Republic of San Marino

National Bioethics Committee

Law no. 34 dated 29 January 2010

VACCINE COVERAGE AGAINST SARS-COV-2.

THE BIOETHICAL BASES FOR A HEALTH PACT

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PRESENTATION

During the first session of its fourth mandate, held on 9 December 2020, the National Bioethics Committee of Republic of San Marino (CSB) unanimously considered that it should continue, as a matter of priority, to study the bioethical aspects of the Covid-19 pandemic.

Vaccination against Covid-19 is of crucial importance in solving the pandemic, as it is the only answer to a disease for which there is still no available treatment and which is having devastating effects in every area of society.

Yet the Covid-19 vaccine is the subject of conflicting and often unfounded reports, which confuse the public and complicate decision making.

In view of the vaccination campaign about to begin in the Republic of San Marino, the National Bioethics Committee has drafted this document in order, on the one hand, to support decision-makers in their choices concerning the vaccination of the population, and, on the other, to help the general public to understand the ethical and scientific aspects involved and, consequently, to make an informed choice.

It has been possible to draft this document as a matter of urgency since CSB had already addressed the issue of vaccinations in its extensive and articulated 2016 document entitled *The bioethical value of vaccinations* (*for individuals and the community*), thereby enabling it to contextualise reflection on the aspects relating to the current pandemic situation.

The document is structured along two lines:

bioethical reflection on the most complex issues, such as the priority of access to vaccination according to criteria of justice and fairness, the moral and deontological obligation to be vaccinated for certain professional categories, the protection of the elderly who have paid the highest price in terms of human lives, attention to persons with disabilities (a constant focal point in the work of CSB), the transparency of information, the economic benefits of large-scale vaccination and the consequent ethical allocation of resources;

the scientific discussion of the topics which more than others have provoked debate in the population, such as trial procedures in an emergency situation and the safety of the end product, the vaccine research and development process, the characteristics of authorised vaccines and those in the process of being authorised.

For ease of reference, the purely technical-scientific aspects have been included in special boxes in the appendix in order to make available the references unanimously shared by the international scientific community.

This document is the result of the work of all the members of the National Bioethics Committee of Republic of San Marino, who immediately consented to work quickly, each contributing their own high level of scientific and bioethical expertise in a context of full cooperation.

The document was unanimously approved during the meeting held on 13 January 2021 by the participants: Borgia, Cantelli Forti, Griffo, Guttmann, Hrelia, Iwanejko, Raschi, Santori, Selva, Strollo, Tagliabracci. Carinci, who did not attend the meeting, notified his approval.

The Chairperson
of the the National Bioethics
Committee of Republic of San
Marino

Luisa M. Borgia

INTRODUCTION

The current Covid-19 health emergency has confronted Bioethics with numerous critical issues, some of which require new ways of thinking. Ethical committees, international organisations and states are discussing these issues in order to effectively manage the current crisis and in view of possible recurrences and future pandemics.

In order to understand the epochal proportions of the Covid-19 phenomenon we must go beyond considering it an exclusively health-related event.

In fact, the pandemic has brought with it disruptive general economic problems which, for determinate categories and individuals, are quite serious and which in themselves constitute a breach of the **bioethical principle of justice**. These problems could in turn lead to a social imbalance such as to prevent the full implementation of necessary healthcare measures.

In this context, by its very nature, bioethics is called upon to synthesise between elements that contribute to the complexity of a phenomenon, scientific findings of a biomedical nature and the benefits/drawbacks which all stakeholders can expect. Bioethics can therefore play a lead role in the debate on this issue, in order to support responsible, transparent and balanced political choices in line with a democratic approach to civil coexistence.

The global spread of infection by a new coronavirus, SARS-CoV-2, from which Covid-19 disease (COronaVIrus Disease 2019, i.e.*'the severe acute respiratory syndrome coronavirus 2'*) derives, has exacerbated social inequalities and shown how difficult it is to safeguard (even in the most developed countries) fundamental freedoms and human rights, wrongly deemed to be established and inviolable, such as **the right to life and health protection and the principle of equity of access to healthcare**[1].

The National Bioethics Committee of Republic of San Marino is aware that the still limited knowledge of the characteristics and modes of development and transmission of Covid-19 make the conditions for overcoming the current pandemic situation extremely uncertain and changeable.

International scientific research has embarked on a new course, concentrating enormous efforts on identifying preventive and therapeutic responses at an unprecedented pace.

There is an awareness of the fact that preventing contagion from SARS-CoV-2 and stopping the pandemic largely depends on the possibility of identifying an effective and safe vaccine and ensuring this is administered to the largest number of people in order to protect, first and foremost, the most vulnerable individuals - those most exposed to the risk of infection and who suffer from comorbidities - thus preventing the development of COVID-19 disease and the aggravation of pre-existing diseases.

The Covid-19 vaccine is currently becoming the subject of a number of critical bioethical issues.

[1] Article 3 of the Oviedo Convention, *'Equal access to healthcare*' does in fact state that «The Parties, taking into account health needs and available resources, shall take appropriate measures with a view to providing, within their jurisdiction, equitable access to healthcare of appropriate quality».

CSB has previously addressed the vaccination issue with a specific and particularly well-articulated document[2] , to which reference is made; however, in the light of the global pandemic context, it has deemed it necessary to issue an appropriate opinion taking into account new and specific bioethical issues, including the fair distribution of treatment, the choice of allocation priorities and the critical issues related to emergency trial testing.

[2] *Bioethical value of vaccinations (for the individual and the community),* 2016: http://www.sanita.sm/on-line/home/bioetica/comitato-sammarinese-di-bioetica/documenti-in-lingua-italiana.html

EQUAL AND FAIR ACCESS TO TREATMENTS AND VACCINES

The current pandemic has brought to the fore, as never before, the global dimension of equity of access to care and resources, through choices on the priority allocation of both ventilators and intensive care beds in hospital wards[3] and tests.

Similarly, there is growing awareness of the fact that vaccines and drugs for Covid-19 will not be able to meet global demand as soon as they are available: a disproportion already exists between demand for the former and the availability of the minimum doses needed for sufficient coverage to resolve the pandemic[4].

Determining who should be prioritised (*triage*) will require careful consideration and informed planning, taking into account experience with past pandemics[5], identification of the most at-risk and vulnerable population groups and understanding of disease transmission mechanisms.

In the case of limited supplies, governments should communicate in full transparency the criteria they have used to prioritise the supply of medicines and vaccines[6].

The difficulty in ensuring access to essential treatments and medicines in accordance with the principle of equity and justice has not only affected disadvantaged countries, whose situation has worsened tragically[7], but has also had a devastating impact in all countries on the most vulnerable population groups, such as people living in residential and nursing homes, the elderly and persons with chronic conditions or disabilities, sometimes highlighting gaps in social care, as well as delays in providing adequate protective equipment and correct and timely treatment[8].

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3 At the outbreak of the Covid-19 pandemic, CSB issued its Opinion on the bioethical duty to provide health treatment on the basis of the criteria of clinical appropriateness and proportionality of care and in full compliance with the principles of equality and non-discrimination, including in the event of scarcity of resources (*Response to the request for an urgent opinion on ethical aspects related to the use of assisted ventilation in patients of all ages with severe disabilities in relation to the COVID-19 pandemic*, 16 March 2020: http://www.sanita.sm/on-line/home/bioetica/comitato-sammarinese-di-bioetica/pareri-San Marino Bioethics Committee.html)

4 All governmental and non-governmental institutions, together with national bioethics committees around the world, have spoken out strongly and unanimously to contextualise bioethical principles to the current global emergency and ensure equitable access to treatments and vaccines. Key pronouncements include the United Nations General Assembly Resolution calling on the WHO and other agencies, including international financial institutions, to cooperate internationally to ensure global access to medicines, vaccines, medical equipment and diagnostic tests. Similarly, the Declaration of the European Committee of Social Rights, echoing the European Social Charter, reaffirms the obligation of States to guarantee the right to health protection, giving it the highest priority in policies, laws and other actions taken in response to a pandemic; it also reaffirms that the right to health protection includes the right of access to healthcare and that access to healthcare must be guaranteed to all without discrimination; finally, it calls on States to implement widely accessible vaccination programmes and to promote, fund and coordinate vaccine research among public and private actors.

5 Institute of Medicine (US) Forum on Microbial Threats (2007), *Ethical and legal considerations in mitigating pandemic disease: workshop summary.*

6 The UK government has announced that the experimental psychiatric anti-viral drug, Remdesivir, will be offered by the National Health Service and treatment will be restricted to patients most likely to achieve the greatest benefit. *See Independent* (26 May 2020) *Coronavirus: NHS to offer drug that can shorten recovery time by four days.*

7 The Lancet (8 May 2020), *Evidence mounts on the disproportionate effect of COVID-19 on ethnic minorities*; Institute for Fiscal Studies (2020) *Are some ethnic groups more vulnerable to COVID-19 than others?*; Winskill P, *et al.* (2020) *Equity in response to the COVID-19 pandemic: an assessment of the direct and indirect impacts on disadvantaged and vulnerable populations in low- and lower middle-income countries Imperial College London*.

8 The Health Foundation, *What has been the impact of COVID-19 on care homes and the social care workforce?* - COVID-19 chart series, 15 May 2020.

THE ASSIGNMENT OF PRIORITIES IN VACCINE DISTRIBUTION

The rapid development of effective vaccines against Covid-19 and the pandemic spread of the virus mean that there will undoubtedly be an initial and inevitable shortage considering global demand.

It is therefore necessary to rapidly draw up a distribution plan that defines priorities for allocation on the basis of fundamental bioethical principles and, at the same time, provides people with clear and transparent information on the criteria used for such allocation and on the safety and efficacy of vaccines.

This objective should also take into account the characteristics of the different vaccines authorised and made available, which are able to completely prevent the transmission of Covid-19 or prevent the most serious forms of the disease.

In accordance with the **principle of beneficence/non-maleficence**, on the basis of proven efficacy and safety data, priority must take into account - and dynamically adapt to it - the risk/benefit assessment for the prevention of serious harm to the affected individual and those in contact with him/her who require immune protection.

Given the continuous updating of scientific knowledge on the virus, all the priority criteria, and above all those relating to the **principle of beneficence/non-maleficence**, must be constantly updated[9].

According to the **principle of autonomy**, vaccination requires informed, aware and voluntary consent, which excludes any general and undifferentiated compulsion. If a decision is made in favour of compulsory vaccination, this may be justified on serious grounds of general health protection and, already from the start, involve clearly defined groups of persons, such as, for example, health workers in constant contact with high-risk persons or patients with vaccination contraindications.

According to the principle of **justice and equality-equity**, basic care must be provided for as many people as possible rather than the best care for as few people as possible. However, justice is inextricably linked to the **principle of solidarity and subsidiarity** towards those who run a significantly higher risk than the general population of contracting serious or fatal forms of the disease or those who, because of their personal or professional status, may expose other people to serious risks through the transmission of the virus.

Finally, justice and equity can also be achieved if **free** and **fair medical care,** and **compensation** in the event of vaccination-related adverse events, is also provided[10].

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[9] Bubar KM et al. *Model-informed COVID-19 vaccine prioritization strategies by age and serostatus*. MedRxiv. 2020 Dec 7;2020.09.08.20190629. doi: 10.1101/2020.09.08.20190629. Preprint

[10] San Marino legislation provides for compensation in case of vaccination-related injuries. In fact, article 8 of Law no. 69 dated 23 May 1995 requires the ISS (National Institute of Health) to take out a suitable insurance policy against any damage which may be caused by vaccinations.

A further element of choice is the **urgent** need for preventive protection of the health of those who are more vulnerable because of age, comorbidity or social circumstances that make access to care particularly difficult (e.g. the homeless), or of those who are more likely to require intensive care or suffer serious or fatal harm after contracting the disease.

All these aspects of the problem will be discussed in more detail in the following sections.

This right is also enshrined in the Oviedo Convention, in art. 24, "*Compensation for undue damage*": «*The person who has suffered undue damage resulting from an intervention is entitled to fair compensation according to the conditions and procedures prescribed by law*».

VACCINE CLINICAL TRIALS IN SITUATIONS OF URGENCY

The development of drugs and vaccines can take years. Nevertheless, collaborative efforts and new technologies are reducing the time needed to develop new drugs to combat Covid-19[11].

Given the urgency imposed by the pandemic and the critical need for drugs and vaccines, the timeframes and processes for the development of such products are being speeded up in a way previously unimaginable, thanks to the support of the regulatory authorities. For example, previously approved drugs are being entered into late-stage clinical trials in an effort to shorten the timeframe.

However, while accelerated trials may promise quicker access to suitable drugs, it will be essential to ensure that this is carefully balanced with adequate consideration of risk for enrolled participants, so that patient safety is given absolute priority[12] and robust and relevant data are produced in accordance with ethical standards and quality of results.

To this end, none of the regular verification steps must be neglected for each vaccine. The short timescales leading to rapid registration must be made possible by the research already conducted on the vaccines, by the vast human and economic resources made available, and by the careful, rapid and progressive ongoing evaluation of the results acquired by the Regulatory Agencies, without necessarily waiting for the completion of all the trials rolling review.

Although the overall safety profile identified in healthy subjects does not lead to specific contraindications (reported serious adverse events include allergic reactions to medicinal products), specific indications must be established for those with critical health situations or special conditions (e.g. pregnancy, breastfeeding, etc.). In these situations, as well as in the case of a new medicinal product being placed on the market, adverse events not known in the clinical trial and potential adverse events should be monitored over time, in agreement with the regulatory authorities, using available observation and follow-up tools.

In order to understand the choices behind the various techniques used in the production of current and future vaccines, it should be recalled that the SARS-CoV-2 virus infects humans using a cell entry key represented by a surface protein called Spike, and exploits the 'signal translation' mechanisms of these cells to reproduce itself. All vaccines currently under assessment have been designed to induce a response that blocks the Spike protein and thus prevents the whole process. Researchers are therefore focusing on the development of:

- RNA vaccine: this is a sequence of RNA (ribonucleic acid) synthesised in the laboratory which, when injected into the human body, induces cells to produce a protein similar to the one towards which the immune response is to be induced (by producing antibodies that will consequently be active against the virus);

[11] Torjesen I (2015) *Drug development: the journey of a medicine from lab to shelf,* Pharm J, online URI: 20068196.

[12] The recent speeded up approval of Remdesivir by the FDA is an example.

- DNA vaccine: the mechanism is similar to the previous one. In this case, a fragment of DNA (deoxyribonucleic acid) synthesised in the laboratory is introduced, inducing the cells to synthesise a protein similar to the one towards which the immune response is to be induced;
- Recombinant protein vaccine: using the RNA sequence of the virus (in the laboratory), proteins or protein fragments of the viral capsid (shell) are synthesized. When combined with substances that enhance immune response, once injected into the body they induce an antibody response from the individual.
- Viral vector-based vaccines: typically based on an existing virus (usually a non-replicating adenovirus) which bears the genetic code sequence coding for the Spike protein.
- Inactivated viral vaccines: produced by culturing the SARS-CoV-2 virus in cell cultures and chemically inactivating it.
- Live attenuated vaccines: produced by generating a genetically weakened version of the virus that replicates to a limited extent, not causing disease but inducing immune responses similar to those induced by natural infection.

In the event of several vaccines with different characteristics being available, the choice cannot be left to the single individual, but must be made by the Health Services, which, in an equally safe and effective way, will take into account the characteristics of individuals with higher-risk comorbidities.

In the light of these considerations, the National Bioethics Committee of Republic of San Marino believes that the subjects to be vaccinated should be provided with balanced and professional information on the likelihood of the occurrence of a serious adverse reaction (ADR - Adverse Drug Reaction), such as anaphylaxis, while however balancing the possibility of such a risk with the specific benefits of vaccination.

Pending such consultation, deferral of vaccination may be justified in individuals with a suspicious medical history until reliable information on the risk of ADRs becomes available.

Such considerations should, therefore, encourage dialogue with the pharmaceutical company in order to arrive at a more accurate assessment of the risk following vaccination in particularly susceptible individuals.

SAFETY OF COVID-19 VACCINATION

With regard to doubts about the ***safety of vaccination***, including with regard to the current pandemic, it should be stressed that:

- the vaccines used are drugs that comply with national and international production standards;
- every batch of vaccine registered and authorised for sale undergoes safety and efficacy checks by the competent authorities;
- any vaccine must come from an official source with a traceable path. In the present situation, the National Bioethics Committee of Republic of San Marino strongly recommends that the information to be provided to the general population should stress that the initial shortage in the availability of vaccines against Covid-19 cannot and must not be compensated for by any obscure availability of vaccines through direct online purchases or through parallel markets.
- vaccination is a medical procedure which is simple to carry out in practice but, at the same time, is made safe by the immediate availability of certain essential first-aid items (adrenaline, cortisone, oxygen, defibrillators - *Outpatient management of anaphylaxis after vaccination*[13]);
- all vaccines are therefore safe if administered by qualified personnel in accordance with the rules of good practice (use of properly stored vaccines, use of appropriate sterile, single-use syringes, compliance with prescribed inoculation procedures and locations), taking into account anamnestic and/or objective findings that may temporarily or permanently contraindicate vaccination.

[13] http://www.sip.it/per-il-medico/gestione-ambulatoriale-dellanafilassi-dopo-vaccinazione

BENEFIT AND RISK ASSESSMENT

If vaccinations did not bring any benefits whatsoever, both individually and collectively, even one serious adverse event would be unjustifiable and unacceptable.
On the contrary, vaccinations have saved millions of lives and prevented countless cases of disease and complications in both industrialised and developing countries.
Scientific and ethical considerations therefore require that mass vaccination programmes should continue to be implemented in forms and ways that are appropriate to the epidemiological and socio-sanitary situation in each country.
However, from a communication viewpoint, a profound difference exists between indicating the use of drugs (prescribed to treat sick persons) and vaccines (means of prevention recommended or made compulsory to prevent a healthy person from contracting a specific disease – which is probable but not certain - or from being a means of transmission).
This difference makes the hypothesis of a risk associated with vaccinations less acceptable to the individual and imposes a very high safety profile, with regard to which a correct scientific-rational approach to **risk assessment** must be adopted, based on three assumptions:

- risk identification
- estimation of the level and extent of the risk of potential damage;
- assessment of the acceptability of the hazard in relation to other risks.

Institutions and their subordinate bodies, which have a constitutional responsibility to protect the health of the individual and the community, are obliged to take every rational precaution, by applying legislative, ethical and deontological principles to risk/benefit assessment during the risk management phase.
Wherever scientific uncertainty exists such as to make impossible a full assessment of the potential risks (and, therefore, of the possibility of damage occurring in practice), it is up to the institutional decision-makers, taking into account the concerns of the public, to identify what is the minimum level of 'acceptable risk' for society.
The precautionary principle, which is closely linked to the Hippocratic ethical principle of *'primum non nocere*', is the cornerstone of the logical risk assessment process and guarantees prudence in the absence of scientific certainty and in the presence of risk elements.

In assessing benefit, the following points should be considered:

- **benefit of vaccine administration** in terms of the efficacy of a specific dose;
- **likelihood of contracting the disease**, which in turn depends on the incidence of the disease and the level of vaccination coverage in the population, as well as possible exposure to a positive case for various reasons;
- **frequency and severity of complications** of the disease, which in turn are influenced by variables such as age and the presence of other debilitating conditions.

USE OF PLACEBOS

A critical bioethical issue in the Covid-19 vaccine trials concerns the use of placebos. The treated and control groups remain under observation for a long time, in order to be able to attribute or not exclusively to the vaccine, with reasonable certainty, the differences observed in the subjects involved in the trial.

This implies the need to maintain a double-blind, i.e. the impossibility for volunteers and investigators to know to whom was administered the drug and to whom the placebo. Moreover, such an approach, while having unquestionable scientific validity, may conflict with bioethical principles because:

- it is impossible to comply with the **principle of beneficence/non-maleficence** for the volunteers in the control group, since they could contract the disease without any possibility of prevention;
- the **principle of justice** is not guaranteed, inasmuch as the volunteers are not all in a position to have the same risks and benefits.
- according to the **principle of autonomy**, if the volunteers were to ask to know which group they belonged to in order to perform the actual vaccination, the blind would be opened and the observation of effectiveness would cease.

At the same time, it should be emphasised that, in the process of research and development of any drug, the use of placebos is ethically justified if, as in the case of vaccines, no therapy of established effectiveness is available for the control group.

In order to ensure its ethicality for the purposes of specific research, at the time it is proposed to the patient, use of the placebo must have already received authorisation from an ethics committee which has analysed the protocol from all possible points of view.

The information provided to the patient is therefore essential in order to be able to take a motivated and informed decision.

However, the information on placebos is sometimes insufficient and can lead to a possible 'therapeutic misunderstanding' (incomplete understanding of the message about the treatment) or a misinterpretation of placebos as a completely useless treatment.

In point of fact, the placebo group is fundamental in order to keep numerous confounding factors under control (including possible errors on the part of patients and doctors, suggestions, spontaneous fluctuations over the course of time and symptoms of the disease, etc.) which may invalidate the reading of the results of the entire trial, thereby eliminating the possibility of recognising and extending the truly beneficial effects of a therapy to an increasingly wider audience.

In view of the above considerations, of what is stated in the Declaration of Helsinki: "*in medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society*" and of the bioethical implications related to the use of placebos in light of the overwhelming advantage of the anti-Covid-19 vaccines tested

so far (> 90% protection), in the current context the National Bioethics Committee of Republic of San Marino considers it essential to proceed with an accurate and timely epidemiological verification of the prevalence of cases of infection and disease in the absence/presence of vaccination in a condition of so-called "real life" and no longer in that of a randomized and controlled trial.

TRANSPARENCY OF INFORMATION

An effective vaccination plan can only be achieved if it is supported by trust and by transparent and complete information to the population, which will be prompted to take part on a voluntary and aware basis.

In fact, a 'Health Pact' should be activated with the population, based on the strategic lines of epidemiology, prevention and awareness-raising, information, training and communication.

Communication plays a central role, especially in the initial stages of the vaccination campaign and in the choice of categories with priority access to the vaccine.

To date, in fact, a form of 'vaccination hesitation' persists even among some health professionals, in relation to the trial timeline and marketing of Covid-19 vaccines.

Among the causes which have contributed to such uncertainty is a 'highly publicised' communication strategy, which has seen numerous 'experts' take part in talk shows together with guests with little knowledge of scientific subjects, thus producing an overlap of often conflicting news not supported by scientific literature.

Finally, the social media have been filled with unsubstantiated news, making it impossible to clearly and adequately understand the issues relating to the new SARS-CoV-2 virus.

It is therefore crucial that, first and foremost, communication provide transparent and complete information on the efficacy and safety of vaccines.

The global involvement of pharmaceutical companies in an extremely rapid search for effective vaccines has caused perplexity and mistrust, probably due to the underestimation by the media of the fact that the study of each vaccine submitted for authorisation has followed or will follow all the research phases required for release on the market - albeit at a speed never seen in the past inasmuch as fuelled by the huge economic support offered by governments worldwide.

The exceptional speed of clinical trials, the unprecedented industrial involvement and the overall risk to the population must be matched by an equally exceptional completeness - and transparency - of information on research data. It is more than ever necessary to make explicit all possible adverse events observed during the trial phases, distinguishing them as clearly as possible from random associations.

To this end, the timely recording of vaccination coverage rates and of adverse events - including unexpected ones - related to vaccination must be ensured through a careful monitoring system (so-called 'vaccine vigilance'), so as to provide public assurance of vaccine effectiveness and safety monitoring.

The possibility of access to such information, provided in a transparent, clear and up-to-date manner, comprehensible to the entire population and shared with the competent Authorities is, in fact, the necessary prerequisite to create and maintain a climate of mutual trust between the public and the institutions.

In this light, the establishment of a public reference body made up of qualified professionals able to provide clear and personalised answers to the questions of single individuals would be a dutiful way of addressing the concerns (including when these are based on scientifically inaccurate information or beliefs) of those who are wavering between disillusionment and the absolute need to regain trust in the authorities. Such an approach would also be essential to create awareness among the public and prevent people from acquiring wrong and dangerous information from unauthorised sources.

Similar transparency is also needed in communicating the criteria for determining priorities, so that the population is able to appreciate the reasons behind delays and apparent temporary exclusions from a procedure by now perceived as universally acquired by birthright.

The greater the understanding of data and selection criteria, the greater voluntary participation will be in the vaccination campaign, which in fact can only achieve levels of real effectiveness in the event of broad approval based on willingness rather than on compulsion.

Similarly, as partly anticipated in the paragraph on safety, the population must be adequately informed about the health risk of purchasing vaccines online or from unofficial and institutional sources: pandemics represent an unprecedented opportunity for criminal and opportunistic behaviour, and the distribution of sub-standard and counterfeit pharmaceutical products, including Covid-19 vaccines, remains among the most sought-after targets of organised crime.

Due to the extensive spread of the disease, demand for treatment may be so high that it risks exceeding that available in many countries, encouraging many people to seek vaccines through channels other than those considered safe.

Counterfeit vaccines, besides being useless in the fight against pandemics due to lack of protection (in fact, they fail to ensure that the threshold percentage of vaccinations estimated for the 'herd effect' is reached), represent a very serious risk to individual and public health due to possible contamination by toxic substances linked to production in laboratories that do not meet the required standards.

In other words, the patient who takes the counterfeit drug will be harmed both by the lack of therapeutic effect and by possible side effects, with probable consequences, sometimes even fatal[14].

[14] https://europa.today.it/attualita/falsi-vaccini-europol-allarme.html

PERSONS WITH DISABILITIES

Public communication about the pandemic, vaccines and their risks must be such as to ensure the entire population is able to access and use the information through appropriate means, including the use of sign language and subtitling for deaf and hearing-impaired people[15].

All persons and operators of homes and day centres for patients with disabilities should also be included among the recipients of the first doses of the vaccine, considering both the high risk of outbreaks in closed facilities and the precarious health conditions of the guests.

Included in the second phase of the vaccination campaign should therefore first of all be persons who are not self-sufficient, those in home care due to the fact that they are only partially self-sufficient and those with comorbidities who are at greater risk (immunocompromised persons or those with oncologic diseases or other particular illnesses which put them at greater risk in case of contagion), together with those who are in direct contact with such persons (home helps or private individuals and caregivers).

All such persons are doubly exposed to the dangers of infection, both because their health conditions could aggravate the course of their illness and because a complex pathological picture adversely affects the type and quality of life of those concerned and of the caregivers themselves, especially if they are family members.

Particularly noteworthy is the case of intellectual, relational or psychosocial disabilities. In all of these, the risk of contagion is, by its very nature, higher than average, due to the extreme difficulty of complying with individual protection measures. This risk is further aggravated during hospitalisation (e.g. for infection with SARS-CoV-2), because of the inability to achieve the necessary active collaboration with care staff, especially when the attendance of the usual caregivers cannot be ensured. The same applies to people who require very high levels of care, including in hospital, due to their inability, on their own, to perform everyday actions such as eating, going to the toilet, turning over in bed, etc.

When administering the vaccine to persons with intellectual and relational disabilities, the staff in charge should be trained along the lines of other similar experiences[16] or be assisted by the *caregivers* of such persons.

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15 See research by the International Disability Alliance, http://www.internationaldisabilityalliance.org/covid-drm, the International Disability and Development Consortium, https://www.iddcconsortium.net/, the Disability Rights Monitor in collaboration with IDDC, the Disability Rights Fund and the University of Pretoria, https://covid-drm.org/.

16 See the DAMA project of the San Paolo Hospital in Milan, which has spread to various Italian hospitals, http://www.progettodama.it
See also the experience of the Italian Society of Dentistry for the Handicapped (SIOH), https://www.sioh.it/centri-di-cura and the SIOH manual. Manuale di odontoiatria speciale. Milan, EDRA S.P.A., 2019.

ELDERLY PERSONS

Vaccination prevention is one of the most appropriate responses to the health and development challenges of a population and contributes to significantly improving the health of the ageing population. The over-60s are at higher risk of severe Covid-19 and account for 95% of all fatal cases[17].

However, it does not make sense to define a standard age of frailty (in the sense of easy susceptibility to various diseases) which, for those who have more than one disease, comes into play as early as 60 years of age, while for others it does not even begin to occur beyond 90 years of age[18]. In view of this consideration, suggesting vaccination priority for the elderly requires addressing, *inter alia*, the problem of ageism[19].

If we then look at how isolated elderly persons have been during the pandemic, not only those staying in residential care homes, but also due to daily, exasperated distancing from any potential (and sometimes imaginary) source of contagion at home on the part of family members, we come to realise how important it is to stress just how devastating the psycho-emotional impact of isolation is not only for the elderly, in whom, among other things, any cognitive disability rapidly worsens, but also for the caregiver. The latter, in fact, especially if they are family members and women, often suffer what is known as burn-out[20], with the onset of sometimes severe anxiety and depression[21].

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17 https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm (last access 26-12-2020).

18 Bergman H, Ferrucci L, Guralnik J et al. *Frailty: an emerging research and clinical paradigm—issues and controversies*. J Gerontol A Biol Sci Med Sci. 62: 731–7, 2007.

19 https://www.treccani.it/vocabolario/ageismo_res-50bce5a1-8991-11e8-a7cb-00271042e8d9_%28Neologismi%29/ (last accessed 26-12-2020). Ageism is defined by Treccani as "a form of prejudice and devaluation to the detriment of an individual towards older people" in line with what Apriceno called "hostile ageism" in contrast to so-called "benevolent ageism" (Apriceno MB et al. *Prioritizing Healthcare and Employment Resources during COVID-19: Roles of Benevolent and Hostile Ageism*. Gerontologist. 2020 Oct 29; gnaa165. doi: 10.1093/geront/gnaa165. Online ahead of print.). Both types of ageism, however, conceal within themselves the danger of discrimination, i.e., the serious denial of the bioethical principle of justice. Even the benevolent form, despite the fact that it seems to be inspired by the very best intentions and is therefore far from a negative attitude, the very moment in which it devotes excessive and lexically ill-designed attention to the elderly, it unintentionally creates a clear dichotomy between the efficiency of the young person and the elderly person's need for protection. The 'hostile' form represents a preconception according to which the elderly person represents a burden on society, insofar as largely dependent on others, unproductive, a source of ever-increasing expense and, above all, already sufficiently close to the end of life to be almost made accountable for the 'right' solution to the many daily problems through the acceptance of the inevitability of an imminent exit. In the author's view, benevolent ageism is instead a stereotype, and as such often equally improper, based on the conviction that the elderly person is a member of society to be valued at least as a historical memory of the family, a life experience to be passed on to other generations, a source of savings to be made available to family members, and emotional and educational support. The elderly person thus runs the risk of falling victim to what is known as "learned helplessness", whereby a paternalistic attitude induces a state of stress that leads to an increase in circulating levels of cortisol and other hormones responsible for progressive muscular and cognitive decline and, over time, conditions a lower efficiency in carrying out habitual tasks (Cary, L. A., Chasteen, A. L., & Remedios, J. (2017). *The Ambivalent Ageism Scale: Developing and validating scale to measure benevolent and hostile ageism.* Gerontologist. 2017 Apr 1;57(2): e27-e36. doi: 10.1093/geront/gnw118; Hehman JA, Bugental DB. *Responses to patronizing communication and factors that attenuate those responses.* Psychol Aging. 30: 552-60, 2015). In the very imagery of the elderly, the resulting insecurity - which largely depends on an artificial social image - often anticipates frailty and accelerates its onset precisely because of the associated negative psychological impact (Stewart, T. L., Chipperfield, J. G., Perry, R. P., & Weiner, B. *Attributing illness to "old age": Consequences of a self-directed stereotype for health and mortality.* Psychol Health. 27: 881-97, 2012). A picture is thus configured in itself distant in time, but rejected from a young age because it is experienced as negative, pre-terminal and therefore depressing (Chrisler J, Barney A, Palatino B. (2016). *Ageism can be hazardous to women's health: Ageism, sexism, and stereotypes of older women in the health care system*. Journal of Social Issues,72(1), 86-104. https://doi.org/10.1111/josi.12157 .

20 In the Treccani Dictionary of Medicine (2010), burn-out is described as "a pathological state (from the English 'completely burn out') which occurs in individuals who carry out helping professions... Burn-out appears in professionals who have to adequately support their own psycho-emotional stress and that of the assisted person. If the phase of psychological wear and tear is not managed or controlled, there is a progression of psychological and physical damage which can end up in suicide'. Referring then to the 11th revision of the WHO International Classification of Diseases, the 2019 version of the Treccani Atlas reports as symptoms: feeling exhausted; alienation or cynical or negative feelings towards one's work and reduced professional performance.

21 Carpinelli Mazzi M et al. *Time of isolation, education and gender influence the psychological outcome during COVID-19 lockdown in caregivers of patients with dementia.* Eur Geriatr Med. 11: 1095-8, 2020.

In this context, a well-conducted vaccination campaign can also prevent the serious consequences of such forms of isolation by restoring the conditions for indispensable socialisation and emotional relationality.

Technical solutions are apparently also available from a bioethical point of view: the *Global Vaccine Action Plan*[22] and the *Immunization Agenda 2030*[23] do in fact recommend that all countries break down bureaucratic barriers and implement an appropriate vaccination campaign inspired by the principle of justice.

In this light they suggest that access to the vaccine and the monitoring of the effects and the degree of acceptance among the elderly should be fair and guaranteed not only by the individual government (including by means of specific work groups such as the *National Immunization Technical Advisory Groups or NITAGs*) but also by social voluntary support, private foundations and the responsible involvement of the population as a whole.

This context favours the realisation of the **principle of autonomy** in relation to the elderly person's consent to the vaccine: social volunteering could be a leading element in well-conducted information inasmuch as it is interpreted as being 'neutral', i.e. not piloted by the media, increasingly seen as the 'longa manus' of the powers that be.

Health workers should also be fully involved in this activity but, as already pointed out in the previous document of the National Bioethics Committee of Republic of San Marino on vaccines[24], these will only be convinced of having made the right choice, and in turn make the message they convey convincing if they are fully informed of the ongoing dynamics of the side and/or adverse effects recorded at local and international level.

Transparent information would also fully justify the decision to give priority - always respecting the individual's decision-making autonomy - to health workers involved in caregiving activities and to elderly persons with comorbidities and/or other clinical frailties.

In fact, such health workers are exposed not only to a greater risk of contracting but also of transmitting the disease to their frailer patients. For the same reason, we reiterate that all those who, for work or commercial reasons, have relations with in-patient facilities should be included among the first recipients of the vaccine.

What is more, there is no ethical basis and, above all, no equally certain prospects for the idea that priority should not be given to frail elderly persons because of a misunderstood need to disinvest in projects that are potentially doomed to failure.

In fact, those who think that priority should be given to children-youngsters and adults in order to achieve widespread immunity, which in turn can prevent contagion of the elderly, do not have at their disposal clear information as to either the duration of the immune response in the young or

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22 The World Health Organization. *The Global Vaccine Action Plan 2011–2020*. Geneva; 2013.

23 The World Health Organization. *Immunization Agenda 2030: A Global Strategy To Leave No One Behind*. 2019 January 6, 2020; https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030 (last access 26-12-2020).

24 *Bioethical value of vaccinations*, ibidem.

the possibility of generating a dangerous cohort of healthy carriers who are free to infect frailer persons.[25],[26].

In the light of the above, **the National Bioethics Committee of Republic of San Marino considers it appropriate, including from a bioethical perspective, to prioritise the vaccination of the elderly**.

[25] Lei Q et al. *Antibody dynamics to SARS-CoV-2 in asymptomatic COVID-19 infections.* Allergy. 2020 Oct 10;10.1111/all.14622. doi: 10.1111/all.14622. Online ahead of print.

[26] See note 9.

VACCINATION ACCEPTANCE: LEGAL OBLIGATION OR MORAL OBLIGATION?

Vaccines, like antibiotics, are among the most important medical breakthroughs, and have radically altered the public health scenario and people's life expectancy.

Vaccination is included in the broader category of health treatments and is a medical procedure, the bioethical correctness of which must be assessed according to the criteria of any other medical procedure, and in particular according to the risk/benefit ratio (**principle of beneficence/non-maleficence)** and informed consent.

The individual's informed and aware consent must be as broad as possible, including in the context of prevention, i.e. when vaccination or immunisation practices are used. In this sense, respect for the principle of autonomy requires that every legal relationship in health matters be based not on force or coercion but on consent and free choice.

Respect for the human person must always remain a paramount concern, both when healthcare is directed towards the good of the individual and when common good is involved. However, the lack of acceptance by a sufficient number of patients raises the question of the need for and legitimacy of compulsory vaccination.

Vaccination, if carried out in a widespread manner, is an act of solidarity, representing a means of protection both for those who receive it and for the population as a whole (so-called 'herd immunity'[27]). Solidarity cannot however be deemed an end in itself, but must be backed by the possibility of adequate compensation for any harm caused and related to vaccination[28].

Moreover, as will be illustrated in a specific paragraph, the direct benefits deriving from being immunised against the disease and the indirect benefits deriving from the achievement of "herd immunity" make it possible to reduce the costs of health and hospital care and, at the same time, to allocate public resources for the common good.

The National Bioethics Committee of Republic of San Marino therefore believes that, however legitimate and reasonable the compulsory nature of vaccination may be, it is certainly more desirable to follow the path of voluntary and spontaneous acceptance by the greatest possible number of people, favouring an approach based on responsibility and the formation of a social conscience that helps to understand that vaccination against Covid-19 is a moral duty for one's own good but also, and above all, for that of the weaker or more fragile members of the population.

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27 In order to configure a vaccination campaign as a form of public health intervention (of benefit to society), high levels of vaccination coverage (share of vaccinated subjects compared to the identified target population) must be achieved and maintained. The optimal levels of vaccination coverage to be achieved depend on many factors, including the type of infectious agent, the geographical and socio-cultural structure of a country, and the health condition of the population. The vaccination coverage of a population is a function of several elements, for example, the availability of the vaccine and the way it is dispensed to the public (vaccination policies) but also acceptance by the population and health workers.

28 See note 10.

An essential role in this sense will be played by accurate and truthful scientific information, which not only focuses on the risks, but also illustrates the individual and collective benefits, as well as the possible disastrous consequences of extensive abstention from vaccination.

The position of vaccination hesitancy on the part of persons belonging to a public service and who refuse vaccination or fail to give their consent to vaccination is very worrying, since this could contribute to a delay in the 'herd effect' to the detriment of other persons who, although wanting to do so, cannot be vaccinated in the short term because they are in a class considered to be of lesser risk or lesser urgency in terms of social interest.

It remains legitimate, then, to speak of a moral obligation to look after one's own health and that of others, in view of the fact that, in every community, for well-founded health reasons, some individuals cannot be vaccinated and must therefore be protected by those who can.

Though we are free to risk our lives or health for idealistic reasons, the absolute moral and legal wrongness must be stressed of any behaviour that endangers the health of others and, in particular, of more fragile individuals.

In this regard, it might be a good idea to emphasise that, by analogy with what has been established for cases of compulsory health treatment, the right to health of the community (**principle of beneficence/non-maleficence**) should prevail over the right to freedom of the individual (**principle of autonomy**).

Anyone, therefore, who, despite training and intense persuasion oriented towards respect for others and the corresponding duty to take steps to avoid becoming a vehicle for contagion, decides not to be vaccinated, must at least comply with the obligation to isolate himself or herself immediately at the first appearance of suspicious symptoms.

The National Bioethics Committee of Republic of San Marino believes that doctors, healthcare workers and all those who work in residential facilities and are in contact with vulnerable, elderly and persons with disabilities have a greater responsibility in this regard, including by virtue of compliance with a deontological obligation.

Art. 9 of the Code of Medical Ethics[29] requires doctors to make themselves available to the competent authority in the event of a disaster, calamity or epidemic. This is a duty which doctors cannot evade in the event of occurrences of collective importance.

Healthcare professionals, in particular, are required to ensure adequate vaccination coverage, which is considered an essential prerequisite from the moment they are admitted to their degree courses, precisely because of their responsibility towards themselves and the people they are called upon to protect through the job they do.

If this moral and ethical obligation is required in order to carry out routine activities, it becomes all the more unavoidable in an epoch-making pandemic situation such as the one we are currently facing, especially if it constitutes the only response to a disease for which no treatment is yet available and which is having devastating effects on every area of society.

[29] San Marino doctors endorse the Code of Medical Ethics of the FNOMCEO (Federazione Nazionale degli Ordini dei Medici Chirurghi e degli Odontoiatri italiani – Federation of Italian Doctors Guilds).

In the light of these considerations, any refusal to be vaccinated on the part of healthcare professionals would undermine their commitment to treatment and conflict with the deontological oath of *'primum non nocere'*.

The possible consequences in terms of sanctions would therefore be a matter for the respective professional bodies, which would be called upon to assess, on a case-by-case basis, the reasons for the choice and the responsibility of the refusal to be vaccinated on the part of their members, in relation to the impact on the protection of the health and life of the persons entrusted to them[30].

[30] In this regard it is useful to quote - albeit on the subject of prevention of childhood diseases - what has been reported by *Vaccines and Vaccinations*, Position Paper of the Italian Society of Pharmacology, and the Italian Society of Hygiene Preventive Medicine and Public Health, Italian Society of Pediatrics, Italian Federation of General Practitioners, Italian Federation of Paediatricians, 2017 p. 12: "at the end of July 2016 the State of California (USA) sanctioned that personal beliefs are not acceptable grounds for exemption from vaccination and reinforced the school filter, making it not legally permissible to refuse vaccination on religious or philosophical grounds. The new rule effectively narrows the scope of parental discretion, prohibiting schools from admitting children who do not meet a pre-defined list of vaccinations. The only exceptions allowed are those for health reasons"...omissis.... "Despite the fact that in the United States the issue of individual freedoms is very much felt (it is the subject of the First Amendment of the Constitution), the Supreme Court has clarified, for example, that freedom of religion "does not include the freedom to expose the community or individual child to infectious diseases", especially given the fact that the choice to "not vaccinate" is based on personal opinions and not supported by scientific evidence.

THE ECONOMIC BENEFITS OF LARGE-SCALE VACCINATION

As mentioned in the previous paragraph, in order to achieve an adequate vaccination policy, decision-makers will not only have to obey the principles enshrined in the Universal Declaration of Human Rights (1948)[31], but also take account of the positive economic effects on the National Health System of massive and continuous immunisation, as is recognised in literature.

Vaccination is one of the health procedures with the best cost-benefit profile. In fact, thanks to the number of prevented cases of disease and related avoided complications, these can generate significant savings for a country's health system and for society as a whole.

Vaccination plays a major role in the sustainability of health services, especially in the context of increasing pressure on their budgets.

Vaccines generate savings by avoiding hospitalisation, medical intervention, drug use and nosocomial infections.

Among the economic benefits mentioned above, in addition to a reduction in annual quality-adjusted life year individual expenditure (QALY, € 20-30,000 in Europe[32]), is a reduction in the frequency of occurrence or exacerbation of comorbidities and the consequent use of combination therapy (high number of drugs). Combination therapy is typically associated with poor compliance (compliance with medical prescriptions), thus causing considerable economic and health damage in terms of wasted medicines and worsened chronic diseases, respectively[33].

Finally, a further economic and health benefit of an effective large-scale vaccination policy is the reduced use of antibiotics, with consequent reduction in antibiotic resistance and related problems[34,35].

The National Bioethics Committee of Republic of San Marino believes that these considerations can - and must – result in each Institution choosing to commit and involve as many human and economic resources as possible in an effort to achieve widespread acceptance of the vaccine.

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31 https://www.ohchr.org/EN/UDHR/Documents/UDHR_Translations/itn.pdf (last access 26-12-2020)

32 Szucs TD, Pfeil AM *A systematic review of the cost effectiveness of herpes zoster vaccination*. Pharmacoeconomics. 31: 125–36, 2013.

33 Bonanni P, Picazo JJ, Remy V (2015) *The intangible benefits of vaccination—what is the true economic value of vaccination? J Market Access Health Policy*. https ://doi.org/10.3402/jmahp.v3.26964.

34 Kwong JC, Maaten S, Upshur RE, Patrick DM, Marra F. *The effect of universal influenza immunization on antibiotic prescriptions: an ecological study.* Clin Infect Dis. 49: 750–6, 2009.

35 Lipsitch M, Siber GR *How can vaccines contribute to solving the antimicrobial resistance problem? mBio*. 2016 Jun 7;7(3):e00428-16. doi: 10.1128/mBio.00428-16.

FINAL CONSIDERATIONS AND RECOMMENDATIONS

The problem of fair access to medicines and vaccines, including in the current pandemic context, although different in the various existing health systems, concerns the universal right to health protection, and must therefore be seen from a human rights perspective and respect universal bioethical principles.

Never before as in this pandemic situation has it been so important to orient choices in terms of fairness, gratuitousness and accessibility by identifying, constantly updating and making transparent and comprehensible the scientific data on which choices are based; an ethical duty for all decision-makers, both health workers and politicians, as well as an essential element for the desirable involvement of members of the public in a climate of renewed sense of security and protection.

The acceptance of vaccination depends above all on correct and scientifically grounded information, which constitutes a barrier to the spread of so-called fake news, especially when it spreads unjustified concern about the risks of anti-Covid-19 vaccines, something also caused by their speedy production[36].

In this context, it is also important to reinforce collective education by urging strict compliance with elementary rules of hygiene at both individual and community level. A few rules of hygiene and behaviour can be crucial in preventing the extent and speed of the spread of the virus.

On the basis of the bioethical principles outlined and the vaccination objectives, criteria for **prioritising administration** can be identified, and more specifically

- the protection of the life and health of the most vulnerable members of society (which also helps reduce the social and economic costs of deaths and hospitalisation)
- the protection of professional workers at high risk of exposure to the virus, which in turn can break the chain of possible further sources of spread of infection outside hospitals;
- the achievement of social equilibrium based on the absence of evident treatment disparities;
- the maintaining of essential state functions (police, fire brigade, civil protection, employees of essential public services, ...) and of services that are functionally indispensable to society (transport operators, pharmacies, ...).

In light of the above, **the National Bioethics Committee of Republic of San Marino recommends that:**

- **an efficient and effective system of communication to the public be put in place, based on transparency of information regarding the risks and benefits (individual and social) of vaccination;**
- **an adequate number of vaccination sites be provided in hospitals and/or other healthcare facilities in order to provide appropriate geographical coverage according to population density, thereby avoiding harmful public gatherings;**

[36] For detailed scientific references to the research and development process of vaccines and their safety, please refer to the relevant boxes attached to this document.

- **damaging non-scientific counter-information broadcast via the media be strongly combated through a qualified institutional body able to provide clear and, if necessary, personalised answers to single individuals. It is certainly strategic to counter and scientifically dispel unfounded doubts about the lack of vaccine safety, which are often spread by 'social' channels and find their strength in the emotionalism and unpreparedness of many.**
- **clear communication of the criteria for prioritising vaccination be ensured;**
- **effective vaccine vigilance be ensured through the timely recording of vaccination coverage rates and of adverse events, including unexpected ones, related to vaccination;**
- **accurate and timely epidemiological verification be carried out of the prevalence of cases of infection and disease in the absence/presence of vaccination in a so-called 'real-life' condition rather than in a randomised controlled trial;**
- **the trade in illegal vaccines and drugs be effectively contrasted both online and in the underground economy**
- **vaccination be provided free of charge;**
- **priority vaccination be given to healthcare workers involved in care and to elderly people with comorbidities and/or other clinical frailty conditions, as well as to all those who have relations with in-patient facilities for business or commercial reasons;**

For the latter professional categories, the National Bioethics Committee of Republic of San Marino strongly recommends that vaccination should be morally and ethically compulsory, drawing the attention of the respective professional bodies, where applicable, or of the managers of residency facilities, to the need to assess, on a case-by-case basis, the motivations underlying the choice and the responsibilities of refusal to vaccinate their members, in relation to the impact on the protection of the health and life of the persons entrusted to them.

Finally, in a broader context**, the National Bioethics Committee of Republic of San Marino also recommends:**

for the protection of the community, ensuring that the "Covid-19 vaccine race" does not undermine the prevention of other vaccine-preventable diseases already acquired as a health right for the public.

BIBLIOGRAPHY AND SITOGRAPHY

1. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring
2. https://www.coe.int/en/web/bioethics/covid-19
3. https://www.aifa.gov.it/comirnaty
   https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32623-4/fulltext
4. https://jamanetwork.com/journals/jama/fullarticle/2774383
5. Oliver S.E. et al, *The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine — United States*, December 2020, Morbidity and Mortality Weekly Report 2020 / Vol. 69 / No. 50
6. Polack F.P.et al, *Safety and Efficacy of the BNT162b2 mRNACovid-19 Vaccine*, N Engl J Med. 2020 Dec 31;383(27):2603-2615.
7. US Food & Drug Administration (FDA): *Fact sheet for healthcare providers administering vaccine (vaccination providers): Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19).* US Food & Drug Administration (FDA). Silver Spring, MD. 2020. Available from URL: https://www.fda.g... .
8. US Food & Drug Administration (FDA): *FDA news release: FDA takes key action in fight against COVID-19 by issuing Emergency Use Authorization for first COVID-19 vaccine.* US Food & Drug Administration (FDA). Silver Spring, MD. 2020. Available from URL: https://www.fda.g... .
9. US Food & Drug Administration (@fda.gov): *"The FDA is aware that some vials of the Pfizer-BioNTech #COVID19 Vaccine have contained extra product after five doses are obtained. The agency is working with Pfizer to determine the best path forward, and will share additional updates as we have them."* Twitter. https://twitter.com/US_FDA/status/1339363303185854470
10. Pfizer Inc and BioNTech Manufacturing GmbH: *Fact sheet for recipients and caregivers Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19) in individuals 16 years of age and older.* US Food & Drug Administration (FDA). Silver Spring, MD. 2020. Available from URL: https://www.fda.g... .
11. ClinicalTrials.gov: *Study to describe the safety, tolerability, immunogenicity, and efficacy of RNA vaccine candidates against COVID-19 in healthy individuals.* US National Library of Medicine (NLM). Bethesda, MD. 2020. Available from URL: https://clinicalt... .
12. ClinicalTrials.gov: *A trial investigating the safety and effects of four BNT162 vaccines against COVID-2019 in healthy adults.* US National Library of Medicine (NLM). Bethesda, MD. 2020. Available from URL: https://clinicalt... .
13. ClinicalTrials.gov: *Safety and immunogenicity study of 2019-nCoV vaccine (mRNA-1273) for prophylaxis of SARS-CoV-2 infection (COVID-19).* US National Library of Medicine (NLM). Bethesda, MD. 2020. Available from URL: https://clinicalt... .
14. ClinicalTrials.gov: *Dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 COVID-19 vaccine in adults aged 18 years and older.* US

National Library of Medicine (NLM). Bethesda, MD. 2020. Available from URL: https://clinicalt... .

15. ClinicalTrials.gov: *A study to evaluate efficacy, safety, and immunogenicity of mRNA-1273 vaccine in adults aged 18 years and older to prevent COVID-19.* US National Library of Medicine (NLM). Bethesda, MD. 2020. Available from URL: https://clinicalt... .
16. ClinicalTrials.gov: *A study of a candidate COVID-19 vaccine (COV001).* US National Library of Medicine (NLM). Bethesda, MD. 2020. Available from URL: https://clinicalt... .
17. ClinicalTrials.gov: *Investigating a vaccine against COVID-19.* US National Library of Medicine (NLM). Bethesda, MD. 2020. Available from URL: https://clinicalt... .
18. ClinicalTrials.gov: *A study of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adult participants (ENSEMBLE).* US National Library of Medicine (NLM). Bethesda, MD. 2020. Available from URL: https://clinicalt... .
19. ClinicalTrials.gov: *A study of Ad26.COV2.S in adults (COVID-19).* US National Library of Medicine (NLM). Bethesda, MD. 2020. Available from URL: https://clinicalt... .
20. Poland GA, Ovsyannikova IG, Crooke SN, et al: *SARS-CoV-2 vaccine development: current status.* Mayo Clin Proc 2020; 95(10):2172-2188. PubMed Abstract: http://www.ncbi.nlm.nih.gov/... PubMed Article: http://www.ncbi.nlm.nih.gov/...
21. Moderna, Inc: *Moderna's COVID-19 vaccine candidate meets its primary efficacy endpoint in the first interim analysis of the phase 3 COVE study*. Moderna, Inc. Cambridge, MA. 2020. Available from URL: https://investors... .
22. Ramasamy MN, Minassian AM, Ewer KJ, et al: *Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial.* Lancet 2020; Epub:Epub-.
23. Folegatti PM, Ewer KJ, Aley PK, et al: *Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial.* Lancet 2020; 396(10249):467-478. PubMed Abstract: http://www.ncbi.nlm.nih.gov/... PubMed Article: http://www.ncbi.nlm.nih.gov/...
24. Bos R, Rutten L, van der Lubbe JEM, et al: *Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses.* NPJ Vaccines 2020; 5:91-. PubMed Abstract: http://www.ncbi.nlm.nih.gov/... PubMed Article: http://www.ncbi.nlm.nih.gov/...

ANNEXES

Box 1. VACCINES AVAILABLE IN THE EUROPEAN COMMUNITY

Following EMA's approval of Pfizer Biontech's anti-Covid-19 mRNA BNT162b2 (***Comirnaty***) vaccine, AIFA's approval for Italy was issued on 22 December.

The clinical trials involved a number of subjects ten times higher than the standards of those used to date, which is sufficient, therefore, to demonstrate efficacy and safety despite the shortened timeframe.

It should be specified that the time reduction does not affect the achievement of the efficacy and safety objectives set *a priori* in the trial design, nor the follow-up period identified as valid before the start of the trial. The time reduction is largely due to the efficiency of the administrative steps at the start of the trials, in the enrolment phase and in the regulatory assessment of readily available data.

The phase 3 clinical trial (see Box 5 'VACCINE RESEARCH AND DEVELOPMENT PROCESS') had only started on 27 July, involving 43,500 people in six countries (United States, Germany, Turkey, South Africa, Brazil and Argentina) and had demonstrated 95% efficacy against Covid-19 from day 28 after administration of the first dose of vaccine. Approximately 42% of all participants and 30% of US participants belonged to different racial and ethnic groups; 41% of all participants and 45% of US participants were aged between 56 and 85 years. The observed efficacy in adults over 65 years of age was over 94%.

The ***Comirnaty*** vaccine is composed of messenger ribonucleic acid (mRNA) molecules that contain instructions to initiate the synthesis of Spike proteins from the cells of the vaccinated person. These molecules are placed in a microscopic lipid nanoparticle vesicle which enables them to cross the cell membrane and penetrate into the cytoplasm, where all the instruments necessary for the synthesis of Spike proteins are present. The latter, in turn, stimulate the immune system to produce specific antibodies which, in those who have been vaccinated and are exposed to the contagion, block those that coat the viruses, thus preventing the latter from entering the cells, thanks also to the simultaneous activation of the T cells deputed to prepare the immune system to respond to further exposure to SARS-CoV-2. The vaccine does not therefore contain the virus and cannot cause the disease, but only introduces the genetic information (mRNA) required by the cell to make copies of the Spike protein. The mRNA in the vaccine does not remain in the body, but is rapidly degraded.

Comirnaty is a vaccine intended to prevent coronavirus disease 2019 (Covid-19) in people aged 16 years and over.

On 7 January, AIFA authorised ***COVID-19 Vaccine Moderna*** for the prevention of COVID-19 disease in subjects aged 18 years and older, following approval and recommendation by EMA on 6 January. *COVID-19 Vaccine Moderna* also contains mRNA that carries instructions to produce the spike protein. The *Moderna* vaccine's mRNA does not remain in the body, but is degraded shortly after vaccination. On the basis of currently available data, the safety and efficacy profile of the Moderna vaccine appears to be essentially equivalent to that of *Comirnaty*. Some different features can be noted: *Moderna* is better suited to people over 18, rather than 16; the vaccination schedule includes two shots at 28-day intervals, instead of at least 21 days; immunity is considered fully acquired two weeks after the second shot, instead of one.

In phase 3, randomised, placebo-controlled, blinded observer clinical trial, a total of 30,351 subjects were observed for a median period of 92 days (range: 1-122) for the occurrence of COVID-19. The population for the primary efficacy analysis included 28,207 subjects who received *Moderna COVID-19 Vaccine* (n=14,134) or placebo (n=14,073). The trial population was 47.4% female and 52.6% male, 79.5% white, the remainder African-American or Asian and other ethnicities. The median age of the subjects was 53 years (range: 18-94). Among all subjects in the treated population, no severe cases of COVID-19 were reported in the vaccine group compared to 30 out of 185 cases (16%) reported in the placebo group. The vaccine efficacy of *Moderna* in preventing COVID-19, starting 14 days after Dose 2, was 93.6%.

Box 2. VACCINES AVAILABLE IN NON-EU COUNTRIES OR BEING DEVELOPED

Under development or available in other countries are:

- vaccines using chemically inactivated SARS-CoV-2 virus particles, potentially capable of eliciting an immune response against different viral components. These include a vaccine developed in India (***Covaxin***) and three vaccines developed in China (the ***BBIBP-CorV***, the Sinovach Biotech vaccine and the vaccine developed by the Wuhan Institute of Biological Products);
- vaccines using harmless, non-inactivated, genetically modified viruses that act as vectors for the immunogenic protein. The viruses in question are, for example, adenoviruses (unable to replicate in humans) into which a piece of RNA encoding the SARS-CoV-2 spike protein is inserted. The adenovirus infects human cells, induces production of the spike protein in the infected cells, and promotes the immune system's response to this protein, which is crucial for infection by SARS-CoV-2. There are several vaccines of this type: ***ChAdOx1*** from AstraZeneca (Sweden) in collaboration with Oxford University (England) and IRBM (Italy); ***GRAd-COV2*** from ReiThera in collaboration with the Spallanzani National Institute for Infectious Diseases (Italy); ***Sputnik 5***, from Gamaleya Res Ist (Russia); ***Ad26COVs1***, from Johnson&Johnson (USA); ***Ad5-nCov***, from CanSino Biologicals (China);
- rVSV vaccine platform in the experimental V590 vaccine. For the new vaccine candidate V590, the recombinant vesicular stomatitis virus (rVSV) technology that was the basis for the development of Merck's Ebola Zaire virus vaccine will be used. Research and development is a partnership project between MSD and the International AIDS Vaccine Initiative (IAVI). The genetic insert of the vaccine candidate V590 to be included will be the encoding insert for the SARS-nCoV2 spike protein;
- ***Themis Vaccine Candidate V591***. This experimental vaccine uses as a vector an attenuated measles vaccine containing a modified Schwarz strain into which the spike protein of SARS-CoV-2 has been inserted;
- Vaccines which directly use the SARS-CoV-2 spike protein, usually in combination with an adjuvant. Obviously, such vaccines promote the immune system's response towards the protein crucial for infection by SARS-CoV-2. Such vaccines include: ***NVX-CoV2373*** from Novavax (Maryland, USA) in collaboration with Coalition for Epidemic Preparedness Innovations (CEPI, Norway) and COVAX19 from Vaxine (Australia).

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Box 3. VACCINATION CONTRAINDICATIONS

Vaccination contraindications are the following:

- ***temporary:***

- acute illnesses with high temperature;
- vaccinations with live viruses 30 days before (it must be pointed out that the anti Covid-19 vaccine does not represent such a case, nor is it expected to do so in the future);
- ongoing treatment with drugs that affect the immune system or with high doses of corticosteroids;
- recent administration of immunoglobulins (in this latter case, the risk is not posed by adverse events, but rather by the lack of efficacy of the vaccine).

- ***permanent***

- severe manifest reactions to the same vaccine, previously administered, or to its components.
- presence of congenital diseases of the immune system (valid for live attenuated vaccines only and not therefore for the anti-Covid-19 types envisaged so far). Nevertheless, it is equally important to carry out a careful and accurate assessment of each single case, including as regards the remission phases of a particular disease, inasmuch as, from a bioethical viewpoint, being over-prudent could indirectly harm the patient because of lack of vaccination. In such cases, however, the best thing is to regularly vaccinate family or close contacts (indirect patient protection).

In this regard, reference is made to the WHO's statement on precautions, which are not contraindications and which must be assessed in the light of the risk/benefit ratio for the individual. Contraindications are mainly absolute or relative (temporary, e.g. pregnancy) and may justify subsequent vaccination. The only absolute contraindication applicable to any vaccine is a history of a severe allergic reaction (anaphylaxis) to the first dose of vaccine or to the vaccine constituents[(a)].

The ***side effects of vaccinations*** are generally linked to the very nature of the protein product which, like any therapeutic aid, can cause undesirable effects. In general, the undesirable effects of vaccines are mild and transitory, such as fever and inflammatory reactions at the site of inoculation, which can be treated with anti-inflammatory and antipyretic drugs. Serious ADRs occur only very rarely (frequency of 1 in 100,000 to 1,000,000), and their rarity makes it impossible to assess the extent of the risk. On the other hand, many attributions are unjustified because they have no scientific basis. At present, no serious ADRs or adverse syndromes have been identified from the available data on Covid-19 vaccines in the clinical phase. In fact, given the very similar frequency of ADRs observed between vaccinated and unvaccinated persons (placebo controls), the existence of an actual causal relationship between these serious reactions and vaccination has not been demonstrated.

[(a)] As stated by the WHO: «Contraindication and precaution: A contraindication to vaccination is a rare condition in a recipient that increases their risk of a serious adverse reaction. Ignoring contraindications can lead to avoidable vaccine reactions. One of the worst and most serious vaccine reactions is anaphylaxis. There are two types of contraindications: absolute or relative (temporary). Most contraindications are relative or temporary, and the vaccination can be administered later. The only absolute contraindication applicable to any vaccines is a history of a severe allergic reaction (anaphylaxis) after a prior dose of given vaccine or to a vaccine constituent. Precautions are not contraindications, but are events or conditions to be considered in determining if the benefits of the vaccine outweigh the risks (for example, if the recipient is an immunocompromised person or pregnant woman). There is no evidence of risk to the foetus from vaccinating pregnant women with inactivated vaccines or toxoids and for LAV, the risk to the foetus is theoretical. Precautions stated in product labelling can sometimes be inappropriately applied as contraindications, resulting in missed opportunities to vaccinate. Immunization Safety Surveillance: The safety of vaccines in immunocompromised persons is determined by the type of immunodeficiency and degree of immunosuppression. There is potential for serious illness and death if immunocompromised people are underimmunized; however, inappropriate use of LAV can cause serious adverse events in some immunocompromised people».

https://iris.wpro.who.int/bitstream/handle/10665.1/12620/9789290617457_eng.pdf

Box 4. SAFETY AND VULNERABILITY GROUPS

The ***Cominarty*** registration trial (Polack F.P.et al, *Safety and Efficacy of the BNT162b2 mRNACovid-19 Vaccine*, N Engl J Med. 2020 Dec 31;383(27):2603-2615) showed that the number of symptomatic Covid-19 cases dropped by 95% in subjects who received the vaccine (8 out of 18,198 cases had Covid-19 symptoms) compared to those who received placebo (162 out of 18,325 cases had Covid-19 symptoms). The most frequently observed ADRs (in more than 1 in 10 people) were generally mild to moderate (in the form of pain and swelling at the injection site, fatigue, headache, muscle and joint pain, chills and fever) and disappeared in just a few days after vaccination.

A review of the reactogenicity data (see below for definition) on a randomised subgroup of at least 8,000 participants aged 18 years and older in the phase 2 (see Box 5 'VACCINE RESEARCH AND DEVELOPMENT PROCESS') and phase 3 trial showed that the vaccine was well tolerated, with no serious safety issues: the only adverse events observed with a frequency of more than 2% were fatigue (3.8%) and headache (2.0%). Safety and efficacy data are not yet available in people with autoimmune diseases included in the initial trials, but no differences in the occurrence of symptoms attributable to autoimmune or inflammatory diseases were observed between vaccines and placebo-treated subjects. Therefore, anyone with an autoimmune disease who has no specific contraindications can receive the vaccine. Data on the use in immunocompromised subjects (i.e. whose immune system is weakened) are limited. However, although they may not respond as well to the vaccine, they have not been shown to have any particular safety problems, and can therefore be vaccinated in order to reduce their high risk of contracting the disease.

People with chronic diseases, such as diabetes, tumours, cardiovascular diseases, are at higher risk of serious disease development in case of SARS-CoV-2 infection, and should therefore be given priority as regards vaccination. People undergoing anticoagulant therapy, on the other hand, have a general contraindication to any type of injection due to the risk of haemorrhages from the injection site: for them, vaccination must be assessed by the doctor on a case-by-case basis.

Observational data show that pregnant women have an increased risk not only of pathological development of the pregnancy, such as preterm delivery, but also of severe forms of Covid-19, i.e. involving admission to intensive care with mechanical ventilation or a fatal outcome. At present, data on the safety of Covid-19 vaccines, including mRNA vaccines, in pregnancy are scarce, and studies on animal developmental and reproductive toxicity are limited, but expected side effects are similar to those in non-pregnant women, and consequently no suggestion is made to stop trying to conceive after Covid-19 mRNA vaccination.

There are no indications regarding the exposure of infants breastfed by vaccinated mothers.

For the paediatric population, to date, the indications for the influenza vaccine apply: children with cardiological, respiratory and neurological syndromes, may be advised to receive a COVID-19 vaccine, but the trial has not been carried out on minors.

Regarding the ***Moderna*** registration trial (LR Baden, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine, N Engl J Med. 2020 Dec 30), the most common side effects are pain and swelling at the injection site, fatigue, chills, fever, swelling or tenderness of the lymph nodes in the armpits, headache, muscle and joint pain, nausea and vomiting. Adverse reactions were usually mild to moderate in intensity and disappeared within a few days. A slightly lower frequency of reactogenicity events was associated with older-aged persons. Overall, the incidence of some adverse reactions was higher in the younger age groups between 18 and <65 years than in those aged ≥65 years. Systemic and local adverse reactions were reported more frequently after Dose 2 than after Dose 1.

Among all the subjects taking part in the study, no severe cases of COVID-19 were reported in the vaccine group compared to 30 cases of the 185 (16%) reported in the placebo group. 90.9% efficacy was also demonstrated in participants at risk of severe COVID-19, including those with chronic lung disease, heart disease, obesity, liver disease, diabetes or HIV infection. Efficacy remained high regardless of gender, population and ethnicity. Because of the fact that for the ***Moderna*** *COVID-19 Vaccine* the issuing of marketing authorisation has been recommended subject to conditions, the results of the main trial, which is ongoing, will be provided for the next 2 years. The clinical trial and additional trials will provide information on the duration of protection, the vaccine's ability to prevent the severe form of COVID-19, the extent to which the vaccine protects immunocompromised people, children and pregnant women, and the ability to prevent asymptomatic cases.

Finally, it is important to note that in the context of the clinical development of vaccine candidates, the EMA has recommended that participants recruited into clinical trials should be followed for safety and efficacy within their randomised groups for at least one year after completing vaccination. This is recommended even if a conditional approval has occurred based on a convincing interim analysis of efficacy before all trial participants have reached one year after starting treatment. Indeed, long-term data are important to document any late adverse reactions and to

assess whether protection against SARS-Cov-2 diminishes over time[(a)]. To address this specific need, an adequate EU-wide vaccine vigilance system will need to be in place at the time of initial marketing authorisation to collect and report in a timely manner data on ADRs during vaccination campaigns. A Risk Management Plan has already been drawn up to structure the requirements for post-approval monitoring and increased safety surveillance as soon as vaccines are distributed[(a)]. This will enable the EMA to act as quickly as possible when a signal is detected. EMA is in fact working with the ECDC and the Member States to permit the establishment of networks throughout the European Community to conduct surveillance studies on both the safety and the efficacy of the various vaccines[(b)].

[(a)] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/guidance-medicine-developers-other-stakeholders-covid-19#early-support-for-medicine-and-vaccine-developers-section
[(b)] https://www.ema.europa.eu/en/news/ema-establishes-task-force-take-quick-coordinated-regulatory-action-related-covid-19-medicines

Box 5. VACCINE RESEARCH AND DEVELOPMENT PROCESS.

The research and development of a vaccine is a long and risky process for the manufacturer.
On average, 10-15 years elapse from discovery to market licensing, and only about 1 in 10 vaccines that start a clinical development programme make it to market (*Vaccine Fact Book*, 2013).
This process starts with knowledge of the characteristics of the micro-organism responsible for the disease to be prevented and how it interacts with the human body. Initially, *in vitro* experimental studies are carried out, on the basis of which it is possible to establish the ideal qualitative and quantitative composition (type and quantity of the active component and all other envisaged substances).
Once this has been established, the potential vaccine undergoes pre-clinical trials, which include *in vitro* studies and studies in animal models to verify the action mechanism (i.e. the ability to induce an immune response), the toxicological profile and the initial evidence of efficacy and safety in a complex living organism. This phase permits selecting the formulation which is most promising in the experimental models for the preliminary human clinical phase.
At this point, the vaccine enters the clinical trial phase, which can take place in four stages: the first three precede marketing authorisation and the fourth is conducted when the vaccine is already available on the market (vaccine vigilance).
During the first three phases, the population treated with the vaccine gradually increases, the dosage is defined (number of doses for primary immunisation and possible booster) and the efficacy or immunogenicity (the ability to stimulate a specific and sufficient antibody response in humans against the vaccine components) and safety or reactogenicity (the type and frequency of any adverse reactions) are characterised.
The two latter aspects are mainly investigated in phase 3 clinical trials, conducted on very large populations of subjects who receive the vaccine in a form which is controlled (i.e. comparing the subjects treated with the experimental vaccine with the same number of subjects treated with a similar already-authorised vaccine or with an inert treatment called 'placebo') and randomised (i.e. randomly dividing the subjects between one and the other treatment).
Efficacy is assessed as the type and persistence of the immune response, the percentage of subjects responding effectively to the vaccine and, where possible, the reduction in the likelihood of developing the disease after vaccination. The safety study, on the other hand, is based on the recording of adverse events attributable or not to the vaccine and of possible problems linked to the characteristics of the subjects, such as age, sex, race and specific health conditions.
The three phases also explore the possibility of administering the vaccine in development together with other vaccines already on the market in particular categories of subjects to obtain specific information on possible interferences in terms of efficacy and safety.
It is important to note that in the current situation, the continuing spread of the SARS-CoV-2 coronavirus epidemic has obliged the scientific community to identify criteria of efficacy and safety in order to be able, at the same time, to speed up the development of vaccines and drugs as much as possible while always maintaining required safety standards.

In this sense, the vast knowledge acquired over the years with the existing vaccine platforms has made it possible to shorten the time needed to develop candidate vaccines, as reported by EMA.

https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/guidance-medicine-developers-other-stakeholders-covid-19#early-support-for-medicine-and-vaccine-developers-section)

http://www.agenziafarmaco.gov.it/content/le-fasi-di-sviluppo-di-un-vaccino

Box 6. FRAGILITY, INFLAMMAGING AND IMMUNOSENESCENCE IN THE ELDERLY

The frailty of elderly persons depends to a large extent on so-called 'inflammaging', a condition of chronic low-grade inflammation that characterises ageing and creates a continuous background noise for the immune system, which is forced to activate relentlessly to eliminate the debris of altered or dead cells[(a)]. This phenomenon, in turn, contributes both to greatly exacerbating the release of inflammatory cytokines by macrophages during the course of infection and to causing what is known as 'immunosenescence'. The latter is an age-dependent alteration in which both the native T lymphocytes capable of attacking invaders and the B lymphocytes that neutralise and mark the invaders with their specific antibodies, thereby eliminating them, are reduced. Ageing therefore affects both adaptive immunity (production of specific antibodies by B lymphocytes, responsible for the specific memory activated by CD4+ T-helper lymphocytes) and innate immunity (mediated by CD8+ T-lymphocytes, reinforced by CD4+ T-helper lymphocytes for the purpose of memory and aimed at attacking the virus directly with further release of cytokines). In this regard, however, the cytokine storm, which has often been accused of being lethal due to lung toxicity and activation of the intravascular coagulation cascade, does not occur in many elderly persons because of functional exhaustion of the immune system, resulting in total surrender to the pathogen[(b)]. It has also been shown that previous exposure to other types of Coronavirus can easily evoke a CD8+ and CD4+ lymphocyte cross-response to SARS-CoV-2 in the young but not in the elderly, in whom memory cells, and even more so those capable of cross-reactivity, are largely absent. This suggests that it would be useful to develop a line of research aimed at enhancing both the antibody response and strong specific cell-mediated immunity[(c,d)]. So-called vaccine-preventable diseases (VPDs) significantly worsen the quality of life in older persons[(e)] and are responsible for a large proportion of deaths and various forms of disability (myocardial infarction, heart failure, stroke and cognitive impairment)[(f,g)]. All this obviously puts a considerable economic burden on the national production system[(h,i)].

(a) Ferrucci L, Fabbri E. *Inflammaging: chronic inflammation in ageing, cardiovascular disease, and frailty*. Nat Rev Cardiol. 15: 505-522, 2018.

(b) Leisman DE et al. *Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes.* Lancet Respir Med. 8: 1233–44, 2020.

(c) Saletti G et al. *Older adults lack SARS CoV-2 cross-reactive T lymphocytes directed to human coronaviruses OC43 and NL63.* Sci Rep. 2020 Dec 8;10(1):21447. doi: 10.1038/s41598-020-78506-9

(d) https://www.microbiologiaitalia.it/immunologia/il-sistema-immunitario-una-visione-dinsieme/ (ultimo accesso 26-12-2020)

(e) McElhaney JE et al. *T-Cell Immunity to Influenza in Older Adults: A Patho-physiological Framework for Development of More Effective Vaccines*. Front Immunol. 2016 Feb 25;7:41. doi: 10.3389/fimmu.2016.00041. eCollection 2016.

(f) GBD 2017 DALY and Hale Collaborators. *Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017:a systematic analysis for the Global Burden of Disease Study 2017.* Lancet. 392(10159): 1859–922, 2018.

(g) McLaughlin JM et al. *Estimated Human and Economic Burden of Four Major Adult Vaccine-Preventable Diseases in the United States, 2013.* J Prim Prev .36: 259–73, 2015.

(h) Johnson RW et al. *Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective*. Ther Adv Vacc. 3:109–20, 2015.

(i) European Commission. In Sobczak D, editor. *Population ageing in Europe. Facts, implications and policies. Brussels: European Commission Directorate-General for Research and Innovation Socioeconomic sciences and humanities;* 2014.

Box 7. VIRUS MUTATIONS AND WAYS OF BOOSTING THE IMMUNE DEFENCES OF OLDER ADULTS

Like many other viruses, SARS-CoV-2 undergoes continuous mutation not only spontaneously, but also as a result of the host organism's own immune response[(a)] making the degree of immunization provided to the elderly person by the vaccine somewhat uncertain. Such uncertainty would seem to be confirmed by the phase I study of the Pfizer-BioNTech vaccine, according to which the antibody response in older adults is halved compared to that of young persons. However, the finding of good results in older adults in some ongoing trials leads to a more optimistic view. For example, in the 40 participants in the phase 1 trial over 50 years old, the ***Moderna*** vaccine has been shown to induce an antibody titre similar to that of younger persons, and, according to a press conference on 9 September 2020, a phase 1-2 study of the Chinese Sinovac vaccine shows an antibody response superimposed on that of younger persons in 421 subjects aged between 60 and 89. In any case, in order to overcome the possible discovery in older adults of a vaccine potency lower than necessary for a valid policy of 'herd immunisation', the hypothesis has been put forward of enhancing the response of the vaccine by differentiating the dose, using adjuvants or even boosting the immune defences with supplements with an antioxidant and immunostimulating effect, or with drugs that are apparently as valid as they are safe, such as losmapimod, rapamycin and metformin, which we mention here for information purposes only and with regard to which we are still awaiting reliable data[(b)].

[(a)] Wang R et al. *Host Immune Response Driving SARS-CoV-2 Evolution*. Viruses. 2020 Sep 27;12(10):1095. doi: 10.3390/v12101095.
[(b)] Willyard C. *How anti-ageing drugs could boost COVID vaccines in older people*. Nature. 586(7829): 352-4, 2020.