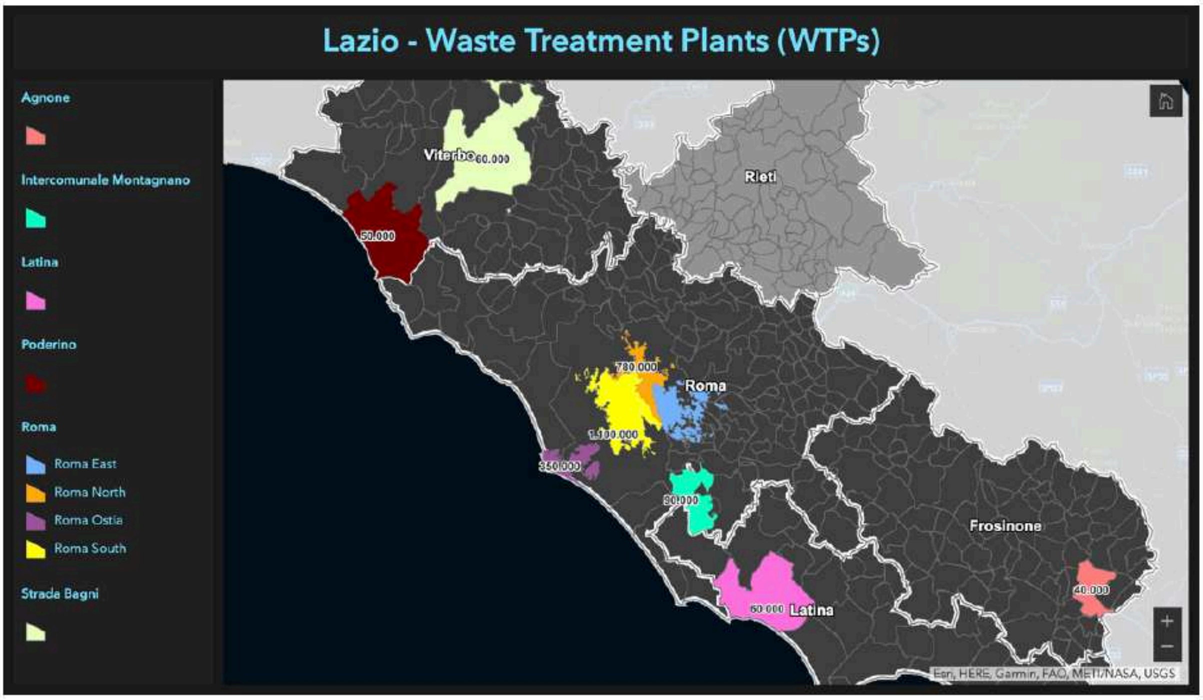


*Fig. 51 - Lazio Map: catchment areas for each **W**ater **T**reatment **P**lant (WTP) involved in the SARI project. For each WTP, the number shown on the figure indicates the number of equivalent inhabitants.*

Regional managers have access to the Regional Dashboard which collects information on the analysis of samples taken from the WTPs on regional soil (Fig. 52).

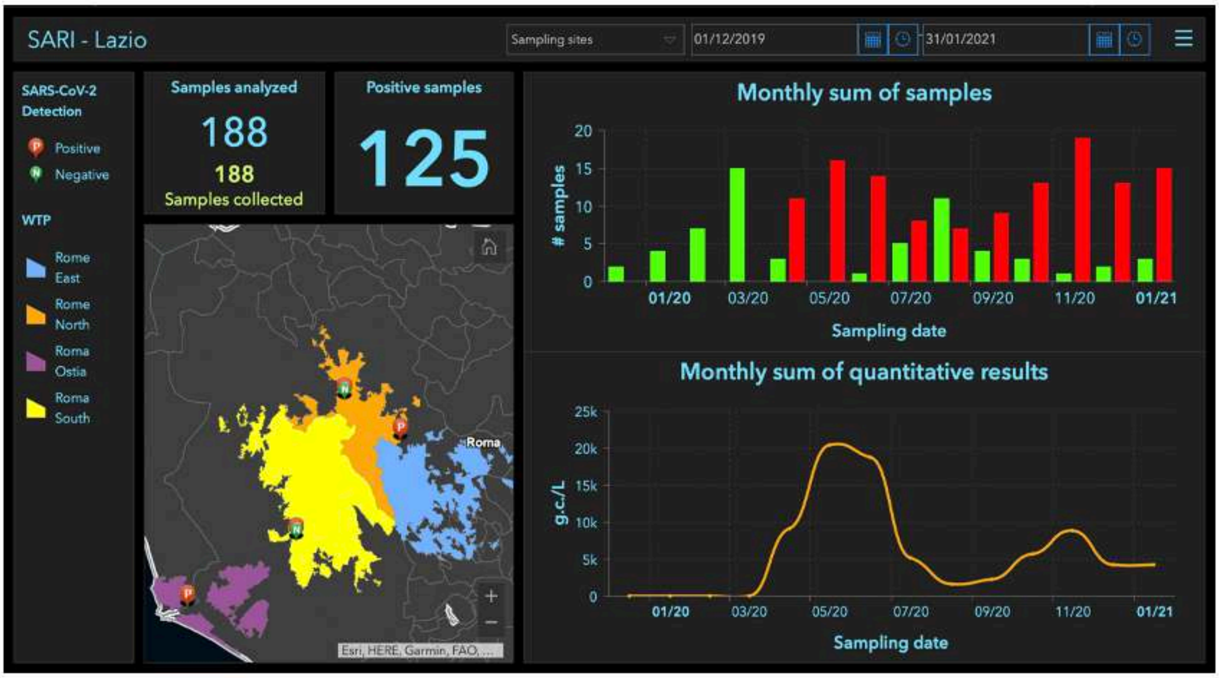


Fig. 52 - Lazio Region Dashboard: regional managers have access to the Dashboard where the results of the analyses carried out on the samples taken from the water treatment plants (WTP) selected for the SARI project are reported. In particular, information in the figure refers to the samples collected by the 4 WTPs in Rome in the period December 2019 - January 2021.

When the user accesses the Dashboard, the displayed data refers to the results sum of the regional WTPs:

- Number of samples analyzed from the total number of samples taken.
- Number of positive samples.
- Time evolution of the sum of positive and negative samples number grouped per month.
- Temporal evolution of the sum of individual quantitative results, or the number of genomic copies per liter of effluent, grouped per month.

At the right of the header, in the upper portion of the Dashboard, there are two selectors that allow to filter data by selecting a single WTP or to display the time evolution in a certain range of interest. When a selector is activated, the information displayed on the Dashboard changes depending on the choice made.

To date, data on occurrence and concentration of SARS-Cov-2 have been obtained from the 4 WTPs in Rome, which cover the entire city. The 188 samples taken between December 2019 and January 2021 were subjected to molecular analysis (Real-Time RT-PCR) to detect the possible presence of SARS-Cov-2 RNA and, in case of a positive result, subsequent analysis to determine the concentration of genomic copies per liter of wastewater.

Focusing on the qualitative analysis results (Fig. 53), the first thing that is noticed is the absence of positive samples before the month of April 2020. Starting from April, the time trend is very similar to the one discussed in the previous paragraph regarding data at a national level: the first wave has a peak in May 2020, with a progressive decrease in summer (in the months of June, July and August) and then rises again in September, reaching a peak in November to return to decrease again.

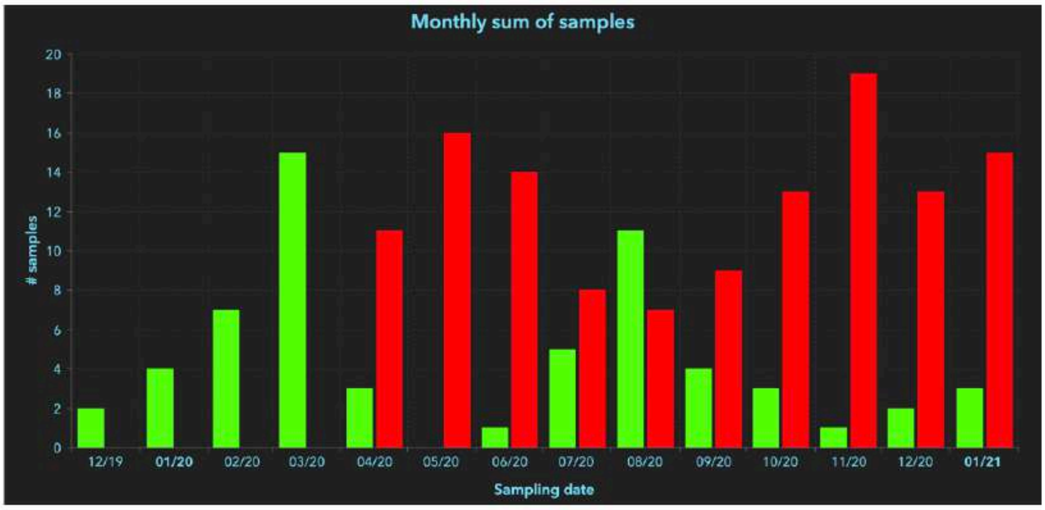


Fig. 53 - Temporal evolution of the monthly sum of the samples analyzed with Real-Time RT-PCR based on the obtained result, positive or negative of the 4 WTPs of Rome. Positive samples are indicated in red, negative samples in green.

The following figure is a quantitative results analysis (Fig. 54).

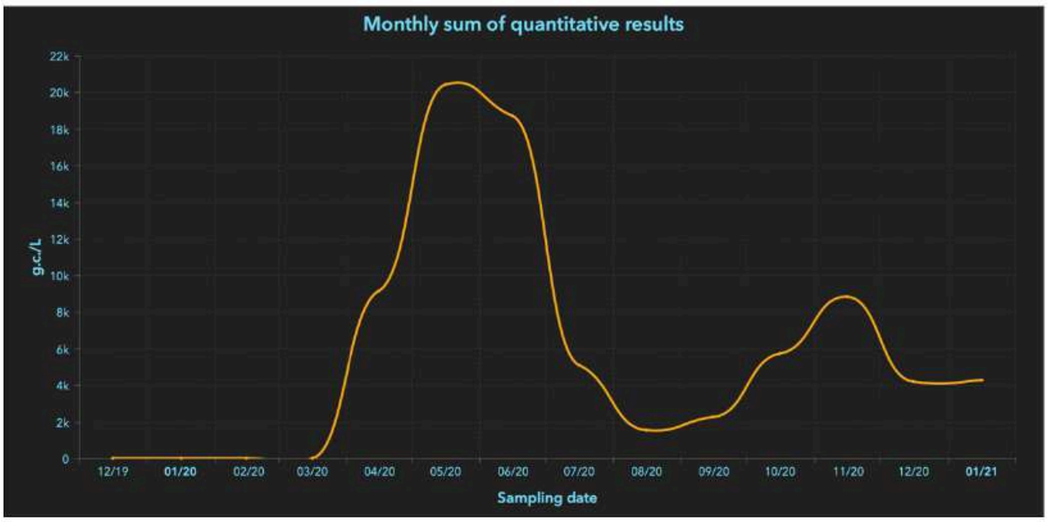


Fig. 54 - Temporal evolution of the monthly sum of genomic RNA copies of SARS-Cov-2 obtained from the quantitative analysis of samples taken from the 4 Rome WTPs and positive results to the analysis with Real-Time RT-PCR.

The curve has a double bell shape, the first with a peak in May and a second, lower in intensity, with peak in November; the drastic decrease in July and August reflects the impact of national blocking measures on virus transmission (as well as the decrease in December) as well as the low transmission rate expected in warmer season.

It is interesting to compare the results of environmental data with epidemiological data (or clinical data) obtained by performing rhino pharyngeal swabs to individual citizens. Before making this comparison (which is purely qualitative) it is, however, necessary to make a premise: the Civil Protection provides, for individual provinces, only the data on the sum of the total number of Covid-19 cases, this is probably not the most appropriate indicator for comparison with epidemiological data. It would be more appropriate to compare environmental data with indices such as the number of individuals currently suffering from Covid-19 in a particular way, but also with the number of hospitalized patients and the number of places in intensive care units, which however are available on a regional basis.

As far as Lazio is concerned, the province of Rome represents a major contribution to regional data. As we can see in the following figure (Fig. 55), from the comparison between the sum of the total number of confirmed cases in the Lazio region emerges a correlation in terms of temporal evolution and a contribution of relative data to Rome equal to approximately 75% of the regional data.

Fig. 55 - Temporal evolution of the sum of confirmed cases for the Lazio region (at the top) and for the single province of the Lazio region (at the bottom). The trend for the province of Rome is a scaled form of that of the total region, in particular the average scale factor is about 0.75. Data made public by the Civil Protection (https://github.com/pcm-dpc/COVID-19).

Starting from this consideration, it is reasonable to assume that the total number of current subjects affected by Covid-19 (number of COVID-19 cases), the number of hospitalized patients (number of hospitalized patients) and the number of beds occupied in intensive care (number of Intensive Care Units occupied) in the region of Lazio (Fig. 56) closely approximate the data of Rome, except for a corrective factor.

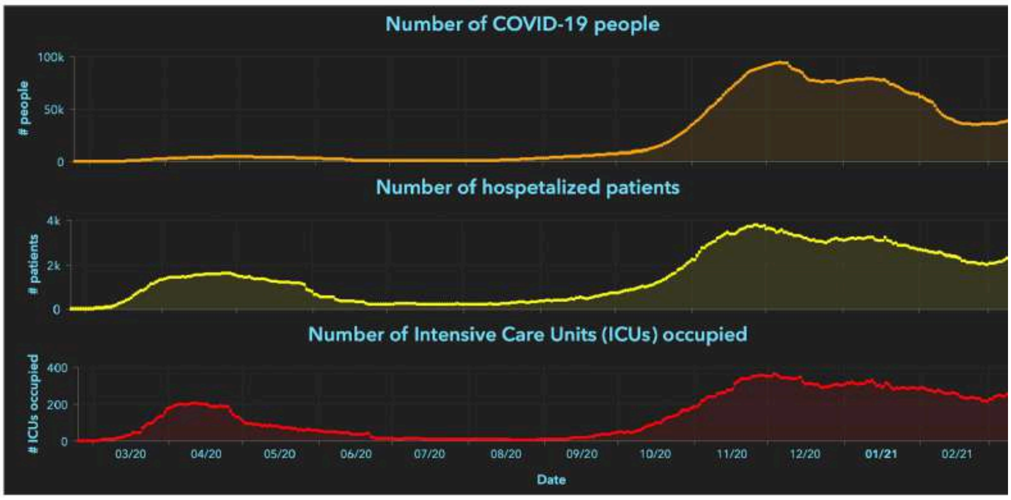


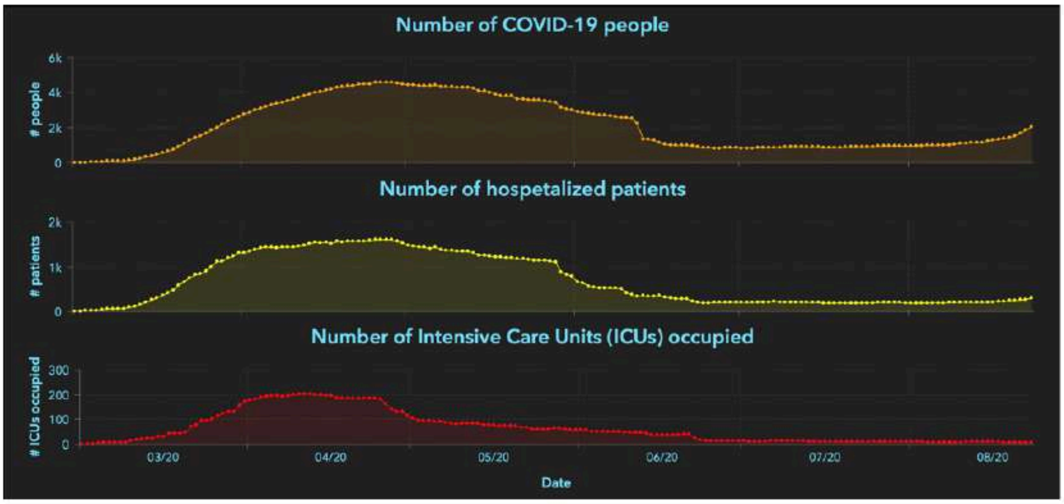
Fig. 56 - Lazio Region. Temporal evolution of clinical data from 01/03/2020 to 31/01/2021: number of confirmed cases, number of patients admitted to hospital and number of Intensive Care Units employed. Data made public by the Civil Protection (https://github.com/pcm-dpc/COVID-19).

To analyze the comparison between the quantitative results of environmental data and epidemiological data, the epidemic period of analysis was divided into two phases:

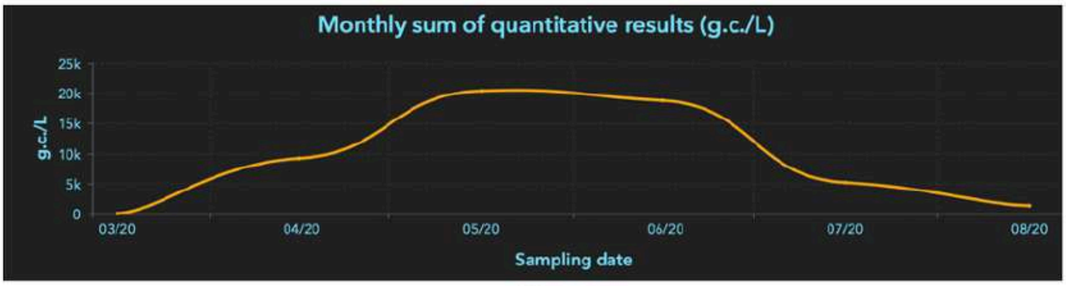
- First phase, from March 2020 (date of first positive wastewater sample) to the third week of August 2020;
- Second phase, from the last week of August 2020 to January 2021 (date of the last wastewater sample taken).

The following figure (Fig. 57) shows the first phase of the temporal trend of the epidemiological data (Fig. 57a) and the results of the quantitative analysis on wastewater samples (Fig. 57b) in the March-August 2020 period. The number of currently positive patients grew in the early epidemic period, increased steadily until it reached a peak in the second half of the month of April and then decreased until it tended to a plateau in the second half of June, which then remained about constant in the following weeks until the end of August. The number of hospitalized patients and occupied ICUs beds has a trend similar to that of the total number of Covid-19 patients but shifted to the left by a couple of weeks (peak in the first week of April).

Analyzing the temporal evolution of the environmental data (Fig. 57b), like for the clinical data, an increment is evidenced in the months of March and April. This trend continues up to a peak in May and then decreases less quickly than the result of epidemiological data and reaches a minimum value only in August.



(a)

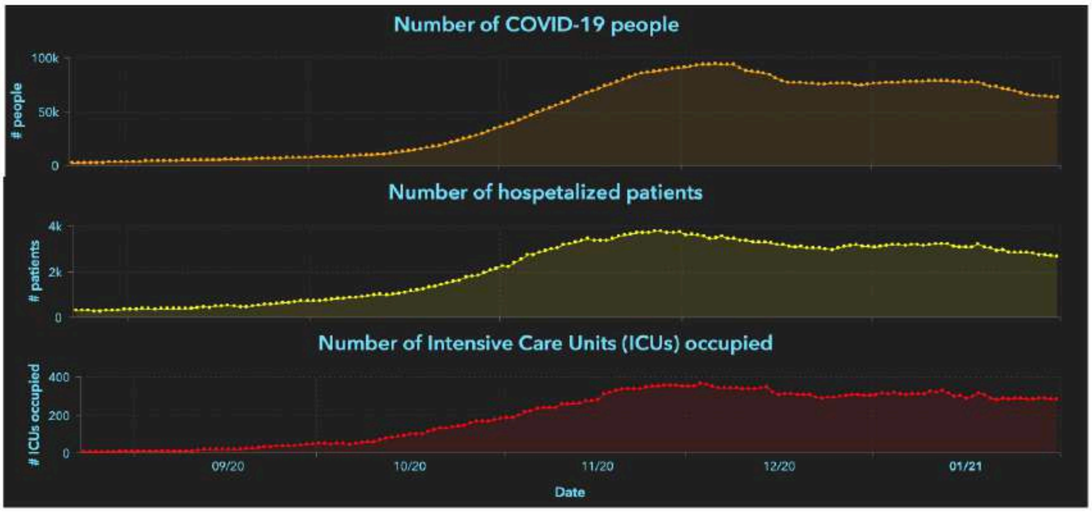


(b)

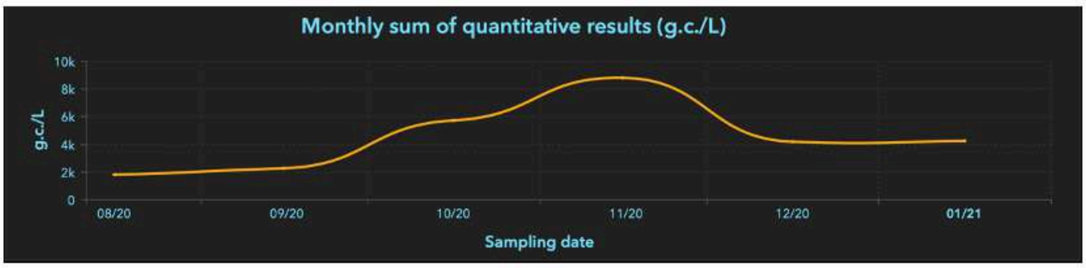
Fig. 57 - (a) Lazio Region. Temporal evolution of clinical data from 01/03/2020 to 23/08/2020: number of confirmed cases, number of patients admitted to hospital and number of Intensive Care Units employed. (b) Temporal evolution of monthly sum of genomic SARS-Cov-2 RNA copies obtained from the samples quantitative analysis taken from the 4 Rome WTPs in the period from 01/03/2020 to 23/08/2020.

The difference between the trends in clinical data and environmental data is likely to be due to the number of swabs carried out and the selection method of individuals to be tested for rhino pharyngeal swab in the first phase. In fact, because of the difficulty in finding the necessary reagents for the processing of swabs and the limited capacity of laboratories that analyzes the tests, daily in the Lazio region were carried out tests on an average of about 2,650 people (43,000 in all Italy) compared to the average of 19,000 tests (167,000 in all Italy) carried out in the second phase. In this first phase, the tests were carried out only on individuals falling into certain priority categories - hospitalized, at-risk health professionals and more fragile patients - and that "all other symptomatic individuals can be considered probable and isolated cases without additional testing", resulting in the inability to detect most Covid-19 cases, especially asymptomatic cases, underestimating the extent of the epidemic.

Let us now focus and analyze the second phase. From the last week of August 2020 the clinical data shows a light increment and then to endure a fast increase on October and November (Fig.58a), to therefore diminish in the month of December and to maintain a value approximately constant on January 2021. The temporal evolution of the quantitative results sums of the 4 WTP of Rome (Fig. 58b) shows a trend analogous to that evidenced from the clinical data, but with an advance of approximately two weeks. At the end of September, when an average of 200 new cases were recorded per day in Lazio (around 1500 per day throughout the country), the environmental data curve was already increasing, anticipating an increase in the spread of SARS-Cov-2 confirmed by clinical data in October. Similarly, in the second half of October, the environmental data curve spiked with a peak around 15 November 2020, confirmed by clinical data with a delay of about two weeks (between the end of November and the beginning of December) from epidemiological data. Finally, even the decrease in the number of Covid-19 cases from the first days of December 2020 shows a delay of about 2 weeks compared to what evidenced by wastewater analysis.



(a)



(b)

Fig. 58 – (a) Lazio Region. Temporal evolution of clinical data from 23/08/2020 to 31/01/2021: number of confirmed cases, number of patients admitted to hospital and number of Intensive Care Units employed. (b) Temporal evolution of the monthly sum of genomic SARS-Cov-2 RNA copies obtained from the samples quantitative analysis taken from the 4 Rome WTPs in the period from 23/08/2020 to 31/01/2021.

4.3 SARI – Lombardy

Lombardy was the most affected Italian region by the SARS-Cov-2 virus. The first case of patient suffering from Covid-19 was identified in Lombardy (in Codogno, in the province of Lodi): the patient, at first not considered at risk of infection with COVID-19, showed a severe form of pneumonia that did not respond to traditional treatment. Hence the arrangement to be subjected to the rhino pharyngeal swab which determined the presence of SARS-Cov-2 RNA. Within a few hours, the number of cases reported rose to 36, bringing to light an already difficult situation to control, resulting in an average of about 1300 cases a day in March.

Partly due to the fact that the Region had to move quickly to limit the spread of the contagion and partly thanks to a network for the collection and analysis of water already well established, Lombardy responded with great commitment and interest from the outset to help implement the proposal of the SARI project. The network (Fig. 59) has the largest number of WTP (33) covering a large part of the regional territory.

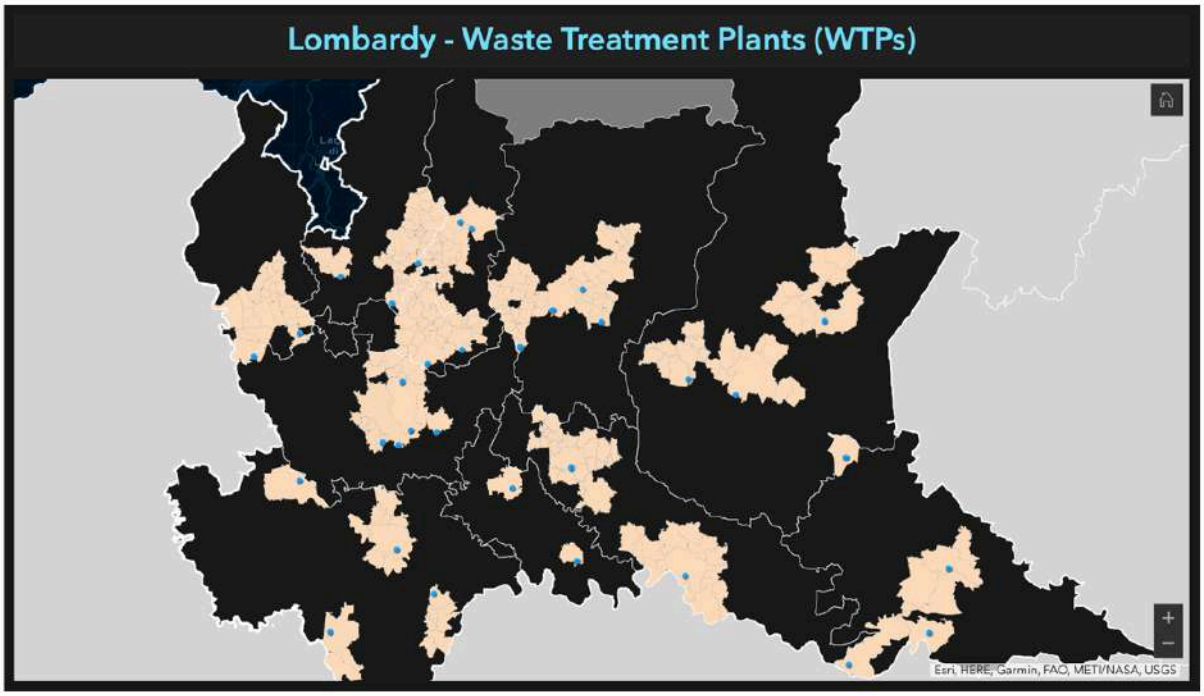


Fig. 59 – Map of Lombardy: catchment basins for each Water Treatment Plant (WTP) involved in the SARI project.

In the following figure (Fig. 60) the Dashboard accessible to regional managers with Lombardy region data is illustred.

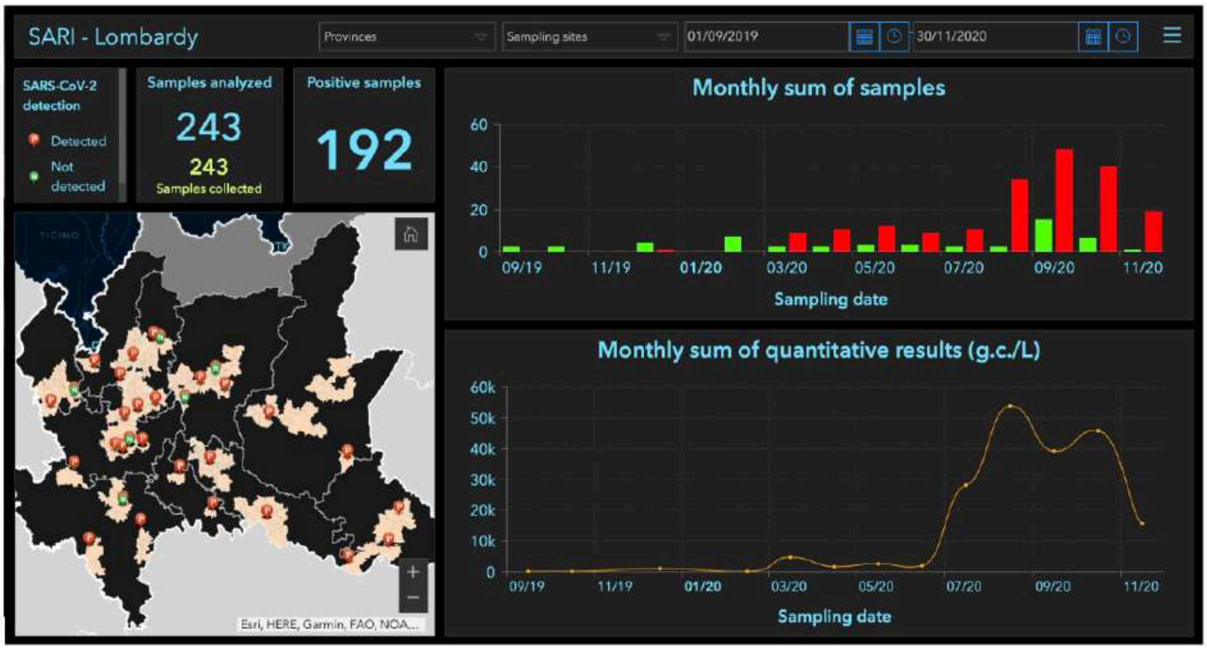


Fig. 60 – Dashboard of Lombardy: regional managers have access to the Dashboard where the results of the analyses carried out on the samples taken from the water treatment plants (WTP), selected for the SARI project, are reported. In particular, information in the figure refers to the samples collected by the 33 WTPs of Lombardy in the period September 2019 - November 2020.

The dashboard shows the analysis results of the 243 samples taken from the Lombardy WPTs between September 2019 and December 2020. In fact, at the time when the first cases appeared in the Region, previously collected samples were thawed- as part of other projects - to detect the possible presence of SARS-Cov-2 RNA traces indicating a virus circulation prior to the identification of the first case (20 February 2020). From the chart in the upper part of the Dashboard in figure 60, which shows the results of the qualitative analysis as a function of time, it emerges the presence of a positive sample already in December 2019, taken from one of the three WTPs in Milan, confirming the initial hypothesis.

Figure 61 shows a zoom of the graph on the temporal evolution of the qualitative analysis (presence/absence) in the epidemic period, that is from the end of February (when the first case was identified) to November 2020 (date of the last analyzed sample). Unlike Lazio, Lombardy samples taken in March 2020 were already positive. The percentage of the number of positive samples for each month remained approximately constant until August, when there was a strong increase. Thus, in September the percentage decreased slightly and then increased again in October and November.

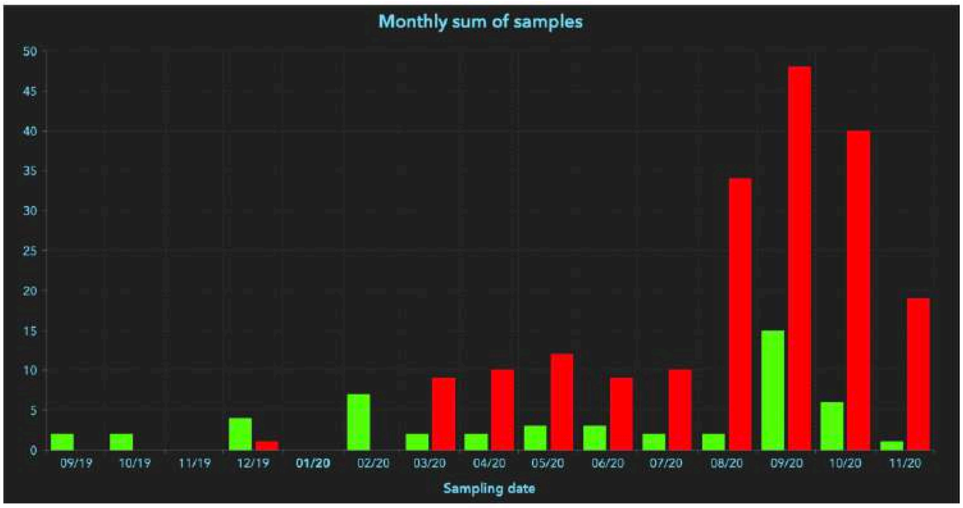


Fig. 61 – Temporal evolution of the monthly sum of analyzed samples with Real-Time RT-PCR based on the obtained result, positive or negative. Positive samples are indicated in red, negative samples in green.

The following figure (Fig. 62) shows the quantitative analyses carried out on wastewater samples which were positive for RT Real-Time PCR. Analysis of the temporal evolution shows an increase in the concentration of genomic copies in March 2020, a subsequent decrease tending to a plateau in April and May and a subsequent increase in the second half of June. From the end of June, the curve increased sharply until it reached a peak at the end of August and then reversed the trend, then increased in October and decreased drastically in November.

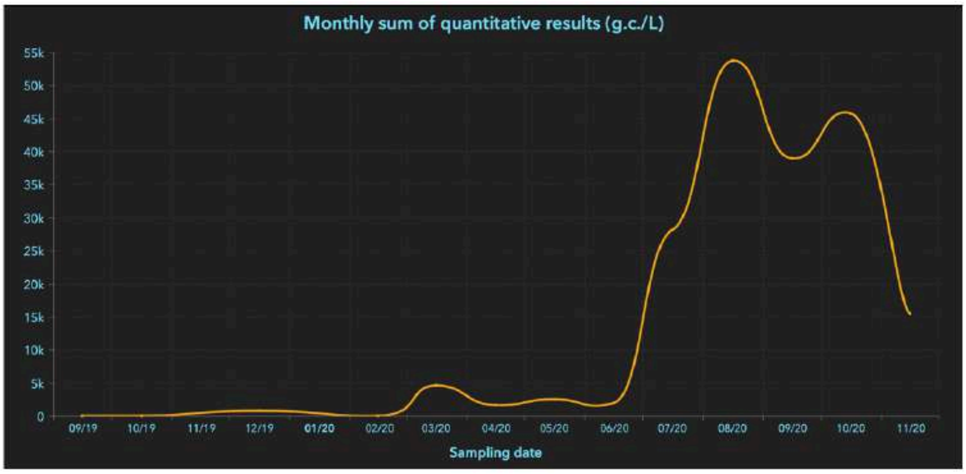


Fig. 62 – Temporal evolution of the monthly sum of SARS-Cov-2 RNA genomic copies obtained from the quantitative analysis of samples which were positive to the analysis with Real-Time RT-PCR.

By comparing from a graphical point of view the curve trend, sum of quantitative results, with the number of daily COVID-19 confirmed patients' cases (Fig. 63) a similarity emerges.

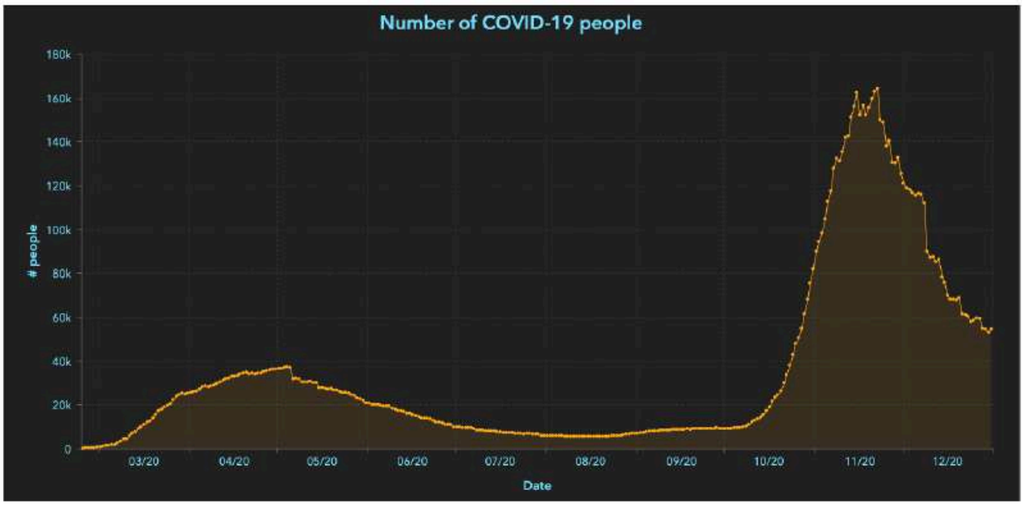


Fig. 63 – Temporal evolution of COVID-19 patients' number in the period from 20/02/2020 to 30/11/2020.

Both curves show the presence of a double bell shape. Both for the first phase (before summer 2020) and the second phase (after summer 2020), the peak of environmental data seems to anticipate the clinical data. The main difference concerns the months of July and August, during which environmental data suggest a wide spread of the contagion, while clinical data have the lowest values since the beginning of the epidemic. This difference probably can be explained by the decrease in the number of rhino pharyngeal swabs carried out in these two months (in Lombardy, the average in July and August was about 9000 swabs per day against 22000 in the two-month period September-October).

Further data will be needed of the samples collected from November 2020 (currently being analyzed in the laboratory) to be able to deepen the comparative analysis between environmental data and clinical data.

4.4 SARI – Autonomous Province (AP) of Trento

The system proposed by the Autonomous Province of Trento consists of 4 WTPs: Trento North and Trento South which collects wastewater from the municipality of Trento; Levico, that covers a group of west municipalities; Rovereto, which covers a group of south municipalities (Fig. 64).

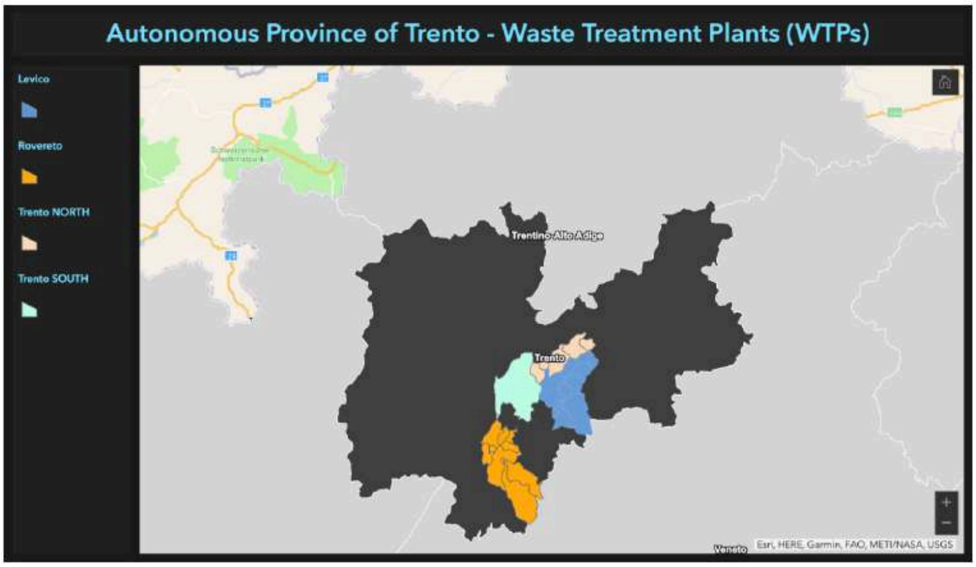


Fig. 64 – Map of the Autonomous Province of Trento: catchment areas for each water treatment plant (WTP) involved in the SARI project.

Below is the regional managers Dashboard (Fig. 65).

Fig. 65 – Dashboard of AP of Trento: regional managers have access to the Dashboard in which the results of the carried out analyses on the samples taken from the water treatment plants (WTP), selected for the SARI project, are reported. In particular, the information reported refers to the samples collected by the 4 WTPs of the AP of Trento in the period September 2020 - February 2021. it is noticeable that the time scale (Sampling date) does not coincide in the qualitative graph (above) and quantitative graph (below).

Of the 45 samples taken between September 2020 and February 2021, only one sample showed no trace of SARS-Cov-2 (this was the sample taken at the entrance of the Levico WTP on 13/12/2020). For this reason, the analysis of the ratio evolution between the number of positive and negative samples does not provide a useful tool for any kind of comparison.

To date, the quantitative analysis has been carried out on 25 samples collected between December 2020 and January 2021. Therefore, the data are not yet sufficient to analyze the temporal evolution (Fig. 66). However, it can be said that the trend "matches" that of clinical data, which shows a decrease in the last days of December and January.

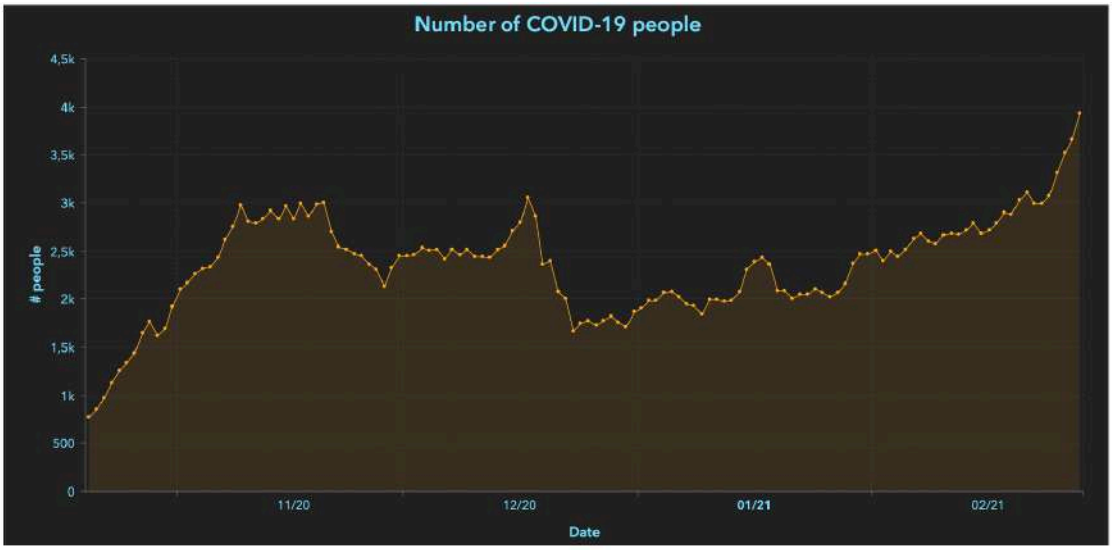


Fig. 66 – Temporal evolution of the number of COVID-19 patients in the period from 20/09/2020 (least recent sample date) to 28/02/2021 (most recent sample date).

4.5 SARI – Apulia

Apulia network has 9 WTPs: 1 for the province of Foggia, 2 for the province of Barletta-Andria-Trani, 2 for the province of Bari, 2 for the province of Taranto and 2 for the province of Lecce (Fig. 67).

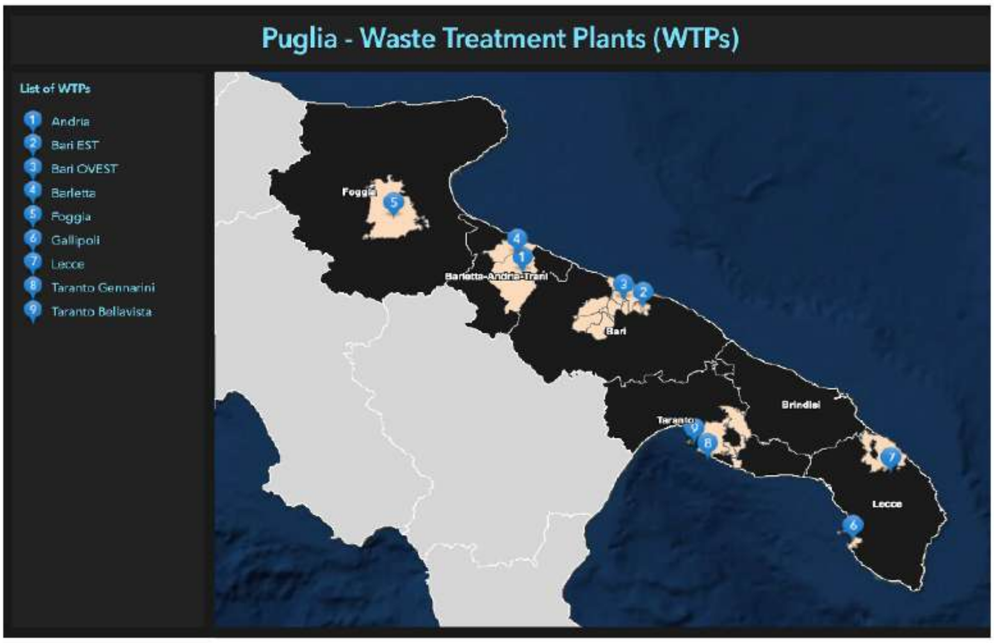


Fig. 67 - Map of Apulia: catchment basins for each water treatment plant (WTP) involved in the SARI project.

The following figure (Fig. 68) illustrates the dashboard containing the results of the analyses on the wastewater samples.

Fig. 68 - Dashboard of Apulia: regional managers have access to the Dashboard where the results of the analyses carried out on the samples taken from the water treatment plants (WTP), selected for the SARI project, are reported. In particular, information shown in the figure refers to the samples collected by the 9 Apulia WTPs in the period July-November 2020.

Facilities in Apulia region began collecting and analyzing wastewater samples for the SARI project in July 2020, when the number of COVID-19 cases in the Region was less than 100. Of the 82 samples collected, only 21 were positive (the first in September), 13 of which have already been subjected to quantitative analysis.

The following figure (Fig. 69) shows the number of people affected by COVID-19.

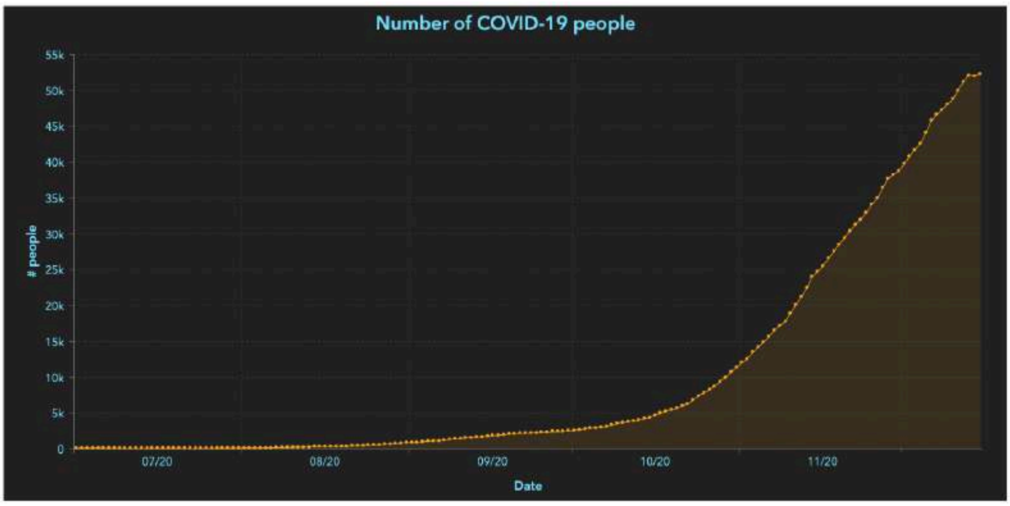


Fig. 69 - Temporal evolution of the number of COVID-19 patients in the period from 19/07/2020 (least recent sample date) to 30/11/2020 (most recent sample date).

Starting from September 2020, the percentage of positive samples increased to exceed that of negative samples in November. The temporal evolution of the genomic copies' concentration confirms the increase, with a slow growth in October and a real surge in November, as described by the graph of clinical data regarding the number of currently positive cases.

4.6 SARI – Piedmont

As part of the SARI project, Piedmont has recruited 10 purification plants which partially cover the provinces of Alessandria (1 WTP), Asti (1 WTP), Biella (3 WTPs), Cuneo (1 WTP), Novara (2 WTPs) and Turin (2 WTPs) (Fig. 70).

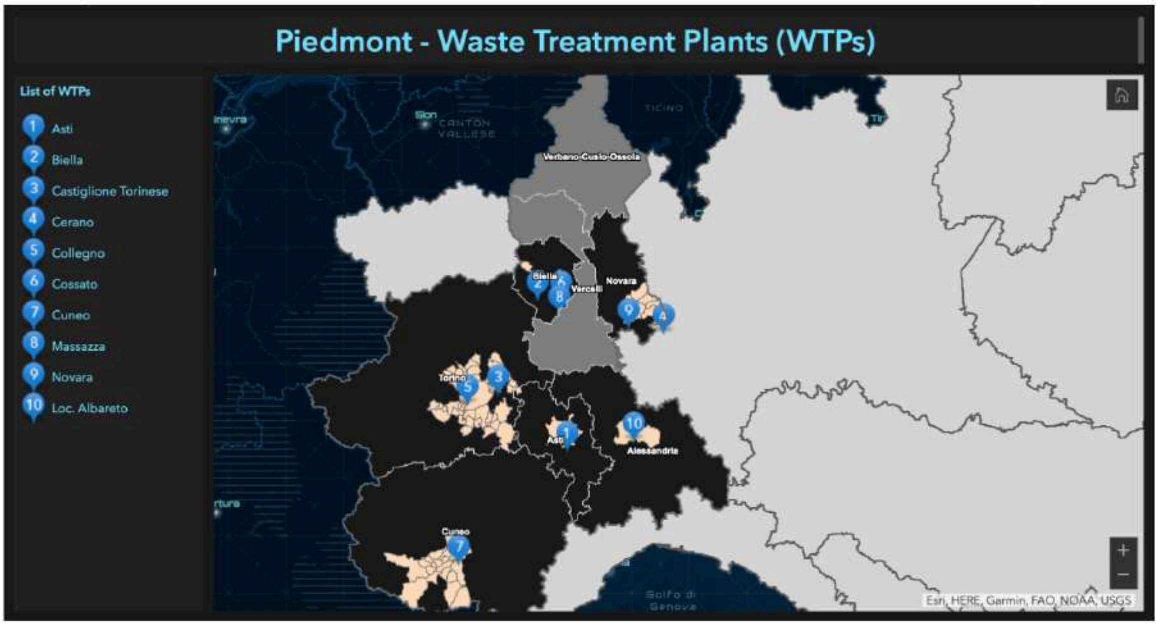


Fig. 70 - Map of Piedmont: catchment basins for each water treatment plant (WTP) involved in the SARI project.

In the following figure (Fig. 71) the Dashboard with the results is shown. As in the case of Rome (Lazio) and Lombardy, Piedmont carried out analyses on frozen samples which had been taken in the pre-epidemic period and found the presence of SARS-Cov-2 in a sample of December 2019, taken at the "Castiglione Torinese" WTP. With the currently available data, temporal evolution of the obtained data from the qualitative analysis does not provide any relevant information; the quantitative analysis has not yet been carried out on any sample. Piedmont is in fact waiting for reactive orders from a few months, which have not yet been delivered due to the large amount of orders received from companies, necessary for the execution of the protocol of samples analysis.

Fig. 71 - Dashboard of Piedmont: the regional managers have access to the Dashboard in which the results of the analyses carried out on the samples taken from the water treatment plants (WTP), selected for the SARI project, are reported. In particular, information in the figure refers to the samples collected by the 10 Piedmont WTPs in the period October 2019 - January 2021.

4.7 SARI – Emilia-Romagna

Emilia-Romagna's participation in the SARI project consists of 8 WTPs distributed in as many provinces: 2 WTPs in the province of Piacenza, 1 WTP in Parma, 1 WTP in Reggio Emilia, 1 WTP in Modena, 1 WTP in Ferrara and 1 WTP that joins the provinces of Rimini and Forli-Cesena (Fig. 72).

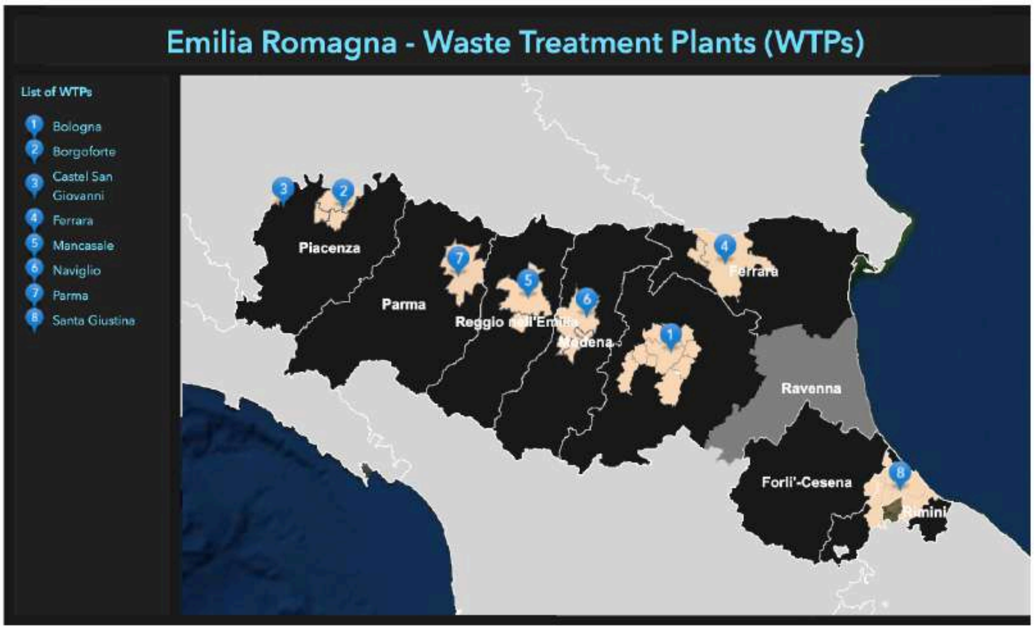


Fig. 72 - Map of Emilia-Romagna: catchment basins for each water treatment plant (WTP) involved in the SARI project.

Emilia-Romagna, like Lazio, Lombardy and Piedmont, also analyzed "historical" samples. As it is shown in the qualitative results graph (Fig. 73), in the sample taken from the sampling site of Bologna on 2nd February 2020, SARS-Cov-2 was detected, demonstrating also in this case the circulation of the virus weeks before the detection date of the first case in Italy (end of February 2020).

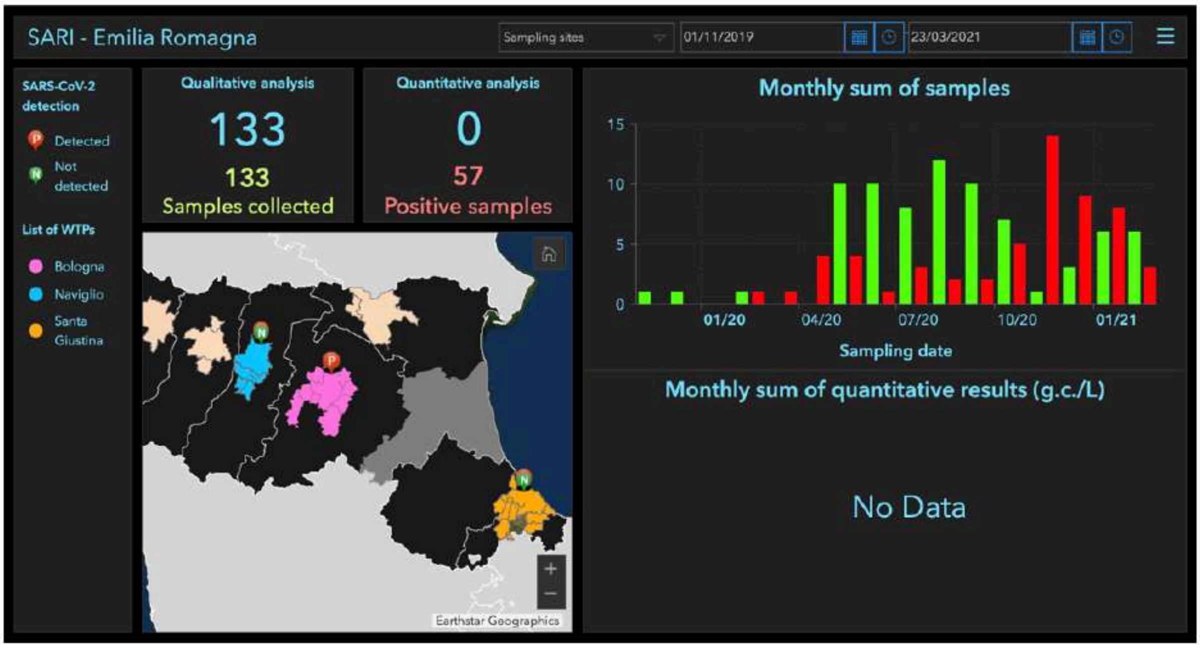


Fig. 73 - Dashboard of Emilia-Romagna: regional managers have access to the Dashboard where the results of the analyses carried out on the samples taken from the water treatment plants (WTP), selected for the SARI project, are reported. In particular, information in the figure refers to the samples collected by the 8 WTPs of Emilia-Romagna in the period November 2019 - February 2021.

Visual analysis of the temporal evolution of the positive and negative samples per sampling date number, allows to assert that the percentage of positive samples was very low in the period between July-November 2020 to then grow rapidly within two months and then return to decrease. In order to confirm this hypothesis, we will also need to analyze the quantitative analysis data. However, Emilia-Romagna, unfortunately, is suffering delays in the availability and delivery of materials.

4.8 SARI – Sicily

The WTP network structured by the Sicily Region is the one that, after Lombardy, has the largest number of WTPs (21) and involves all provinces (Fig. 74).

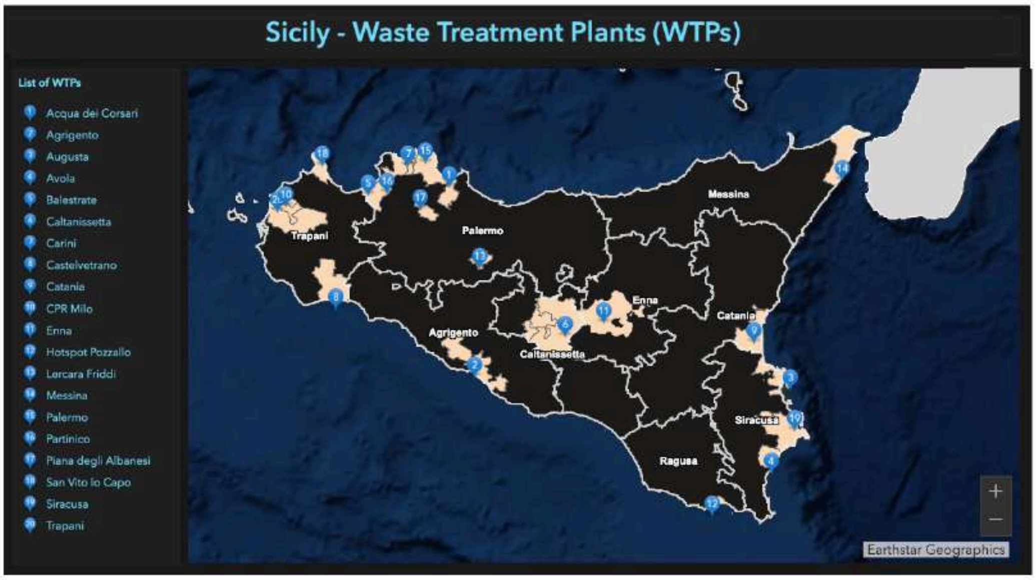


Fig. 74 - Map of Sicily: Catchment basins for each water treatment plant (WTP) involved in the SARI project.

Of the 138 samples taken from 11 of the 21 WTPs, only 50 have been subjected to qualitative analysis and none of the positive ones to quantitative analysis due to the difficulties, common to other Regions, in finding the reagents kits (Fig. 75).

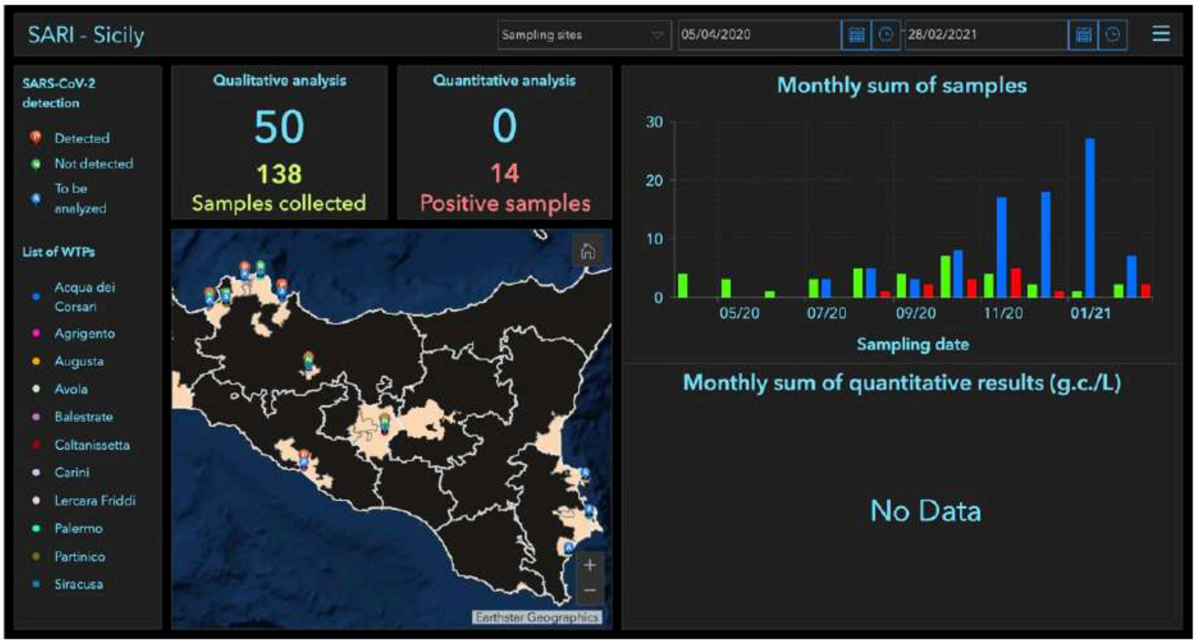


Fig. 75 - Dashboard of Sicily: regional managers have access to the Dashboard in which the results of the analyses carried out on the samples taken from the water treatment plants (WTP), selected for the SARI project, are reported. In particular, information shown in the figure refers to the samples collected from 11 WTPs in Sicily in the period from 05/04/20 (date of the least recent sample) to 28/02/21 (date of the most recent sample).

The amount of data does not allow conclusions on the temporal evolution of environmental data. It is, however, interesting to note the absence of positive samples until August 2020, which confirms what emerges from the clinical data that indicate Sicily as one of the least affected regions by the COVID-19 epidemic, particularly in the first phase (March-August 2020).

4.9 SARI – Other Regions

In the following section, information on the structure of the other regions that have joined the project – but have not yet started data entry – are illustrated.

4.9.1 Aosta Valley

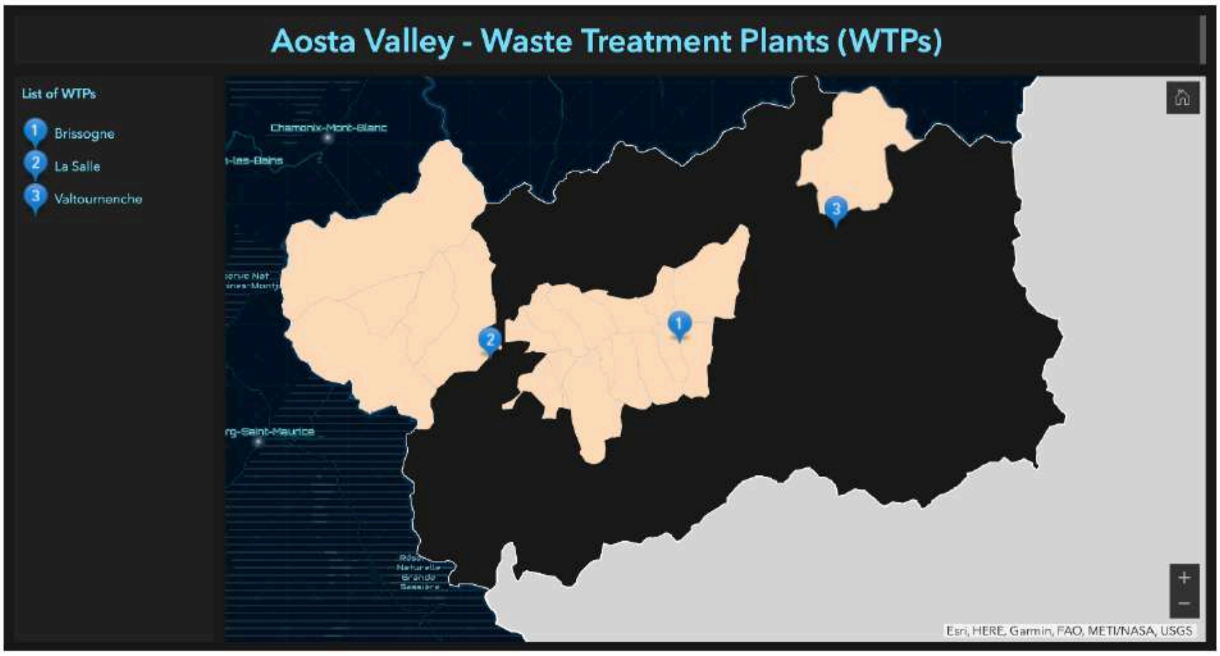


Fig. 76 - Map of Aosta Valley: catchment basins of the 3 water treatment plants (WTP) involved in the SARI project.

4.9.2 Autonomous Province (AP) of Bolzano

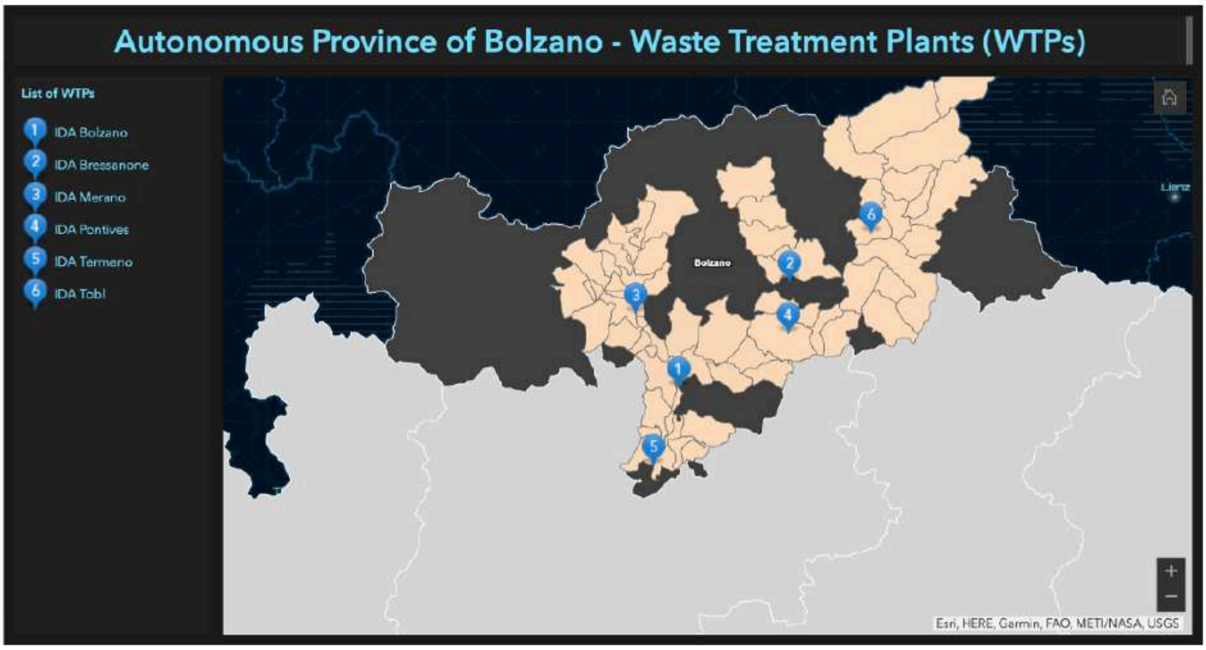


Fig. 77 - Map of Autonomous Province of Bolzano: catchment basins of the 6 water treatment plants (WTP) involved in the SARI project.

4.9.3 Friuli-Venezia Giulia

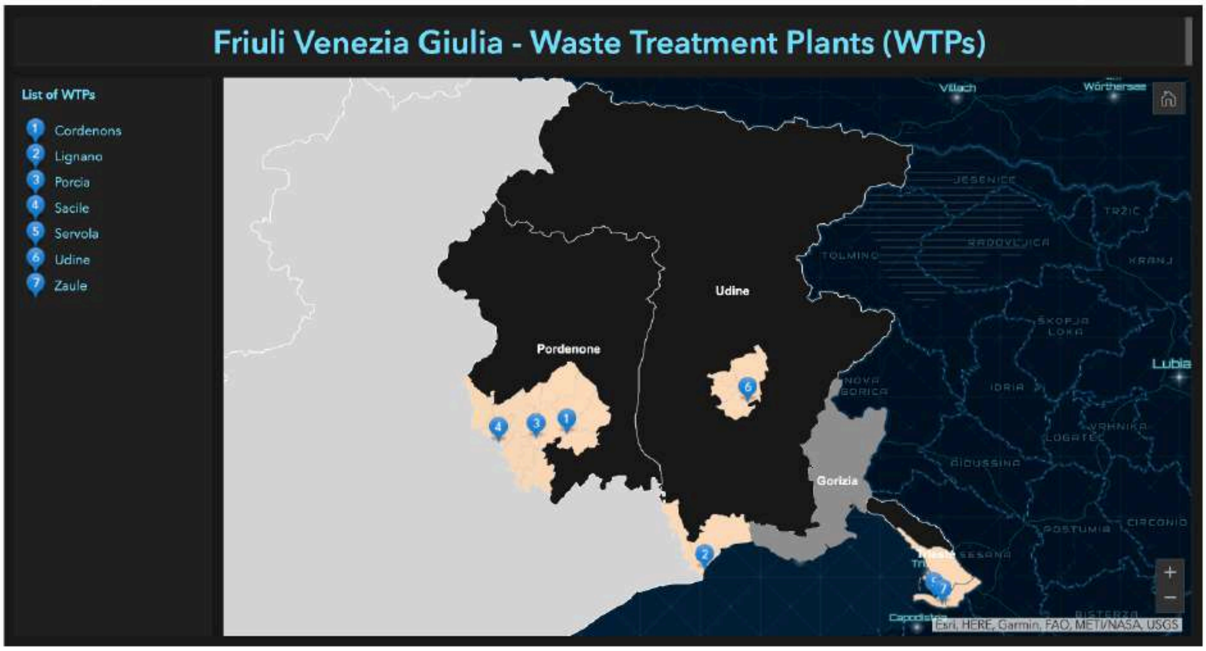


Fig. 78 - Map of Friuli-Venezia Giulia: catchment basins of the 7 water treatment plants (WTP) involved in the SARI project.

4.9.4 Liguria

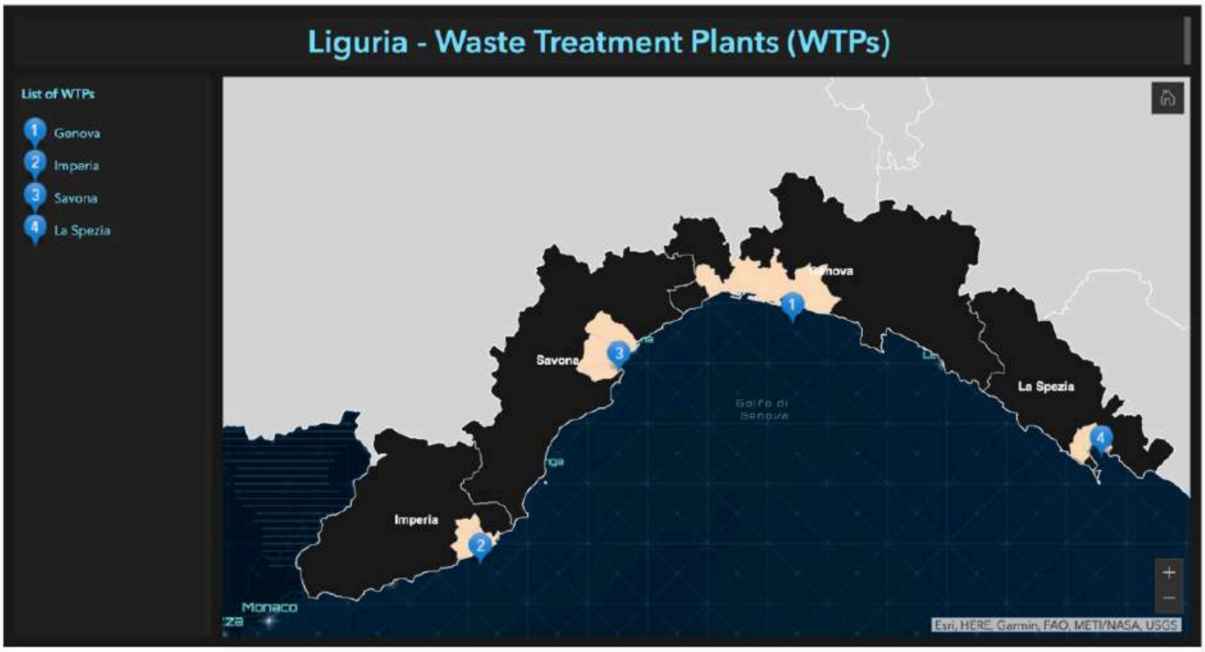


Fig. 79 - Map of Liguria: catchment basins of the 4 water treatment plants (WTP) involved in the SARI project.

4.9.5 Marche

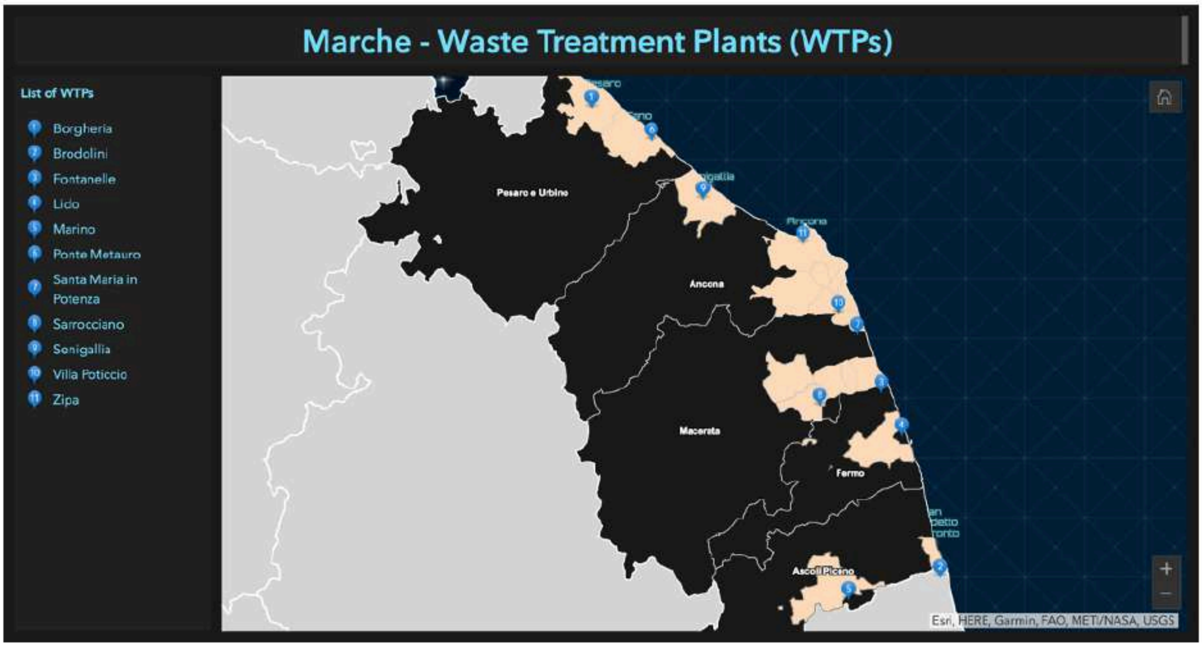


Fig. 80 - Map of Marche: catchment basins of the 11 water treatment plants (WTP) involved in the SARI project.

4.9.6 Tuscany

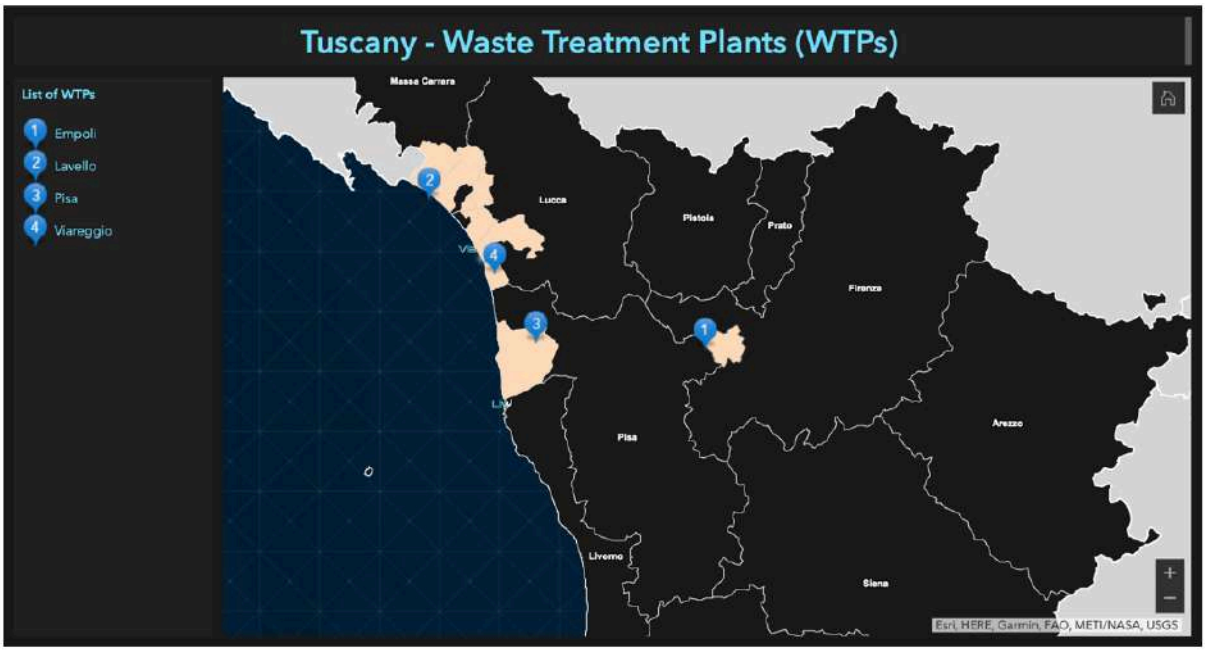


Fig. 81 - Map of Tuscany: catchment basins of the 4 water treatment plants (WTP) involved in the SARI project.

4.9.7 Veneto

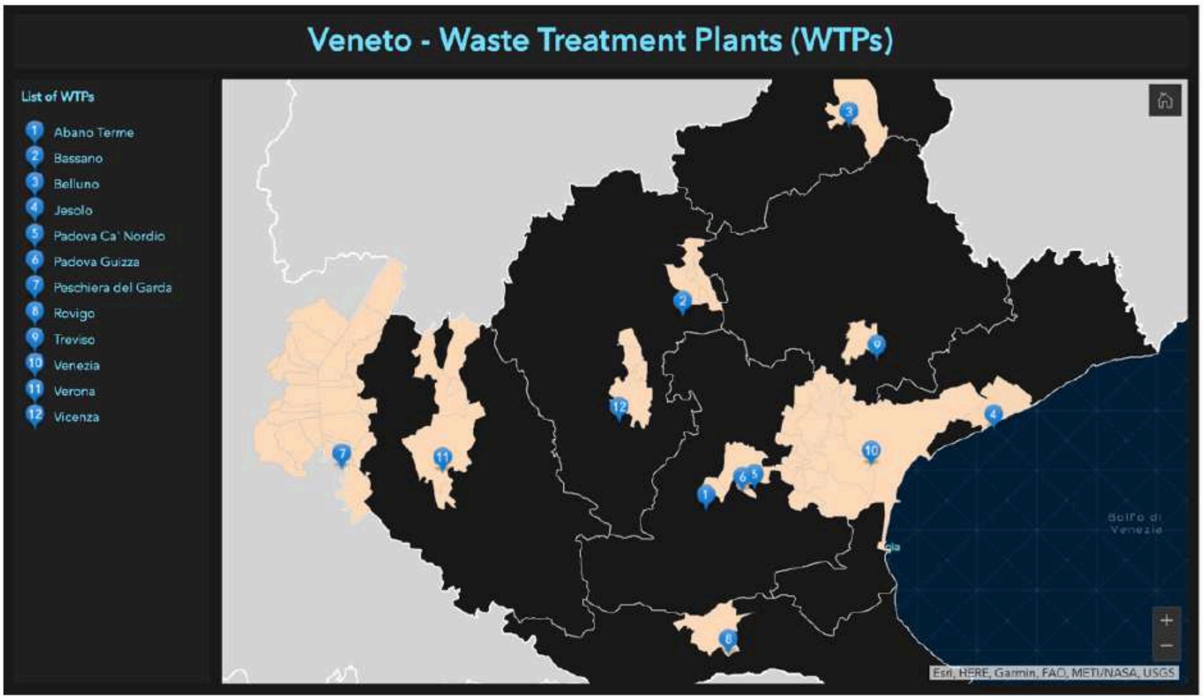


Fig. 82 - Map of Veneto: catchment basins of the 12 water treatment plants (WTP) involved in the SARI project.

5 DISCUSSION & CONCLUSION

This thesis is taking part of the change process we are witnessing in our days, defined as “digital revolution”. The digital revolution, which began in the industrialized countries of the world during the late 1950s with the adoption and proliferation of computers and digital memories, continues until these days. The process of digital massification can be placed between the twentieth and twenty-first centuries, with the appearance and initial implementation of the Internet and eCommerce. In particular, 2002 is considered the year of the beginning of the digital age since it is considered as the moment when humanity was able to store more information in digital form rather than in analog form. The digital age or information age is therefore the historical phase characterized by the wide diffusion of different digital products and by a series of social, political and economic changes occurred in relation to the advent of digitization of a large part of access to information. In the possible hypothetical future scenarios, digital revolution will continue to transform society in all its aspects: the approach to culture and the work environment, interpersonal relationships, the way in which leisure time is used, etc. This technological tsunami has also inevitably involved the world of health (eHealth).

Thanks to the exponential increase in data processing capacity and the reduction of its costs, resulting in the unprecedented spread of mobile and wearable technologies (smartwatch, smart-glasses, sensory t-shirts, etc.) intended to become the cornerstone of our lives, as well as progress in their innovative application to address health priorities, has developed a new branch of eHealth, known as mobile health or mHealth. This phenomenon is driven by the progressive adoption of innovative technologies: Artificial Intelligence, Big Data Analytics, Internet of Things, Extended Reality (Virtual Reality, Augmented Reality, and Mixed Reality), Geographic Information System (GIS), high-performance mobile connectivity (5G) and robotic systems contribute to a real redefinition of the system aimed at ensuring sustainability and increasingly rewarding care and care for the patient. Despite its undoubted complexity, especially in terms of governance, health system is also reaching the 4.0 paradigm that has its enabling factors in the digital and data-driven approach.

In recent months, also due to health emergency caused by the SARS-Cov-2 infection, there has been a strong acceleration of the development and adoption of digital health solutions. However, focusing on Italy, the path to adopt such solutions is still in its early stages: data collection for most health care facilities is currently paper based, resulting in problems that digital development could easily solve, such as loss of patient data, too much bureaucracy, higher prices, and low efficiency. The full implementation of digital health is a major challenge for Italy and, more generally, for whole Europe: it must include a commitment from central and local health authorities, a shared national strategy supported by appropriate regulatory actions and, in general, a new cultural approach geared toward innovation and technology. Local and national authorities can encourage and promote common frameworks through the harmonization of information systems and their integration, through definitions, standard and shared classifications and information infrastructures so as to make it possible to conduct in-depth assessments of the efficiency of health interventions, analysis of savings and benefits on the economic and social system of the country. In fact, the benefits of eHealth and mHealth, both for citizens and for the country, in terms of improving quality, appropriateness of care, governance and cost reduction, cannot be achieved without adequate integration of clinical, economic, and organizational data. To this end, it is clear that there is a need for accurate, timely, clear and comparable data to enable cost-benefit analyses, political assessments, both national and international comparisons, analysis of which makes it possible to identify best practices, evaluate quantitatively and qualitatively the benefits, calculate budget savings and above all improve health conditions of the population. In a citizen-oriented system, existing data must be made available to both patients and health facilities, each for its own necessity and needs. The data must therefore, in this area more than ever, be accessible and transparent: on the one hand the citizen must have the opportunity to access his personal data; on the other hand, while maintaining anonymity, the community must be able to know health conditions of the population, the policies that governments implement for the promotion and protection of health, for governance and health management. For the future it is hoped that the fragmentation currently existing in Italy and in most of the European countries regarding data on eHealth and mHealth will be overcome through the implementation of common technical infrastructures. To support this initiative, shared criteria, guidelines and the involvement of various institutions (governments, hospitals, private companies, associations of citizens and professionals, etc.) would be needed: briefly, a widespread cultural approach oriented towards innovation.

Finally, when developing a new technology, especially in health sector, the patient must play a leading role in concepts such as accessibility to technological devices and social inclusion must be considered. If, on the one hand, technology is mature, on the other, digital revolution in the health field could contribute to create a digital gap. A large proportion of the population, although with large differences between countries but also within them, is currently unfamiliar with mobile technologies. While mobile technology for health and disease management will continue to be seen primarily as a fashionable consumer trend for wealthy and educated people, health care systems and professionals are unwilling to incorporate them into their activities and people will eventually stop using it because they will lose enthusiasm and wont trust their safety and value.

In addition, it is essential to consider disabling/impairing conditions that influence the approach to technology for the most vulnerable categories, such as elderly and disabled persons. Less familiarity with technology can limit the potential impact of technology-based web interventions in older people. Older people face numerous physical or cognitive challenges when they encounter technology, including impaired cognition, hearing or vision difficulties, and perception problems. In addition to these physical limitations that require a modified design, older people face barriers that include lack of familiarity with technology, discomfort in requesting assistance, trust issues, and privacy concerns. It should, however, be stressed that the number of older people who have used technology in their working lives is likely to increase considerably in the next few years and therefore the next generation of older people will be better adapted to the new electronic environment. Regarding people with disabilities, however, during the development of a system it is essential to provide alternative modes of interaction to traditional ones with the aim of adapting the devices input to the various patient-specific needs.

To sum up, the development or use of innovative health technologies is constantly growing and the feeling is that we are still only at an early stage with a huge potential to improve the quality of health care while reducing its costs. The main aims of eHealth and mHealth interventions are the following:

- improving the quality of life of the user/patient;
- home care promotion;
- sharing information between users in an intuitive and real-time way;
- providing support in emergency situations.

Four examples of health digitization have been illustrated in this thesis: the first two use Augmented Reality (AR) and Mixed Reality (MR) technology; the other two use a Geographic Information System (GIS) technology for the monitoring of citizens and environmental surveillance in the era of COVID-19. In this final part we discuss the strengths and the main problems for each solution I propose.

♦ CogAR

CogAR is a home-made marker-based Augmented Reality (AR) App designed for smart glasses with the aim of monitoring and supporting people who are affected by both mild age-related cognitive decline and sensory impairment during Activities of Daily Living (ADL). The goal was to present a tool able to support people with multiple impairments that are considered vulnerable with unique needs and challenges.

An AR-supported home environment can be useful for patients while navigating the home itself, providing cues for sensorial integration. This patient empowerment should lead to an improved confidence during ADL, could enhance social life and, ultimately, stimulate to perform a physical activity. The possibility provided by AR to merge cognitive exercises with physical activity is expected to make more effective support intervention. In fact, increasing level of physical activity has now been identified with certainty as a protective/preventive factor against the progression of neurodegenerative diseases (Verdelho et al, 2012; Kou et al, 2019).

Difficulties of older people with learning new skills as well as accessing new technological solutions would limit their ability to acquire the conceptual knowledge needed to interact with a novel interface, in both cognitive and sensory diseases. Furthermore, impaired attentional control would also disrupt their ability to adopt unfamiliar procedures. The proposed system presented could enhance the quality of life of elderly people breaking down these barriers for the following reasons: no need to learn new information or a high cognitive load, neither any input device nor button is required to be pressed, and requires no special equipment beyond smart glasses and stickers to be placed on targeted physical objects. In addition, thanks to the ability to share the screen and GPS integrated in the device, the caregiver can at any time also remotely monitor patient's activity. That of the caregiver is another very interesting point: the constant pressure to meet the care and support required by their relatives can cause debilitating levels of stress for the caregiver, resulting in the placement of the affected person in a long-term care. From the caregiver's point of view, it has been found that even small reductions in load relieves the prevalence of depressive symptoms in this category, reducing the likelihood that they themselves need support. This can lead to more successful informal care, resulting in reduced medical costs and delays in long-term placements.

Therefore, I am confident that our system could meet the criteria of compliance (guaranteed by always having the device by hand), dignity and usability. However, between

January and February 2020, we were in process of applying for funding to plan a pilot study, but the COVID-19 pandemic delayed the organizational procedures.

♦ Mixed Reality Communicator

The second system consists of a MR headset on which is performed a home-made App with the function of allowing individuals suffering from speech disorders and motor disabilities to communicate through the detection of gaze direction. People with speech disorders must use technologies that can replicate the word, such as speech synthesizers, to communicate. If a person who does not have the ability to speak also has motor disabilities that do not allow him to use traditional input devices, one solution is to detect the position of the eyes (gaze). The user, by changing where he looks, can select one of the virtual elements of the table that is shown inside the user's field of view through the head-set display, each of which is associated with a certain phrase that is read aloud by the device through the Text-To-Speech technology.

The eye-gaze interfaces can be an efficient input mean because eye-gaze is natural, fast, and involved muscles are subjected to little efforts (Ball et al, 2010). A previous study engaging amyotrophic lateral sclerosis patients have demonstrated that subjects who used eye-gaze devices were less depressed and showed an improved quality of life in comparison to whom were using a phonetic board (Hwang et al, 2014). The introduction of eye-gaze controlled computers at home and school could enhance children's communication skills, allowing them to express their desires and to carry out recreative activities (Hornof and Cavender, 2005), as well as improving their social activities (for example, choosing their game mate or which song to be listen at school (Van Niekerk and Tonsing, 2015). Employing MR communicators to have a face-to-face conversation, without losing the non-verbal conversational component, requires only a brief learning period (Pasqualotto et al, 2015) and a low workload (Kathner et al, 2015).

The choice in our solution to use sentences rather than showing a keyboard was made with the purpose of reducing the downtime during the conversation (Majaranta and Rih, 2002); moreover, the employment of pictogram was originated by the fact that disabled people, children in particular, prefer symbolic images instead of words (Wolk et al, 2017). Regarding dwelling time for eye-gaze element selection, previous researchers (e.g., (Majaranta et al, 2006; Stampe and Reigold, 1995) stated that few hundred of milliseconds are considered a good tradeoff between false selections and speed of communication. Since our system is developed for disabled individuals, we set a selections threshold that equals 2 seconds.

Main critical points are the technological limits related to gaze-based assistive technologies. In general, accuracy could be not considered as good as a traditional mouse, for both technological and eye-features properties. In fact, eye-movement are subconscious, while a total and constant eyes' control is required. If on one hand, people with disabilities in may find difficult to search and select simultaneously (Ball et al, 2010), it is important to underline that in some cases they don't have other ways to communicate.

As with CogAR, the COVID-19 pandemic delayed the organizational procedures of the experimental study.

♦ GIS systems to monitor COVID-19 pandemic situation through daily reports of the citizens

The recent COVID-19 pandemic clearly showed that we were not ready for this kind of event. Our society has reached a level of global interconnection that makes an epidemic a very problematic event to contain with traditional quarantine measures. This means that a highly contagious disease can spread easily throughout the world resulting in putting health systems under tremendous pressure, especially in countries where these systems are already in a precarious state.

It is, therefore, necessary to find a way to effectively limit the spread of the pandemic in the shortest possible time, retrieving the information of people who have had contact at risk with a patient tested positive for SARS-Cov-2 (contact tracing). Although contact tracing is undoubtedly a very promising weapon for containing the exponential contagion spread, the risks involved in the massive application of population control techniques must be taken into account, as problems relating to privacy violations and social stigmatization, as well as the risk of unpopular decisions being taken or civil rights being infringed. Therefore, the objectives of contact tracing must be achieved without causing distrust within the community and maintaining maximum sensitivity in individual situations. In this regard it is likely that the need of European countries to maintain unchanged the citizens' rights (typically mentioned in the constitutions of democracies) using the GDPR (*General Data Protection Regulation*, EU Regulation 2016/679) leads to the loss of effectiveness of contact tracing activities. In the initial phase of the pandemic (March and April 2020), several regions in Italy have independently developed the Apps made available to citizens through smartphone stores. The incompatibility between the various Apps and among the various tools used by provincial organizations has made it very complex the flow of information between various regional bodies and between the

Regions and the Italian National Institute of Health (ISS), responsible for the design and maintenance of a national database, so that in most cases the data were transmitted by e-mail. Interoperability between systems has inevitably led to delays in the communication of data and communication of incomplete and/or incorrect information.

Unlike most of the systems developed, in the system I propose, the technology is not used to independently detect any contacts at risk, but rather to collect information sent by citizens in digital format on a centralized database, managed by the ISS which, as a health authority at national level can access patient information without harming the privacy of the citizen. The information entered is then shared in real time between the citizen, the doctor General Practitioner (GP), local and regional health authorities through field apps and visualization tools avoiding the loss of information and delays in communication. Similarly, the ISS has access to a constantly updated database through which it can view and analyze data on the condition of citizens in general, identifying quickly and intuitively the most affected areas by the spread of the virus which therefore require a higher level of attention and probably more stringent containment measures.

This system can be very effective for two purposes: 1) digitization of communication between citizens and medical staff; 2) direct collection on a centralized database. Under the pressure of GPs that, according to the collected testimonies would welcome the system in its daily activity, the system could reach a large part of the population, becoming one of the main channels for the collection of data. Once the COVID-19 emergency situation is over, the data will be deleted, and the system withdrawn. If mass adoption is found to be acceptable to citizens, the system could be converted to continue to serve as a channel of communication between GPs and citizens even later.

♦ GIS systems to monitor COVID-19 pandemic situation through wastewater analysis

A GIS system is well suited to environmental monitoring of urban wastewater which contributes to the active surveillance of the population through a community-focused control approach rather than individuals, articulated for population aggregates on a territorial basis. The environmental SARS-Cov-2 surveillance, on the model of Wastewater Based Epidemiology, is able to provide important information both during the epidemic period, to assess the temporal and spatial evolution of the spread of the virus, and in the post epidemic period, in order to detect in a timely manner the possible resurgence of the virus in a certain community.

Environmental surveillance has the intrinsic advantage of providing objective sampling within a given catchment area (i.e., without bias introduced by selective clinical testing criteria) which has the potential to be used to complement clinical surveillance but also to enable more comprehensive surveillance in areas with poor clinical performance, for example in crowded environments with extremely limited resources such as informal settlements or more generally in marginalized populations. In addition, it can be used to test historical samples to document the early circulation of the virus in different contexts. It is stressed that the possibility of Wastewater Based Epidemiology to fully express its potential, both with regard to monitoring of epidemiological trends and as an alert system with regard to the reactivation of the virus circulation in the population, is highly dependent on several factors, such as the frequency of sample collection, the frequency of analysis, the frequency of data collection and analysis, as well as the degree of resilience of the territorial network in the long term (for example, phenomenon of drop-out by participants). The definition of appropriate spatial sampling is also important: the samples taken must be as representative as possible of the target population, therefore, collection points should draw on geographically and demographically different populations and should also include areas and populations not connected to the municipal sewage system. Given the inability to target specific individuals due to the aggregate nature of environmental samples, this approach does not allow the identification of infected individuals and therefore does not give rise to ethical issues.

The environmental surveillance system in Italy (Environmental Surveillance of SARS-Cov-2 through urban wastewater in Italy, SARI), presented in this thesis, includes 15 regions and has about 90 facilities and over 180 sampling sites distributed evenly within the Regions. Data management and risk assessment is entrusted to the health sector of the Regional Authorities, under the technical-scientific coordination of the Italian National Institute of Health (ISS) However, a protocol to translate environmental evidence into public health actions has not yet been defined or implemented. This is mainly since only recently the Ministry of Health has recommended environmental surveillance by offering funding to cover, at least partially, management costs.

From the results obtained at this preliminary stage of the project, it was found that environmental surveillance describes the trend line related to the cases detected following the buffer (in some cases they even seem to anticipate the clinical data, but further analysis is needed to be able to state it with certainty and above all to quantify the advance) confirming therefore that WBE can also be used to verify the reliability of epidemiological trends, which could be affected by several factors, such as test delays, test positivity rates and delays in data transmission.

Therefore, environmental data can provide a sensitive complement indicator as support to decision-making including the lifting of restrictive measures, the general opening of schools, catering, and meeting places, etc. This approach can also be extended, through targeted sampling, to specific communities of interest (e.g. residential, prison, hospital, schools, etc.) taking into account, however, the need to have representative wastewater samples in space-related terms requires not too circumscribed territorial areas. For any site that produces positive samples, it would therefore be necessary to undertake a field survey in the catchment area, including active case research, to try to identify any suspicious cases together with the application of initial social and health measures while further investigations are under way.

The main critical points are the lack of definition of a threshold value for virus concentration, beyond which the situation requires to be under observation; the minimum number of COVID-19 cases so that the virus can be detected in wastewater samples. Identifying the relationship between viral RNA concentrations in wastewater and the incidence of the disease in a local population is very complex due to many variables: differences in viral RNA excretion between individuals and over time, methodological determinants concerning the composition of wastewater, such as effects of meteorological events, sampling and analysis methods and demographic factors (sewage systems, corresponding population, etc.). On the other hand, it is possible to identify the course of an infection by repeated observations of the same sites in the short and long term. Finally, it should be noted that while the detection of SARS-Cov-2 in wastewater samples indicates the presence of infected individuals in areas where no clinical cases are present, on the other hand, the absence of viral RNA cannot be considered as a criterion for excluding the presence of infected cases as the quantity may be below the detection threshold.

The data that some Regions have already started to update with constancy along with the data that other Regions are starting to insert, will allow to deepen the considerations that have been made up until now and to define a reliable index that puts in relation quantitative results of the analyses on wastewater samples with epidemiological data able to provide support to the Authorities who are responsible for the decision-making processes.

In conclusion, I can say that SARS-CoV-2 environmental monitoring should be included in the list of indicators selected by the National Scientific Technical Committee and established in the decree that regulates actions and restrictive measures in Italy during the "second wave", through which the risk assessment is determined and therefore the classification of each Region, but also of limited areas within the Regions themselves, in one of the three bands provided: red (high risk, maximum limits applied), orange (medium risk, high restriction) and yellow (moderate risk, basic restrictions).

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