Republic of San Marino

National Bioethics Committee of Republic of San Marino

Law n° 34 of January 29, 2010

BIOETHICAL VALUE OF VACCINATION

(TO THE INDIVIDUAL AND TO SOCIETY)

Approved in the plenary session of May 11, 2016

Translated by Giorgio Cantelli Forti

CONTENTS

"We no longer see children stricken with polio in wheelchairs or hear of those suffocating from diphtheria, of babies born to mothers with rubella whose eyes are clouded by cataract and hearts deformed. The success of protecting against such pathogens has removed a sense of their immediacy and caused many to forget their horror. But that may change, as we receive reports of outbreaks of infections due to unvaccinated children and mothers.

The world of my parents, and that of their children, dramatically improved in the latter half of the twentieth century as modern medicine introduced an array of effective vaccines and antibiotics.

The idea of preventing or curing dreaded infectious diseases "naturally" relying on the body alone, hardly entered our minds.

But two generations later, such ideas have considerable traction in our society."

From Eula Biss,
"On immunity: an Inoculation"

INTRODUCTION

The decision taken by National Bioethics Committee of the Republic of San Marino (CSB) to prepare a document on vaccination has originated not only because it is highly topical within the general public but also, and above all, from the firm belief that a reflection on the many ethical implications to be made available to different stakeholders was urgently needed and more important than ever.

Exactly because it can be approached from a number of different perspectives, the topic of vaccination can generate very different positions, if not conflicting and fierce reactions, between the various opinion groups. Reflections on this issue involve different viewpoints.

First and foremost, the recipients: unlike any other medical act, vaccination is carried out on healthy persons, blurring the borders between rights and bioethical principles, for example, such as, benefit/non maleficence, risk/benefit, individual responsibility/collective solidarity, compliance with regulation/individual autonomy, fair information/informed consent, right to health/other rights.

When recipients are vulnerable persons such as minors or persons unable to give their informed consent, the complexity of relations between rights and duties increases exponentially.

In this breeding ground the decisive a crucial factor has flourished, i.e. the redundancy of Internet-based information available, not all verifiable as origin and authenticity.

All the above factors lead to a “global” climate of suspicion and distrust and loss of confidence in mandatory vaccination, in particular against those diseases apparently far-off in space and time, resulting in an alarming decrease in vaccination, which is nearing well below the percentage values considered suitable for providing the population with adequate safety levels.

This phenomenon had an impact also in the Republic of San Marino, with an intense debate involving citizens and institutions, whose representatives were heard by the National Bioethics Committee of Republic of San Marino for carrying out a review of the different viewpoints.

These are the reasons why CSB wanted to prepare a document to provide stakeholders (decision makers, health professionals, associations, citizens, information professionals) with a guidance for reasoning in bioethical terms about health policies with special regard to infectious diseases prevention policies, through the offering and administration of vaccines.

The document is divided into and deals with those issues that CSB identified as crucial issues for a proper evaluation of the subject, acknowledging important cues for reflection from the hearings with the "Gruppo Genitori per la Vita"[1], "Comitato Obiettori Pratiche Vaccinali"[2] and Riccardo Venturini[3].

In particular, CSB points out the crucial and decisive role of accurate and fair information to be provided to the subjects who are planning vaccination for themselves and for persons unable to give informed consent themselves.

To this end, CSB identifies in all health and information professionals the key actors for providing citizens with comprehensive, accurate, fair and transparent information, essential for securing a conscious choice on vaccination.

Believing in the need for transparent and effective information, CSB formulates a number of proposals including the establishment of a specific observatory for the exhaustive collection of all data, indispensable including to adequately support policy decision-makers during the adjustment path of a regulation taking into account the characteristics of the population.

The working group, set up in January 2015, was co-ordinated by Giorgio Cantelli Forti, together with Nicola Romeo, an external expert of the National Bioethics Committee of Republic of San Marino and by the Deputy Chairperson, Luisa Borgia, and included Carlo Bottari, Adriano Tagliabracci and Monica Tonelli.

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1 "Gruppo Genitori per La Vita" was established in Italy in November 2013 and its purposes are, as follows: active pharmacovigilance involving parents through the distribution of logbooks/journals to be completed after vaccination, suspension of compulsory vaccination, information and transparency, correct compilation of the vaccination booklet, publication and accessibility of domestic data, publication and disclosure to the public of laws concerning vaccination damage, reporting of adverse reactions, studies and trials on alternative therapies, laying down of a unified document on vaccination procedure.

2 "COPRAV". This Committee was established in San Marino in December 2015 and its aims are, as follows: elimination of compulsory vaccination; removal of the obligation to subscribe an insurance policy for non-vaccinated subjects; reviewing of San Marino current legislation on vaccination and inclusion of a law for the recognition and compensation in the event of damage suffered due to vaccination; access to comprehensive information on the content and on batch of specific vaccine products and possible damage; implementation of a pharmacovigilance system; collection and dissemination of statistical data on vaccinated and non-vaccinated citizens; no economic incentive to medical staff for the carrying out of vaccination.

3 Director of the UOC Minors' Services, Healthcare and Social Department (Dipartimento Socio-Sanitario), Social Security Body (Istituto per la Sicurezza Sociale), of the Republic of San Marino.

During drafting, the working group made recourse to additional contributions by Walter Pasini[4] for the chapter on travellers' vaccination, and by Antonio Morri[5] for the original and precious material on the history of epidemics and vaccination in the Republic of San Marino, in the Appendix: the whole Committee expresses its sincere thanks to both.

The document includes appendices of particular interest: San Marino current legislation for this matter, the history of vaccination in the Republic of San Marino, an in-depth review of infectious diseases preventable by vaccination and of available vaccinations.

This document was approved at the plenary session of May 11, 2016, by the unanimous vote of all those present, as follows: Borgia, Bottari, Cantelli Forti, Casali, Ghiotti, Mangiarotti, Monachese, Sacchini, Tagliabracci, Tonelli. Alonzo, Carinci and Daniele who were absent notified their approval.

The Chairman of the National Bioethics Committee
of Republic of San Marino
Virgilio Sacchini

[4] Chairman of the Italian Society of Medicine for Tourism (Società Italiana di Medicina del Turismo).

[5] Chairman of the Italian Society of Medicine for Tourism (Società Italiana di Medicina del Turismo).

FOREWORD

Over the last two centuries, research and development of vaccines developed consistently with the different needs of society and the requirements of Medicine for reducing the impact of infectious disease.

If the response to unanswered needs is a very important motivation for research, public health objectives are crucial for determining the clinical and pharmaceutical development of the objectives set by public health authorities.

The increasing availability of new vaccination technologies underlines the need to make choices in order to rationalise the use of available resources and maximize the results in terms of health, by ensuring the general population adequate protection against vaccine-preventable infectious diseases. Against this background, it is important to have clear and shared criteria in order to guide decision-making processes concerning the introduction of vaccination among the prevention programmes of a Healthcare Service.

In 2005, WHO published a document that is a point of reference for governments concerning the decisions to be taken on the introduction of new vaccines[6]. The key elements of this decision-making process, shown in this document, can be subdivided into two important areas of assessment: issues related to vaccination policies and planning aspects. The former, highlights the need to investigate the efficacy, safety and economic sustainability profile of the vaccine in order to ensure whether it is a priority for Public Health. In the event the valuations on the first point are positive, i.e. the introduction is needed, a comprehensive assessment will be made on the feasibility of the vaccination programme from a technical and logistic point of view.

In the last decades, risk perception associated with the awareness of damage caused by some infectious disease was missed, while vaccine administration-related adverse events gave rise to concern[7]. The lively debate on vaccination confirms a great need of all citizens to receive information from and dialogue with expert and reliable people. The number of parents having an active role in finding out information, especially on the Internet, is increasing. Unfortunately, the Internet provides unfair information based on data not commonly accepted by the international scientific community but put forward by pseudo-scientific alternative sources.

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[6] *Vaccine Introduction Guidelines. Adding a vaccine to a national immunization programme: decision and implementation.* WHO, 2005: www.who.int/vaccines-documents/

[7] *Vaccinazioni dubbi e risposte. Un aiuto tra vere e false informazioni*. Veneto Region 2015

Disinformation and lack of knowledge may lead to wrong choices from the social and ethical point of view.

The issue of the lawfulness of the medical vaccine act introduces new and complex implications deriving from the change in the relationship between doctor and patient, in the clinical practice and in the ethical code of professional conduct pursuant to Medical Councils and, obviously, under the legislation of the State, in order to more appropriately adhere to the new culture of health and well-being. In this breeding ground, for example, innovative experiences developed on the issue of compulsory vaccination.

The role played by Health Authorities and health professionals may include an advanced dual relationship between citizen and immunization programme offered based on "libertarian paternalism". The State is entitled to intervene on matters related with citizens' private life and personal choices, as in the case of vaccination for protecting health, where individual choices are likely to jeopardise the safeguard of the entire community.

Based on the Ala Ata Declaration (1978) and the Ottawa Charter (1986), the WHO (World Health Organization) committed to urge different Countries to implement projects to "promote health". "Health" meant as a series of interventions and actions capable of providing peoples with tools for ensuring greater control on and improving their health level, by also allotting a value to individual, collective and political aspects affecting their characteristics and changes.

In the Fourth International Conference on Health (Jakarta 1997), key guiding principles such as health solidarity and health equity were reiterated and several specific objectives were set out amongst which the reduction of transmittable diseases.

On the issue of promoting health, with specific reference to the reduction of communicable diseases, undoubtedly, immunization policies promoted and supported by the various countries play a crucial role[8].

[8] WHO acknowledges that immunization is a crucial investment for a Country and for the world to come. WHO estimates that vaccines annually prevent almost 2.5 million deaths among children worldwide (L. Liu et al, Child Health *Epidemiology Reference Group of WHO and UNICEF. Global, regional and national causes of child mortality an update systematic analysis for 2010 with time trends since 2000*, Lancet 2012, 379 (9832):2151-2161). Atlanta CDC put the increasing in vaccine coverage policies worlwide among the ten great public health achievements over the last decade (Centers for Disease Control and Prevention (CDC), *Ten great public health achievements, Worldwide*, 2001-2010" MMWR 2011; 60:814-8.), estimating, in the United States only, a reduction in deaths for infectious diseases of about 42,000 cases and over 20,000 cases of morbidity (*Centers for Disease Control and prevention* (CDC), id. MMWR 2011; 60:619-23).

Furthermore, the target of promoting health involves the ongoing need to care thoroughly for the relationship between people and the environment being capable of *combining individual life choices with social responsibility*[9], at least as regards the protection of individual and collective health.

Social responsibility issue concerning health and safety are crucial issues and involve many ethical aspects.

Although today's vaccines are known for their highly technological content such as to ensure their safety and efficacy, currently there is a cultural paradox , creating increased worries and concerns in the population as the possible adverse events related to the use of vaccines[10].

As shown in recent studies carried out by the *European Centre for Disease Prevention and Control* (ECDC, 2015), the phenomenon of *vaccine hesitancy*, increasingly widespread in Europe and in socially developed countries, involves extremely varied groups of citizens expressing their indecision/fear of vaccines differently: some accepts vaccines but are generally concerned by their use, others tend to postpone their administration or refuse only some vaccines, while others completely reject them.

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[9] WHO Glossary, Social responsibility for health: "A comprehensive understanding of health implies that all systems and structures which govern social and economic conditions and the physical environment should take into account the impact of their decisions for the health and wellbeing of individuals and of the community as a whole."

[10] By way of example, consider what is currently happening globally with respect to measles: in Europe, from October 2014 to September 2015, 4202 measles cases were reported of which 65.7% were confirmed by positive laboratory results (Source: Morbillo e Rosolia News, November 2015); Germany accounted for 2630 cases reported. In Italy, in the same period, 248 cases were reported. The highest notification rates were reported by Croatia (50.4 cases/per million population), followed by Austria (38 cases/per million population), Slovenia (33 cases/per million population) and Germany (32.6 cases/per million population). In Italy, the estimated impact is of 4.1 cases/per million population). In the same period, a measles-related death was reported and six cases were complicated by acute measles encephalitis (Source: *ECDC Surveillance data and Surveillance Atlas of Infectious disease*). http://ecdc.europa.eu/en/healthtopics/measles/epidemiological_data/Pages/annual_epidemiological_reports.aspx

These alarming data induced WHO to request governments to adopt suitable measures to contain possible epidemics. In the United States, in January 2015, California Health Authorities denounced a measles epidemics among children who had visited Disneyland; then, the measles infection spread to other States including Utah, Washington, Oregon, Colorado and Mexico, too. The epidemics that in early February had affected more than 100 people in fourteen States, is increasingly drawing the attention of the American public opinion, reopening the debate on the current conflict between parents' choice and social responsibility. Many parents attacked families that do not vaccinate children, "The measles war is ugly and intense, with fear motivating both sides. It also presents vexing questions for policymakers. "What should a democratic society do when a determined minority does something that seems to endanger not only itself but also the majority?" (*Bloomberg BusinessWeek*). In addition, it should be noted that in the current year, widespread measles epidemics involved Kazakhstan, Mongolia, Sudan and China, and are still involving the Democratic Republic of the Congo, where 36,110 cases and 474 deaths were reported as of the beginning of the current year. (Source: *WHO Measles surveillance Data*, 2015)

http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/index1.html

In order to understand better the expansion of the phenomenon of *vaccine hesitancy*, an assessment of the current citizens' perception of vaccination is appropriate.

A valuable reference is provided by the investigation carried out in Italy by the Veneto Region in 2010[11], showing that there is a widespread belief among parents that the serious adverse effects of vaccines are covered up and that the information provided by health professionals is more based on benefits, that there is a conflict of interest, the number of vaccines administered in a single administration is excessive and that they are proposed to very young children[12].

The agreement to immunization for preventing well-known infectious diseases and with an epidemiological spread under control has been decreasing, as demonstrated by the reduction of vaccination coverage. This phenomenon demonstrates pretty well the paradoxical effect deriving from the efficacy of immunization; with the increase of vaccination coverage the number of cases of disease decreases and, as time goes by, the clinical relevance of the disease prevented is forgotten on an individual and collective level. As a consequence, new cases of disease start to be reported again, possibly with endemic peaks[13].

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11 "Progetto Indagine sui Determinanti del Rifiuto dell'Offerta Vaccinale nella Regione Veneto", Investigation Report, Data Analysis and Operational Guidelines – VENETO REGION, 2010.

12 In detail:

- Parents certainly consider vaccines useful in developing countries but no more needed in industrialised countries;
- Doubtful parents, representing the 15% of those surveyed, have a profile very similar to those who partially immunize their children with respect to those who regularly vaccinate them;
- The 55% of parents who partially vaccinate their children use the Internet against the 41% of doubtful parents and 25% of parents who vaccinate their children;
- Word of mouth is widely used by parents who partially vaccinate their children and by doubtful parents (60%) with respect to the 39% of parents who vaccinate;
- The 46% of parents who partially vaccinate their children collect information on vaccination from associations against immunization with respect to the 16% of doubtful parents and the 5% of parents who vaccinate;
- The 19% of parents who vaccinate their children, the 40% of doubtful parents and the 51% who partially vaccinate their children, declare that they know children who suffered damages from vaccination;
- The 12% of parents who vaccinate their children, the 37% of doubtful parents and the 42% who partially vaccinate their children, declare that they received conflicting information from health professionals.

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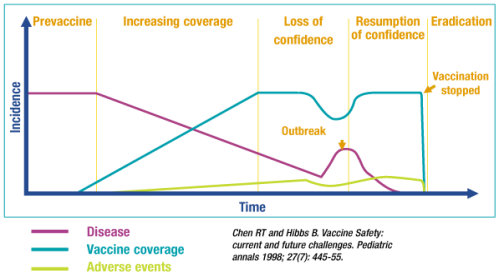

During the epidemics of new infectious diseases or in the event of global level health crisis, the problem may also be observed from another point of view, taking into account that the need for social and health safety requested by Institutions, Health Authorities, Professional Bodies and the same population, is concretised in the search for new prevention tools to be used in a brief lapse of time. The most recent cases are the Ebola epidemics in Africa and the current health crisis in South America due to the emergency of Zika virus-related diseases.

Therefore, the efforts of the scientific community and health authorities should now be made for controlling vaccine-preventable diseases through the effective and safe vaccination tools available, always maintaining the epidemiological and health promotional warning system activated, including through more effective communication to the health world and population.

ANALISYS OF THE RISK-BENEFIT BALANCE OF VACCINATION

In spite of the important results achieved as their prevention, infectious diseases are one of the leading causes of sickness, disability and death, still representing a problem for public and individual health in many countries.

Immunization was defined as one of the main medical breakthroughs made by man, which has significantly contributed to rising life expectancy of the population, and its importance in terms of public health can be compared to the possibility to provide people with clean drinking water.

Vaccination is the most efficient and safe measure available to Public Health for the primary prevention of infectious diseases directly benefiting vaccinated subjects and indirectly benefiting those not vaccinated (*herd immunity*) and the control of pathological conditions within a target population.

The *European Union of Geriatric Medicine Society* (EUGMS) and the *International Association of Geriatrics and Gerontology – European Region* (IAGG-ER) recommend and integrated preventive approach not only for the paediatric population but extended to all age groups.

If keeping high vaccination coverage in children still today ensures the control of infectious diseases in the paediatric population, health authorities have to face new challenges for public health, increasingly meaningful, deriving from the increase in average life expectancy:

- **Long-term survival of patients with chronic conditions** (heart disease, obstructive pulmonary disease, metabolic disorders, etc.), provoked a considerable increase in the number of fragile individuals that in the event of vaccine-preventable infectious diseases may more frequently suffer from complications, or a decompensation of the underlying chronic pathology, and whose clinical management is complex and entailing a significant commitment in terms of both human and financial resources.

- **Immunosenescence,** progressively reducing the immune system's function, does not ensure an adequate physiological response to infectious diseases and combines with the reduction of the immunization acquired in childhood. This phenomenon makes it necessary to plan booster vaccination programmes.

- **Active ageing and health:** furthermore, increased life expectancy in good health in the elderly extended the adult and elderly population who can work or engage in recreational activities well beyond retirement; these people play a crucial social and family role.

- Demand for health - and therefore healthcare resources – is going to increase in the next years, determined by socio-demographic, epidemiologic and technological factors. The most important dynamics are those related to the ageing of the population and chronic diseases. The number of European adults above 80 will increase in the future, reaching 10% in 2050[14]. The prevalence of chronic diseases – such as diabetes, cancer, cardiovascular diseases and neurodegenerative diseases - will increase, further accentuating the need for more resources to grant citizens the best possible care. Also from a socio-economic point of view, in 2050, the current demographic change will result in a ratio of two working people for one retired (today the ratio stands at 4:1).

In addition to bringing about a significant improvement in clinical conditions and/or epidemiologic situations, such as the prevention of infectious diseases and their outcome, the benefits deriving from vaccination provide a positive socio-economic impact to the countries, including through poverty reduction.

The economic value of vaccination in addition to its scientific value is something that should promote its greatest possible dissemination.

In brief, disease prevention through vaccination is a cornerstone within the Health System, where its efficient implementation needs an active involvement of all health professionals, each for its competence and responsibility, to facilitate the proper attainment of vaccine coverage goals provided for by specific prevention policies.

Nowadays, vaccination represent only 0.3% of healthcare spending in EU countries, such as France and Italy. Although only a small fraction of the health budget is allocated to vaccination programmes in Europe, they play a key role in prevention policies and are acknowledged as one of the most virtuous Public Health interventions in favour of the efficiency of the health system[15].

Institutions, as their dependent bodies, have the responsibility of safeguarding individual and public health and, in the risk management phase, have the duty to apply any possible caution, by resorting

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[14] *Organization for Economic Co-operation and Development (OECD). Health at a Glance 2013: OECD Indicators. OECD Publishing. 2013: pp 163.* http://dx.doi.org/10.1787/health_glance-2013-en

[15] The most comprehensive study carried out on paediatric vaccination in the United States showed that for each dollar invested in children immunization, 3 and 10 dollars respectively are saved in direct and social costs. Beyond its impact on health resources, vaccination contributes to productivity, economic growth and to the sustainability of all National Healthcare Systems. In Italy, for example, the annual economic burden of infectious diseases has been estimated in approximately € 97 million; therefore, through an appropriate vaccination strategy said burden can be reduced to approximately € 50 million. [Bonanni et al. *Economic evaluation of varicella vaccination in Italian children and adolescents according to different intervention strategies: The burden of uncomplicated hospitalised cases*, Vaccine 26 (2008) 5619–5626]

to regulatory, ethical, and deontological, community and universal principles including through the analysis of the risk-benefit balance.

In this respect, it has to be pointed out the fundamental difference between the indication to use drugs (prescribed to ill subjects to cure them) and vaccines (recommended or made compulsory for healthy subjects in order to avoid more or less probable conditions in a generally long timeframe). Such difference makes the hypothesis less acceptable for the individual the risk associated with vaccination and it requires a watertight safety profile that in fact has been largely proven as vaccines are concerned.

The foundations of the evaluation and logic process related to risk assessment are the precautionary principle and the principle of benefit-non maleficence.

National Bioethics Committee of Republic of San Marino think that current scientific knowledge and possible ethical considerations fully justify the implementation of mass immunization programmes, through forms and modes to be adjusted to the epidemiological, health and social situation of every Country.

PHARMACOVIGILANCE

Even if relatively simple to carry out, vaccination requires to be performed under a physician's direct responsibility and immediately available essential medical emergency supplies.

Indeed, vaccines are safe when administered by trained and qualified health professionals and complying with standards of good practice (use of vaccines that have been stored appropriately, using sterile syringes for single use, respecting inoculation routes and prescribed inoculation sites), considering possible circumstances that may contraindicate vaccination, temporarily or permanently[16].

Vaccines used are drugs complying with national and international rules of manufacture; in addition, each vaccine batch registered and marketed is subject to safety and efficacy controls by competent Authorities.

The manufacturing of vaccines is a very delicate process leading to their introduction only after a lengthy period of study. Continuous monitoring – during the manufacturing phase and when used – makes vaccines highly safe drugs among those placed on the market.

It is important to realise that "events" observed following a vaccination have not necessarily a causal relationship with the vaccination but only that these events are temporarily associated with a vaccination.

Risks related to the use of vaccines, however low, should always be compared with their benefits.

Vaccines are complex biological products that may include multiple antigens, live organisms, adjuvants, preservatives and other excipients and each one of these components may have product safety implications.

[16] Temporary contra-indications – temporary circumstances excluding vaccination only in the limited period of time in which they occur: acute diseases with high fever; vaccination containing live viruses (such as MMR and OPV) if in the 30 preceding days another vaccine containing live viruses has been administered; current treatment using diseases acting upon the immune system or high-dose cortisone-based drugs. Final contra-indications – it is not appropriate to administer vaccines to children when: the child has experienced serious reactions to previous vaccination; suffers from neurological diseases in evolution or immune system congenital diseases; is allergic to egg (where the vaccine contains it) or to some antibiotics such as streptomycin and neomycin (where the vaccine contains them).

Differences in the manufacturing process, new components and a new manufacturing and the different technologies used by manufacturers may have an impact on safety. This may require specific pharmacovigilance systems[17].

The risk/benefit of vaccines also depends on factors that act at population level: incidence, geographical distribution, seasonal characteristics/conditions and risk of transmission of the infectious disease within the population, number of people infected with clinical disease, seriousness of this disease, immunization coverage of the vaccinated population. Effective communication regarding the safety of vaccines and immunization is challenging. Despite strong evidence that a serious adverse event is not related to immunization, perceptions of harm may persist and may potentially have a negative impact on immunization of the population.

As any other medical product, no vaccine is risk free. Consistent systems and procedures have to continuously monitor quality, safety, tolerability and efficacy.

Therefore, CSB deems that San Marino Health Authorities should implement a well-organised pharmacovigilance system, capable of reporting:

- Vaccination failure (i.e. occurrence of the disease against which the vaccination was administered);

- Misuse/administration or operating error (overdose, underdose, vaccine beyond expiry date when used, storage related – e.g. cold chain, etc.) with or without adverse reactions;

- *Off-label* use (any use that is not specified in the description of the medical product) with or without adverse reactions;

- Defects/complaints after vaccine administration from physicians, pharmacists, other health professionals and citizens who were administered vaccines, parents/guardians.

[17] **Pharmacovigilance:** the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO 2002).

Vaccinovigilance: the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues and the prevention of untoward effects of the vaccine or immunization (CIOMS WHO 2012).

VACCINATION IN THE REPUBLIC OF SAN MARINO

In the Republic of San Marino, in the last five years that can be assessed (2009-2013), there has been an alarming decline in vaccination, with percentage figures well below those considered appropriate to provide appropriate protection for the general population, with the following significant increase of the risk for infectious diseases epidemics against which there are suitable prevention weapons, i.e. vaccines.

As in other European countries, health problems related to infectious diseases in the Republic of San Marino have ancient origins that have been witnessed starting from the Statutes of 1600, a century in which the most important and only health concern was the plague.

The fear that this mortal illness could arrive also on Mount Titan was so serious that the Statutes granted the Captains Regent the same powers as the Council exempting them from any form of control i.e. the maximum power that may be exercised in the Republic of San Marino.

The 19th century registered the outbreak of many epidemics: smallpox, measles, scrofula, tuberculosis, typhus, malaria and cholera.

The Republic authorities were especially worried by cholera because of its particularly rapid development and blatant symptoms.

There are no many information on smallpox so it may be held that it did not affect the Republic so seriously. With regard to smallpox, vaccination was discussed for the first time in the Republic of San Marino: the Republic of San Marino officially provided for the beginning of vaccination practice on April 24, 1849.

In 1888, the Chief Surgeon was assigned the task to reach appropriate agreements with the Captains Regent and other health professionals for promoting the vaccination of the general population every year in spring, to collect relevant records and transmit them to Captain Regents with the relevant report.

In the Twenties, the Republic was affected by the Spanish flu that destroyed entire family groups; in 1924-1925, there was a serious typhus epidemic and again in 1943, 1944 and 1945, years in which many refugees had already invaded San Marino and who were joined by Italians suffering from typhus and paratyphus. The level of hygiene worsened so much that in 1944-45 more than 400 patients were hospitalised in the isolation ward of the Hospital.

In 1943 smallpox vaccination and the vaccination against diphtheria became mandatory in the Republic for all 2-year old children, followed by a booster smallpox vaccination at 8 years of age.

Since 1955, through the establishment of “ISS” (Istituto per la Sicurezza Sociale – Social Security Body), the “Ufficio di Igiene and Sanità” (Office of Public Health – former “Ufficio Governativo” – Government Office) was still responsible for vaccination and the recording of infectious diseases. In 1967 this service became part of ISS then assuming responsibility on vaccination, through the “Servizio di Medicina Preventiva and Medicina di Base” (Preventive Medicine and General Medicine Service) later “Cure Primarie Salute Territoriale” (Territory Primary Health Care).

Finally, the Law of May 23, 1995, regulates vaccination, including the concerned subject’s right to object to vaccination (or the subject’s parents or guardians in case the subject is a minor), including to mandatory ones.

TO COMMUNICATE THE POSITIVE VALUE OF VACCINATION OVERCOMING *VACCINE HESITANCY*

In the light of the investigations carried out on this issue, CSB recognizes the need for an appropriate management of information/communication to be provided to citizens/parents, setting out the aims, as follows:

- to increase their knowledge on the validity and crucial importance of vaccination for health, to ensure the protection of individual and collective health;

- to answer their questions on the benefits and risks of vaccines;

- to eradicate their false convictions;

- to increase their independent decision-making in different contexts, including things to be observe/do after vaccination.

Furthermore, timing is crucial for providing information to citizens/parents.

CSB deems that information have to be provided before the notification for beginning the vaccination process, possibly through specific meetings.

In the case of new-born infants, the CSB deems useful to offer parents an information booklet concerning at least vaccination to be administered during the first years of life, that the paediatrician can give them at the first visit after the infant was discharged from the hospital where was born.

Where possible, it would be important to plan specific meetings during which competent and expert health professionals including to manage communication and relational aspects, complete the provision of information on vaccines and reply to the possible questions asked by parents. Informed choices related to their children's vaccination will depend largely by the clarity and completeness of the information provided during these meetings and by the *counselling* skills of said health professionals.

Therefore, in the current context, CSB deems crucial a fair and carefully planned communication, based on evidences and confirmed data aiming to involve all actors, from physicians to parents, stressing out the key role played by general practitioners and paediatricians as intermediaries between health authorities and citizens.

A recent document by ECDC[18] shows that including among health professionals there is an hesitant attitude to vaccination, a reason why said health professionals must represent a reference target of choice aimed at the promotion of vaccination, also taking into consideration their great involvement in the information process of patients and raising their awareness, for which we hope physicians still represent a reference point.

Therefore, Health Authorities have to support health professionals as information strategies are concerned and, even before, provide them with appropriate and in-depth training.

Furthermore, CSB points out the danger for a common misunderstanding that is the conviction that vaccination hesitancy may exclusively derive from an insufficient specific knowledge on this issue.

In reality, different surveys conducted including in Italy[19], show that most subjects who refuse vaccination pertain to well-off and cultivated classes, with an average-high level of education. Therefore, communication on immunization, in addition to transfer important technical information, has also to take into account and be able to manage a two-way approach also for other vaccination choice determinants.

In order to avoid very serious errors, such to threaten public health, CSB deems that Health Authorities should commit to providing an effective a communicative relationship with citizens, that can motivate and make them capable of making independent and informed choices in relation with the proposal submitted. In this way, the "Health Pact" repeatedly called for in/by health policies may be implemented and be based on the synergic and collaborative interaction between authorities and citizens.

CSB identifies the correct collection of patients' history as a relevant aspect of vaccination strategy that health professionals have to deal with correctly in order to ensure the subjects to be vaccinated or parents/guardians where minors are concerned, on the extreme care paid by health professionals in verifying possible contraindications at the time of vaccination.

In addition, among other things, the correct collection of patients' history will help strengthen the good communication and trustworthy relationship with families considered essential between authorities and citizens

[18] htpp://www.rifday.it/2015/11/027report.ecdc

[19] "Progetto Indagine sui Determinanti del Rifiuto dell'Offerta Vaccinale nella Regione Veneto", Id.

Therefore, from the bioethical point of view it is essential to grant citizens detailed, updated and as straightforward as possible information on vaccines. This include mentioning also differing views on vaccination and mentioning the lack of scientific data supporting those opinions, to distinguish between scientific sources and scientific data supporting them from unsubstantial allegations risking to become dogmatic.

It is necessary for information to answer parents' doubts and answers have to be focused on vaccines safety and efficacy being also capable of valuing social aspects recommending their widespread use.

Furthermore, information has also to be transparent and reliable in order to remove from the public opinion the so-called conspiracy theory deeply rooted because of some unethical and often market-related behaviours (profit at any price), and also against an unacceptable culture of disinformation in which media play an important role as they contribute to the dissemination of such disinformation through frequent sensationalism and headline-grabbing in presenting the news, as well as the lack of control on the quality and truth of the news, especially on the Internet and social networks.

CSB emphasises how information used for promotional or sensationalist purposes or for creating news at all costs (*good news, no news*), where not supported by objective results and confirmed by clinical trials conducted with scientific rigour and authority, created and disseminated without control, lead to dangerous disinformation encouraging people to believe in illusions or false myths, having consequences on the implementation of the principle of autonomy and the following right to make informed, free and conscious choices.

If the dissemination of information offers society indisputable benefits and growth opportunities, the illegitimate or irregular use of information may damage individuals and their health, interfering with their capacity for self-determination. The pervasiveness of the Internet and social networks brought about unprecedented access to a wealth of information and resources rising ethical and social responsibility issues, in particular, on the theme of health.

There are examples of how an unfair communication can influence disease prevention through vaccination and how the impact of the media is massive and essential. No longer just the press but also web sites and social media, show increased public consultation and users take a position on immunization, basing their opinion on information and statistical data collected from the Internet[20].

[20] Some dimensions of the phenomenon: about 80% of the Internet users looked online for health information. Of these, 1/5 looks for data on vaccines and 70% of users said to have been influenced by the information provided (A. Kata, *Anti-vaccine activist, Web 2.0 and the postmodern paradigm - An overview of tactics and tropes online by the anti-vaccination movement.* Vaccine, 2012;30:3778-3789). It is important to underline, as on the Internet are particularly popular websites of anti-vaccine associations. It was noted that visioning one of these sites for only 5-10 minutes

On close examination, the information provided on the Internet are mainly not precise or unfounded. As a matter of fact, one of the principles governing the Internet is the freedom of disseminating a content, however, making very difficult to verify its origin and reliability.

In the medical and scientific field, some news are so potentially disruptive on the individual and collective plan to require that their production, dissemination and the use of the Internet have to be regulated within the framework of information ethics.

Damages caused by misinformation that has been linking the vaccination against measles with the occurrence of autism is the most recent and glaring example, despite the denials by the scientific world.

CSB is convinced that the purpose of the medical and scientific information sector is to inform citizens stimulating their attention and increasing their interest in social aspects of general relevance, which is precisely the one of population health.

The more correct the information is, the greater will be the social involvement because it is capable of rising interest, credibility and trust in the individual citizen.

In addition to contents, special care has to be paid to the language used; the message has to be understood by citizens and this requires the upmost clarity and simplicity.

Therefore, CSB restates that medical and scientific communication has to be based on ethical fairness and knowledge in order to transfer it to people for consolidating and increasing the awareness, they need to guide them in the choices concerning their health and the health of the environment in which they live. To speak of transparency dealing with the issue of disease prevention through vaccination, the ethical principle of credibility should be taken into account[21], representing the level of trust existing between institutions and population.

It is necessary to build up credibility to be able to listen to the population, understanding relevant needs, greatly involving it in health-related issues and seeking feedback.

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increases the perception of the risks related to their use (C. Betsch et al., *The influence of vaccine critical websites on perceiving vaccination.* Health Psycol 2010;15(3):446-455).

[21] D. Isaacs , *An ethical frame work for public health immunisation programs.* NSW Pulm Bull. 2012,23 (5-6):111- 115; A. Mc Dawson, *Ethical principles for collectivity immunization programmes.* Vaccine 2004; 22:3122-3126.

CSB identifies as crucial for a transparent communication on immunization, the elements as follows[22]:

- information on technical aspects, such as vaccine characteristics and the mechanism of action of vaccines;

- information concerning planning, i.e. which were the guidelines and criteria used for preparing the vaccination schedule;

- information concerning clinical-epidemiological aspects, such as vaccination risk-benefit, what do we intend when we discuss about vaccines safety and efficacy, what is the frequency and dangerousness of the disease that we want to prevent.

However, CSB is aware that in order to overcome false beliefs or "demystify" them, it is not enough to provide citizens with more facts and information; it is wrong to think that a clear and explicit presentation helps people awareness and restore a strong bond of trust towards science. Often, you obtain the opposite effect that is to reinforce the "myth".

In other words, in order to weaken a belief it is not enough to oppose it with scientific evidence: the thought opposing it is selective and tend to maintain what confirms the opinions, ignoring or underestimating everything contradicting it. This is what happens with vaccination[23].

[22] G. Bartolozzi, "Vaccini e vaccinazioni". Milan: Elsivier Masson 2012

[23] M. Colucci, A. Ferro, "Leggende metropolitane e vaccini: come gli antivaccinatori "tessono" una loro realtà alternativa". Vaccinare Oggi e Domani, 2014, Vol. V (Dossier 1): 8-13.

VACCINATION AND RISK COMMUNICATION

Increasingly, risk communication is intended as an interactive process to exchange information and opinions between individuals, groups and institutions. To understand how risk is intended and relevant *biases* of supplier and beneficiary is the key for a good communication on risk[24].

An effective communication of risk depends on knowledge, respect of different experiences and distinct values that characterise the population, timely exchange of information, supported by the best evidence possible and by the guarantee that trust between different stakeholders exists.

Citizens may be classified based on their acceptance of vaccine risk, as follows:

- persons who tend to adopt decisions already taken by the majority, thinking this behaviour uncritically wiser (*Bandwagoning*);

- persons who think they do not need vaccination, because they are protected by the vaccination of other people. To this category seems to belong a good part of non-vaccinators (*free-riding*);

- altruistic persons, i.e. willing to take a personal risk if this is useful for protecting other people.

Other further significant reference elements for decision-making is the perception of the real risk of contracting a disease and its severity.

The decision of being exposed to possible health risks may be taken by citizens not only on the basis of their rational side but also emphasizing their psycho-emotional sphere and religious, spiritual and philosophical beliefs.

Furthermore, it appears that we are more willing to accept natural and controllable risks than imposed risks, as we are more willing to accept ones that are more familiar and considered so than remote and hypothetical risks.

In providing information, even experts rely on their own values and beliefs and are influenced by their personal experience.

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[24] G. Evans et al, *Vaccine Safety forum, Board on health promotion and Disease prevention*, 1997.

Among the different factors capable of altering risk perception, there is the reporting of an adverse event, especially if it is serious and taking place after a vaccination but not surely caused by it.

Indeed, what matters is not that the event is actually related to vaccine but that citizens believe that the event is surely caused by vaccination.

Then, if such belief is reinforced by mass media or anti-vaccination movements, the negative effects on the desired conscious and well-informed decisions of citizens are easy to understand.

Another element that CSB considers worthy of attention is when minors are involved, a category of vulnerable subjects, and vaccination is proposed to the parents of a child in good health and who, at that time, does not seem to be exposed to a specific risk of infection.

Faced with the choice, some parents think it is better to do nothing than act; i.e. they think that risks resulting from action are greater than those resulting from omission (*omission-commission*).

Parents who think that it is more dangerous to vaccine may already take this decision even if some look for different sources of further information.

But if the search for data is affected by a psychological perception that tend to focus on the risks of vaccination rather than carry out an objective review, it is likely that the search is carried out aiming to find confirmation of own position, attaching greater reliability to those sources that confirm the initial hypothesis: *it is better not to vaccinate*.

This introduces the concepts of parental responsibility, best interest of the children and their right to be vaccinated, in accordance with the principle of justice and of fair access to health care.

OBLIGATION TO VACCINATE AND INFORMED CONSENT

The historical onset of the obligation to vaccinate has uncertain origins: the first data concerning the obligation to comply with health provisions decided by the State seem to date back to 1337 when in Ragusa (Dalmatia – Note: today Dubrovnik in Croatia), the decision was taken to keep in quarantine those suspected of being infected with plague.

Later, in 1803, Charles IV of Spain, whose awareness was raised by the fact that his daughter was affected by smallpox, organized the famous Balmis expedition, which took its name from doctor Francisco Javier de Balmis that transported the vaccine to the Spanish colonies in South America and the Philippines, establishing mass vaccination programmes in those countries.

The "obligation" to vaccine all soldiers in his army who were not infected by smallpox yet, is ascribed to Napoleon's decree in 1805.

Originally smallpox vaccine was compulsory for recruits (France Prussia, Kingdom of Sardinia), then was extended to civilians (in Europe in 1871, in the United States a year later).

In Italy, smallpox vaccination for newborns became compulsory in 1888, and smallpox disappeared in 1925.

In 1929 vaccination against diphtheria was made available and, later, became compulsory to all newborns in 1939.

In 1959 vaccination against poliomyelitis is made available, initially using Salk's vaccine and later Sabin', making it compulsory to all newborns from 1966.

In 1963, vaccination against tetanus was made mandatory for workers deemed to be at risk, and compulsory to all newborns from 1968.

The last vaccination made compulsory in 1991 to all newborns is the one against Hepatitis B.

In Europe, only some countries opted to make some vaccinations mandatory and are, in addition to Italy, France, Greece, Portugal and Belgium.

In particular:

- in FRANCE, the vaccinations against diphtheria, tetanus, polio and tuberculosis are mandatory;

- in GREECE and PORTUGAL, the vaccinations against diphtheria, tetanus and polio are mandatory while in BELGIUM only the vaccination against polio is compulsory.

Other countries opted for a voluntary choice, but with an appropriate offering of the service, incentives and propaganda (UK and Finland); others, such as the United States, Canada and, partially, Germany opted for a compromise solution (no penalties in case of non-vaccination but need for a certificate to be admitted at school).

CSB agrees on the concept that vaccination is a fundamental right of every child, considered as an action needed for complying with the *UN Convention on the Rights of the Child* of 1989.

The aim of vaccines is to maintain public health based on the principle of benefit and cannot be considered harmful, let alone, be seen as treatments invading the psychological and physical integrity of the individual, and then the voluntary treatment clause cannot be applied here.

If vaccine is considered the only effective and necessary instrument to prevent a risk, even if only a potential one, its obligation should be reinforced; instead, where a reduction of the risk is perceived and the general situation of immunization can stand a lower degree of vaccination coverage we may choose recommendation without obligation provided that we offer appropriate information interventions/health education.

Therefore, CSB deems necessary that Institutions implement a risk-benefit assessment, the appropriate bioethical basis for an adequate medical intervention, thereby balancing existing individual rights with the collective interest.

While mandatory vaccination has made possible to achieve high rates of vaccination coverage of the population at minimum costs, it also contributed:

- to disseminate a “bureaucratic” approach to vaccination, including among health professionals;

- to make citizens wrongly believe that only mandatory vaccines are important or needed;

- to trigger the ideological rejection towards mandatory vaccination as a consequence of the progressive disappearance of diseases for which vaccination is requested (*“vaccines victims of their own success”*).

In the Republic of San Marino, mandatory and recommended vaccinations for all citizens were provided for by Law No. 39/1995, defined and implemented through an immunization programme, the most recent being the one set for by Decree No. 38 of February 28, 2008.

The existing legislation obliges the citizen who object to vaccination to take out an insurance civil liability policy for damages caused to third parties, together with further measures provided for Article 7 of said law.

CSB deems that such obligation is only a precaution of economic nature for the Republic related to the actual risk for individual and collective health and not, in actual fact, an effective deterrent against the risk of transmitting vaccination preventable infectious diseases.

The same legislation, by imposing the State to refund citizens damaged by mandatory vaccination reinforces their opinion that vaccination does not represent a safe intervention but may cause damages to whom is "mandatorily" subjected to said intervention.

CSB deems that a medical treatment may be made compulsory in the event there is a coincidence between individual and public health protection, provided that the treatments imposed are indispensable, non-experimental or discriminatory (based on race, ethnic group and gender) and the least coercive as possible.

CSB considers involuntary treatment justified where all the above criteria are complied with.

The legitimation of compulsory vaccination is represented by the protection of public health, with the exception of tetanus where the only principle legitimizing compulsory vaccination is the principle of benefit.

However, with reference to minors, the application for an exemption from compulsory vaccination does not represent a dual relationship between institutions and the holder of a conflicting interest but a triadic relationship concerning public interest, parental responsibility and interest of the child.

Institutions generally safeguard the child on the basis of a principle of benefit, therefore the children's interest is what contributes to their health on the basis of the best medical and scientific knowledge available at a given time[25].

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[25] F. Zuolo, "L'obiezione di coscienza alle vaccinazioni obbligatorie: un profilo legislativo e concettuale", Forum sul Biodiritto. Trento 2008. To overcome mandatory vaccination the following is considered necessary:

- An efficient information system based on well-organised vaccination registers capable of cross-referencing/exchange

CSB deems that vaccines, aiming to the protection of public health on the basis of the principle of benefit, cannot be considered damaging and certainly may not be seen as invasive treatments for the physical and mental integrity of the individual and, therefore, consequently the voluntary medical treatment clause is not applicable to them.

However, including for vaccination, CSB recommends to comply with the provisions of the Oviedo Convention, Article 5: *"an intervention in the field of health may only be carried out after the person concerned has given free and informed consent.*

This person will beforehand have been given appropriate information on the purpose and nature of the intervention and its consequences and risks.

The person concerned may, at any time, freely withdraw consent."

The obtention of the consent needed for recommended vaccinations, is not intended to be a simple "permission" granted but as a free and informed consent given by patients who trust the proposal made by their physicians. Said physicians, who in turn, grant their patients the compliance with their duty and professional responsibility providing them with appropriate and comprehensive information/communication.

CSB is aware that, in vaccination practice, the obtention of the informed consent is particular and specific because the medical intervention proposed involves healthy people (not sick people) and/or minors, as in the case of vaccination in paediatric age.

Therefore, it is essential that health professionals comply with the appropriate procedure for obtaining the informed consent that cannot be limited to obtaining a simple signature on a form, in order to ensure its juridical and ethical value.

In addition, CSB deems also necessary to lay down specific vaccination procedures to be complied with, clearly determining the respective/specific/individual task and duties of the different health professionals.

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data with demographic registers databases.

- An appropriate vaccination coverage, both for mandatory vaccination and recommended ones.
- An appropriate epidemiological surveillance system on communicable diseases.
- An efficient vaccination related adverse events monitoring system that can ensure also the follow-up of cases.
- Continuous training of all health professionals involved in vaccination, including honing communication skills (*counselling*).

In particular, the subjects to be vaccinated or their parents/guardians have to be granted every information concerning the characteristics of the vaccine, including components, adjuvants, preservatives and manufacturing process.

In addition, CSB recommends infectious diseases epidemiological data to be made available to the above subjects so that they are informed on the diseases to prevent through the vaccine, highlighting the differences in rates of prevalence of said diseases within the population of vaccinated subjects compared with the non-vaccinated one.

Furthermore, special attention must be paid in establishing an efficient observatory on possible vaccine damages, planning a regular periodic review of notifications received by a commission of specific experts including a citizens' representative (member of the "Comitato Obiettori Pratiche Vaccinali" – anti-vaccination committee), to ensure that the collection and processing of collected data made available is done in a transparent manner.

VACCINATION AMONG RISK GROUPS

Infectious, diffusive and transmissible diseases prevention strategies greatly developed thanks to the immunization of susceptible subjects, especially in the sector of paediatric infectious diseases.

In the sector of public health, the immunization of large segments of population determined the reduction, until the complete eradication, of many etiological agents or the associated clinical syndromes.

The efficacy of immunization against terrible childhood diseases generated considerable benefits not only to the target paediatric population but also to other segments of the population, not directly immunized, that benefited from the indirect effects of vaccination *(herd immunity).*

CSB is convinced that, for achieving every possible benefit from a vaccination campaign, intended as public health intervention, it is crucial to reach and maintain high levels of *vaccination coverage* in the long-term (segment of vaccinated subjects vis à vis the target population identified).

Optimal levels of vaccination coverage to be attained depend on multiple factors, among others the kind of infectious agent, the geography and socio-cultural structure of a country, the general health conditions of the population.

The vaccination coverage of a population depends on several factors such as, for example, the availability of vaccine and the mode for its dispensing (vaccination policies), acceptance by the local population and the same health professionals.

Direct and indirect effects due to the benefits of immunization are related with the nature of the preventable disease and vaccination coverage: every aetiological agent, due to its biological, ecological and epidemiological intrinsic characteristics or those related to the environment in which circulates, can be effectively prevented only where vaccination coverage attains a given value, that changes from pathogens to pathogens and from disease to disease.

CSB deems important to point out that the fundamental change in the epidemiologic scenario[26] , in particular, the steady increase in average life expectancy in the last decades, is such to determine important consequences on:

[26] http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=656&area=Malattieinfettive&menu=vaccination

1. Improved long-term survival of patients with chronic diseases, most at risk of serious complications due to vaccine-preventable infectious diseases, whose possible treatment requires a major effort in terms of economical and human resources;
2. In old age, the possibility that the immunization gained in childhood after infections acquired naturally or after vaccination, including due to the reduction or lack of the so-called ”natural boosters”, ascribable to the efficacy of vaccinations carried out at paediatric age, gradually decreases;

For these reasons, in order to ensure to the general population the best possible standard of living and quality of life until old age and enable the protection from serious infectious complications, in particular in subjects with chronic diseases, CSB considers therefore appropriate that consistent information on vaccination is to be provided to specific age groups and population groups considered at greater risk of contracting preventable infectious diseases.

Age-based vaccination strategies enable to immunize a large percentage of the population that is more vulnerable and susceptible to infectious diseases, such as flu.

The above concerns age-based vaccination strategies[27], i.e. involving healthy population, not suffering from specific fragility and/or morbidity condition; these strategies proved to be winning for obtaining good compliance levels in the target population to be vaccinated.

In the field of vaccination strategies, in addition to age-based, risk-based and per status[28] strategies are becoming increasingly important; those concerning subjects with chronic diseases because they are more vulnerable and fragile and, independently from age, fall within that population group to whom a vaccination can be specifically recommended[29].

Therefore, the right to prevention of subjects with chronic diseases is widely disregarded considering the very low degree of vaccination coverage of more fragile subjects, including under the age of 65.

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[27] “*The objective in this strategic area is to deliver health promotion and disease prevention services for healthy ageing with a focus on adults aged 50 years and above*”: World Health Organization*, Main objective of the strategic action plan on healthy ageing in Europe*, 2012-2020.

[28] P. Blank, T. D. Szucs, *Increasing influenza vaccination coverage in recommended population groups in Europe, Expert Rev. Vaccines*, 2009.

[29] “*The life course approach to health promotion and disease prevention contributes to greater awareness and healthier lifestyles, and subsequently improves health and quality of life*”: *United Nations Policy Brief on Ageing from the UNECE*, 2010.

For example, with respect to influenza vaccination, the results of economic models show how the recommendation to extend the yearly vaccination starting at the age of 50 years, is an optimal allocation of the resources devoted to health[30].

Among fragile subjects, older age groups of the population are increasing, due to the global ageing of the population.

Strategies based only on recommendation in case of fragility and/or chronic diseases, may not be entirely effective because it will be more difficult to achieve appropriate vaccination coverage such to grant vaccination coverage benefits for individuals and large number of subjects in addition to the benefits for the population as a whole[31].

The risk is to underestimate the importance of disease prevention through vaccination limiting it only to cases of greater fragility and, in actual fact, greatly reducing the efficacy of the intervention.

An example to this effect comes from those countries including within their recommendations the need to vaccinate health professionals being subject to very high risks of acquiring infections but also to transmit infections to other subjects, in particular to high-risk subjects because of their age and/or condition.

In the context of *risk per status* conditions, specific attention has to be paid to international travellers and health professionals.

TRAVELLERS' VACCINATION

Vaccination also represents a crucial measure of disease prevention for international travellers, not only for protecting them but also the population in the country of departure and in the one that they will visit.

Before departure, travellers must be informed about the epidemiological situation of the country or countries they plan to visit.

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[30] P. Bonanni et al., " *Vaccinazione antinfluenzali: come incrementare le coperture vaccinali. Razionale, strategie e Strumenti."* Rivista Società Italiana di Medicina Generale, August No.4, 2012

[31] "*Take measures to maximise healthy life years for women and men and reduce the risk of dependency through the implementation of health promotion and disease prevention. Provide opportunities to physical and mental activity adapted to the capacities of older people*". *Council of the European Union, Guiding Principles on the European Year for Active Ageing and Solidarity between Generations*, 2012.

The risk to acquire a specific disease depends on the prevalence and incidence of that disease in the visited country, itinerary, duration of travel, life style, gender, health status and traveller's previous immunizations.

On the basis of specific risk assessment, the doctor will be able to suggest a vaccination programme for the intended travel.

There is no vaccination schedule for travellers. Each schedule must be individualized and also based on the amount of time available before departure.

Compliance is crucial i.e. the travellers' active and intelligent involvement in the vaccination schedule proposed by the doctor before the departure.

Travellers are responsible for safeguarding their own health as well the health of people travelling with them, the public health of their countries and of the countries they plan to visit[32].

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[32] The World Health Organization (WHO) and the *International Society for Travel Medicine* (ISTM) divide travellers' vaccines into three categories: 1) Mandatory vaccines required by certain countries; 2) Travellers' specific vaccines for high-risk destinations; 3) Vaccines included in own country immunization schedule. Yellow fever is included in the first category. As of today, only yellow fever vaccination is considered mandatory pursuant to the International Health Regulations. This vaccination is still in force to protect vulnerable countries from the risk of importing the yellow fever virus. Travellers must mandatorily be vaccinated when visiting a country requiring the yellow fever as a condition for entering. This provision applies to all travellers coming from countries or areas where yellow fever is present (Sub-Saharan Africa and Northern South America). Vaccination must be recorded on the Vaccination International Certificate. Until a few years ago, the vaccination must be repeated every 10 years. Nowadays, it is considered that the immunization acquired is life-long. WHO periodically updates on its website and in International *Travel and Health* applicable provisions, country by country. Obviously, also the individual traveller has an interest in vaccination when travelling to countries where yellow fever exists. Saudi Arabia requests pilgrims traveling to Mecca a mandatory vaccination against meningococcal meningitis (Serogroups A, C, Y and W135) and the vaccination against poliomyelitis.

The second category include all those vaccinations capable of protecting the traveller from specific risks based on the destinations chosen and the geographical areas to be visited. The diseases to consider are: cholera, hepatitis A, typhoid fever, Japanese encephalitis, tick-borne encephalitis, yellow fever, meningococcal meningitis and rabies. These are food-borne diseases, spread airborne diseases, via arthropod vectors or animal bite. The physician conducting the examination on the traveller before departure is responsible for providing in-depth counselling on the behaviours to be adopted for minimizing risks. Time before departure is a significant variable to consider. It is recommended that travellers begin vaccination at least one month prior to departure. In fact, this is the period of time necessary to protect travellers in particular from Japanese encephalitis, tick-borne encephalitis and rabies. Another important variable is the current epidemiological situation, the season of the year and the presence or not of disease outbreaks.

The third group includes vaccinations carried out during childhood, adolescent and adult immunization schedules such as, for example, anti-flu vaccination. Therefore, this group include vaccinations against diphtheria, tetanus and pertussis, hepatitis B, type B *Haemophilus influenzae*, measles, mumps and rubella, varicella, poliomyelitis, pneumococcal disease, HPV and flu. Therefore, the doctor has to check travellers' immunization schedule for administering a booster dose where necessary or start a vaccination schedule in the event a specific vaccine was never administered to the traveller before. Special care has to be paid to the risk represented by poliomyelitis because of the

HEALTH PROFESSIONALS' VACCINATION

Due to their contacts with patients and potentially infectious materials, health professionals are exposed to the risk of vaccine-preventable infectious diseases.

CSB's opinion is that an appropriate immunization intervention of health professionals is crucial for the prevention and control of infections: well-designed vaccination programmes may substantially reduce the number of exposed health professionals and the associated risks of both acquiring dangerous work-related infections and to transmit pathogens preventable by vaccination to patients or other health professionals.

Health professionals are a category of workers at greater risk of infectious diseases contagion and transmission as compared with other citizens or category of workers.

At the same time, persons entrusting their health to medical care and according to the collective imagination, justified expectations exist that healthcare professionals are not the very means of infectious diseases transmission.

Dealing with ethical, deontological, medico-legal and regulatory issues related with the vaccination of health professionals the key issue that has to be dealt with is the mandatory or recommended nature of this medical act.

In many countries, the legislator provided for specific vaccination to be mandatory for specific category of workers in view of the risk of acquiring or disseminate infectious diseases, in this way drastically solving the problem and without the need for further justifications.

The Republic of San Marino does not require in its legislation mandatory vaccination for specific categories of workers, including health professionals.

CSB deems that, even though without legal obligation, there is an institutional, social and deontological intrinsic motivation, in addition to ethical motivations which should lead health professionals to participate in the vaccination programmes set forth by the National Healthcare Service of which they are part.

progressive dissemination of this disease due to the failure of the eradication programme promoted by WHO mainly caused by the opposition to vaccinate by Islamic fundamentalist groups in Nigeria and Pakistan

In the opinion of CSB, it would be a paradox if in the framework of the Healthcare Service that the State provides to citizens for prevention, diagnosis, treatment and rehabilitation the same health professionals should feel free to opt for risky behaviour for both themselves and their patients.

Furthermore, the recent Deontological Code issued in Italy in 2014 provides that physicians participate in the prevention process, in the management of adverse events and deals with the safety of care including through the vaccination against communicable diseases[33].

Therefore, health professionals' refusal to be vaccinated is to be considered as act not consistent with their mission and with the stated aims of the Institutions they work for or their professional categories.

In light of the above, CSB deems that immunization for subjects at risk should represent a valid completion of vaccination policies.

For achieving suitable vaccination coverage in this groups at risk, the crucial contribution of all health professionals dealing with it, is essential for the desirable cultural and perspective change and needed to make infectious and non-infectious diseases prevention measures efficient.

[33] Federazione Nazionale degli Ordini dei Medici Chirurghi e degli Odontoiatri, Codice di Deontologia Medica, 2014, art. no. 14, "Prevenzione e gestione di eventi avversi e sicurezza delle cure" (Prevention and Management of Adverse Events and Safety of Care)

CONCLUSIONS

In conclusion, the National Bioethics Committee of Republic of San Marino believes that individuals may face a limitation to their personal freedom in relation with the carrying out of vaccination , acting for the benefit of the community, given the exceptional nature of the risks involved and that undoubtedly do not extend beyond the benefits that the community and the vaccinated individuals enjoy.

From a collective interest viewpoint, special consideration will require the proposal to vaccinate minors or people who cannot legally give an autonomous consent themselves.

In the case of a minor, the demand for independent parental responsibility cannot dispense parents themselves to comply with the "power-duty" of ensuring their children's' health, according to the principle of benefit.

The safeguard of the child's right to have an open future is the responsibility of the State; a future not hampered by the possible consequences due to a preventable disease, avoiding children "*to become martyrs because of their parents' opinions and to be safeguarded by a principle of benefit*"[34].

In general, even more so that in the past, today we need different health policies stakeholders and decision makers to be able to respect the above fundamental ethical principles for meeting a well defined common interest objective i.e. the common good, fully respecting individuals.

To this end, CSB believes ethically necessary to educate the general public on the need for attaining a general immunization, essential to the protection of the individual and of the community, from dangerous infectious diseases.

By achieving this crucial objective, the desirable step from mandatory to recommended vaccination may be taken, representing a greater sensitiveness of the State towards the autonomous requests of individual citizens.

Furthermore, said passage may enable to overcome the present hardly understandable distinction between mandatory and recommended vaccination that risk to represent for the citizens and the same health professionals a further source of confusion in respect of the information to be provided and the choices to be made.

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[34] F. Zuolo, *L'obiezione di coscienza alle vaccinazioni obbligatorie: un profilo legislativo e concettuale*, id.

The last important issue that CSB believes has to be pointed out is to ensure compliance with the principle of solidarity.

The efficacy and safety of preventive vaccines - which has been demonstrated - does not allow excluding the possibility that mandatory or recommended vaccines autonomously chosen may put the health of an individual citizen at risk.

Indeed, it is not reasonable to require individual citizens to expose to hypothetical health risks in order to protect a collective benefit where the same community does not stand ready to share the consequences of possible negative effects.

The duty of solidarity requires the community, i.e. the State, to provide a fair compensation for any possible damage suffered by the citizen as a consequence of mandatory or recommended vaccination.

RECOMMENDATIONS

WHO/Europe has recently issued a warning call concerning the real risk that a new epidemic of vaccine preventable infectious diseases may occur in this area, and this is due to the widespread and worrying phenomenon of *vaccine hesitancy*.

In fact, some recent reports of tragic events due to complications from infectious diseases seem to confirm what said above and therefore, CSB believes that also for the Republic of San Marino there is the need of reviewing existing vaccination strategies, updating them and making them more effective in terms of prevention of infection risks.

To this end, the National Bioethics Committee of Republic of San Marino has the following recommendations to make:

- CSB recommends a total system approach, based on careful and in-depth analysis of the current social framework conditions;

- CSB recommends the implementation of informational and communication actions aimed at citizens for supporting the joining of the proposed vaccination plan, explaining the objectives to be pursued;

- CSB recommends the above actions to be professionally designed in order to "emotionally" involve citizens, beyond the technical/professional completeness of the content provided and the scientific evidence supporting the messages disseminated in addition to the needed clarity;

- CSB invites to engage in an in-depth reflection on the reasons that in recent years led to an increasing loss of confidence on the part of the citizens towards the institutions in general, the Healthcare Service and doctors in particular;

- CSB looks forward to clear and precise actions for supporting vaccination and reporting blameworthy acts from an ethical and human point of view by health professionals.

- Furthermore, CSB, looks forward to an in-depth ethical and deontological reflection by communication and media professionals, in particular, in order to ensure the dissemination of fair and not sensational (at all costs) information to citizens;

- CSB recommends information professionals to be fully aware of the power of media coverage

and of the messages they disseminate, including of the possible serious social drawbacks deriving from the transmission and spread of false, incorrect and ideologically misleading information;

- CSB recommends Institutions and health professionals working for them, to assume full and mindful responsibility for the planning of the interventions needed for the safe and correct carrying out of vaccination, and the careful reporting of possible side effects;

- CSB recommends vaccines manufacturers to comply with voluntary ethical/deontological codes established by themselves in order to achieve their profit target through the lawfulness of research, aiming to enhance general life conditions of individual citizens and of the general population;

- CSB recommends that also in the Republic of San Marino pharmacovigilance activities are carried out, such as to guarantee citizens on the quality and safety of the proposed vaccination programme;

- CSB recommends epidemiological data on preventable infectious diseases in vaccinated and unvaccinated subjects to be made available;

- CSB looks forward to the creation of an observatory on possible vaccination damage; the relevant commission should include experts and citizens' representatives to make even more transparent the way of collecting and processing data to be made available;

- CSB recommends to recognise the right of parents and citizens in general to receive fair and comprehensive information but calls for their parental and social accountability assuming any responsibility that living in a community requires;

- CSB believes that, in case of danger for an individual citizen or the general population the State has the right/duty of resorting to mandatory vaccination, where necessary, providing for sanctions, including economic ones, for those not complying with the above obligation unless justified by sound and substantiated claims;

- Furthermore, CSB looks forward for the State to implement monitoring activities on compliance with the obligation to vaccinate for protecting the right to health of the community, without restrictions to other important acquired rights.

APPENDICES

REGULATIONS AND REFERENCE DOCUMENTS OF THE REPUBLIC OF SAN MARINO[35]

Law No. 69 of May 23, 1995, (published on June 1st, 1995), *"Disciplina delle vaccinazioni" (Regulation on vaccination).*

Delegated Decree No. 38, of February 28, 2008, *"Calendario delle vaccinazioni obbligatorie e raccomandate" (Calendar of mandatory and recommended vaccinations).*

Health and Welfare Plan of the Republic of San Marino. 2015-2017

Guidelines for the annual business plan of the Institute for Social Security. Year 2016

[35] Regulation may be downloaded from the website of the "Consiglio Grande e Generale"

http://www.consigliograndeegenerale.sm/on-line/home/archivio-leggi-decreti-and-regolamenti.html

Epidemie e vaccinazioni nella Repubblica di San Marino

As in other European countries, health problems related to infectious diseases in the Republic of San Marino have ancient origins. As witnessed by Carlo Malagola[36], specific roles and responsibilities were identified in time to cope with these health emergencies:

"The "Soprastanti della sanità" (Health Authorities) are mentioned for the first time in the Statutes of 1600 and, together with the Captains, were appointed especially for protecting the territory from the plague and other infectious diseases and for taking appropriate measures in time of plague. They were vested with whatsoever faculty, in their sole and absolute discretion. Usually, until 1656, the "Soprastanti" were two but forecasting that the plague ravaging Naples and Civitavecchia would soon affect San Marino, their number increased to four. At the same time, the "Borgo" and the city doors were strictly guarded, closing passages and placing iron gates for impeding the access to foreigners and trade with infected places."

As illustrated in the "Rubrica", in the 17th century, the most important and only health concern was the plague.

The fear that this mortal illness could arrive also on Mount Titan was so serious that the Statutes granted the Captains Regent the same powers as the Council exempting them from any form of control i.e. the maximum power that may be exercised in the Republic of San Marino.

The Chiesa del Crocefisso, located close to the city walls, *"is especially dear to the people because it is the last resting place of dozens and dozens of plague infected victims who died in 1540 – 1549 -1630 and during every other epidemics which later affected the Country."*

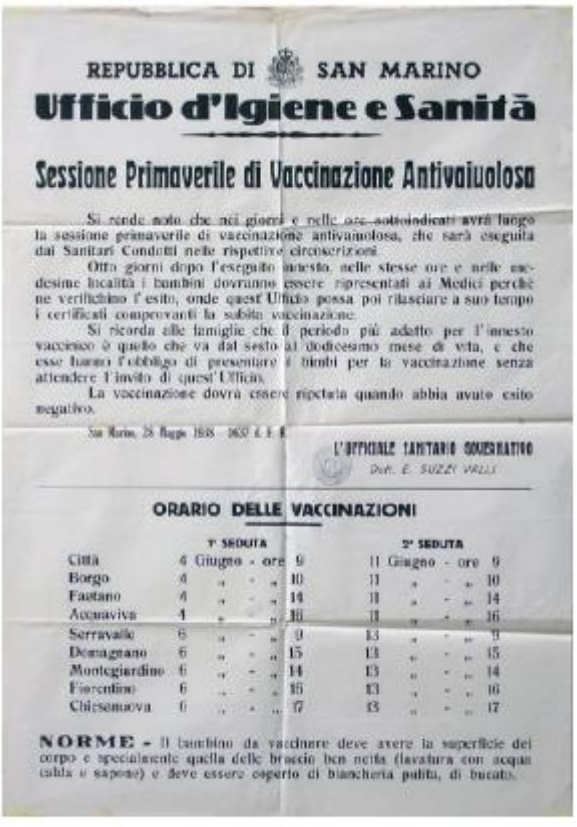
Figure 1. Letter sent by the Captains Regent to call for the vaccination of two children from Rimini

[36] Carlo Malagola, State Archive of the Republic of San Marino, rearranged and described: San Marino Statutes from 1295 to XIV century were included. Typography Fava E. Garagnani, 1981.

It is well known that the nineteenth century was characterised by several epidemics from the point of view of health: smallpox, measles, scrofula, tuberculosis, typhus, malaria, pellagra and cholera.

In particular, the authorities of the Republic were worried about cholera because of the rapid spread of the disease and blatant symptoms. Thanks to the active interest of the Neapolitan physician Andrea D'Emilio, great friend of the Republic, they commissioned a "handbook" to be used by physicians and citizens to the physician Gennaro Spasiano for avoiding, as much as possible, the epidemics that affected Marche and Romagna between 1865 and 1867 to spread also in the Republic.

There is little information on smallpox. Hence, we may held that the Republic was not seriously hit. It is precisely in relation with smallpox that for the first time there was a talk of a vaccine in San Marino. At the end of the sitting of July 24, 1805, the reference made by the Regents in the "Atti del Consiglio Principe" (Council Acts) arouses curiosity *"the request put forward by a Physician commissioned by the Reign of Italy for the injection of smallpox vaccination, in order to agree measures to be taken in concert with our Government. The Generale Consiglio (Great and General Council) designated our Professors to deal with this matter."* In the following years, vaccination was carried out in the Republic and this is confirmed in the Council's minutes. In the documents of the Regents it is particularly interesting the call for smallpox vaccination for "*two robust children*" submitted by Luigi Panni, from Rimini, on May 13, 1835.



REPUBBLICA DI SAN MARINO

Ufficio d'Igiene e Sanità

Sessione Primaverile di Vaccinazione Antivaiuolosa

Si rende noto che nei giorni e nelle ore sottoindicati avrà luogo la sessione primaverile di vaccinazione antivaiuolosa, che sarà eseguita dai Sanitari Condotti nelle rispettive circoscrizioni.

Otto giorni dopo l'eseguito innesto, nelle stesse ore e nelle medesime località i bambini dovranno essere ripresentati ai Medici perchè ne verifichino l'esito, onde quest'Ufficio possa poi rilasciare a suo tempo i certificati comprovanti la subita vaccinazione.

Si ricorda alle famiglie che il periodo più adatto per l'innesto vaccinico è quello che va dal sesto al dodicesimo mese di vita, e che esse hanno l'obbligo di presentare i bimbi per la vaccinazione senza attendere l'invito di quest'Ufficio.

La vaccinazione dovrà essere ripetuta quando abbia avuto esito negativo.

San Marino, 28 Maggio 1938 - XVI E. F.

L'UFFICIALE SANITARIO OSSERVATORE
Dott. E. SUZZI VALLI

ORARIO DELLE VACCINAZIONI

	1ª SEDUTA	2ª SEDUTA
Città	4 Giugno - ore 9	11 Giugno - ore 9
Borgo	4 " - " 10	11 " - " 10
Faetano	4 " - " 14	11 " - " 14
Acquaviva	4 " - " 16	11 " - " 16
Serravalle	6 " - " 9	13 " - " 9
Domagnano	6 " - " 15	13 " - " 15
Montegiardino	6 " - " 14	13 " - " 14
Fiorentino	6 " - " 16	13 " - " 16
Chiesanuova	6 " - " 17	13 " - " 17

NORME - Il bambino da vaccinare deve avere la superficie del corpo e specialmente quella delle braccia ben netta (lavatura con acqua calda e sapone) e deve essere coperto di biancheria pulita, di bucato.

Figure 2. Vaccination schedule showing session times for smallpox vaccination, 1939.

Figure 1. Others will follow confirming that vaccination was not carried out in the district at that time. On April 24, 1849, the Republic of San Marino officially provided for the beginning of the vaccination policy: *"The Captains Regent, taking into due consideration the many requests received by the citizens of the Republic for carrying out smallpox vaccination in this district, made the "Consiglio Principe" to issue the relevant Decree. It was unanimously ordered to carry out the smallpox vaccination in this Republic and, in addition to other existing obligations vested with the physicians; the obligation to immunize children against smallpox is added."* Soon after the Council had also to deal with the economic side of vaccinations: *"Please, read also the Report submitted by S. D. Lazzarini, Chief Surgeon, stating to have carried out his assignment i.e. of having carried out vaccination also this year. From the report, results that the efforts made by the above mentioned physician were greater than*

the last time for which he was remunerated with fifteen "scudi" (golden coins), we hereby agree to pay him with twenty "scudi". In 1865, the physicians Gaetano Rastelli and Plauto Dal Monte Casoni submitted a report on the vaccinations carried out on 184 children[37] obtaining the praise of the Council. On June 26, 1887, the "Resto del Carlino" newspaper wrote about San Marino that: " *As early as December 20, 1886, some students returning home for Christmas festivities from Bologna imported a mild form of smallpox in San Marino. Immediately, the disease infected in particular the students' relatives but without serious consequence. However, two months later during which no trace of contagion had been reported, smallpox reappeared stronger than before and caused dire consequences including some deaths. It transformed into black smallpox and notwithstanding the treatments performed by the several physicians in our Country and, in particular by Plauto Dal Monte, has continued to affect and frighten our peaceful population."*

On September 6, 1888, the Draft of Health Regulation for doctors was read during the Council. Among the tasks to be fulfilled by the Chief Surgeon, Article 4 included the following: *"Every year the Chief Surgeon shall agree appropriate measures with the Regents and other physicians to call for the State general vaccination and once it is over proceed with the collection of the registers to be transmitted to the Regents with the accompanying report."*

In 1924-1925, the Republic was affected by a serious typhus epidemic. In fact, we know that some cases of typhus occurred always because of water, especially in the Serravallese area, starting from the beginning of the 19th century, concurrently with the difficult food situation. In 1817, in April, there was a new outbreak affecting "Parrocchia Pieve" and then Serravalle. Up to 40 deaths were reported and the local parish priest recorded the cause of death as "epidemic typhus".

After a relatively calm century - because it was cholera that hit hard in these one hundred years – there were a few cases of abdominal typhus, in different areas of the district, towards the end of November 1924. Then, later in the year, the outbreak of the epidemic took place. The first cases were reported in the Castle of Fiorentino, were the springs of the public aqueduct were located, the only aqueduct ensuring drinking water throughout the territory of the Republic. From Fiorentino – as it was exactly following the aqueduct pipeline, the outbreak spread in the City and later affected

[37] The vaccinations carried out were 225 in 1864, 184 in 1865, 239 in 1867, 172 in 1868 and 152 in 1869 and 509 in 1873. In general, vaccinations were carried out in summer, injecting from 4 to 6 doses, in the first year of life even if there are a few cases of subjects aged 16 to 28.

Serravalle, where the aqueduct ended. The Healthcare Office was established in 1935. Before that date, when the Chief Surgeon, responsible for the healthcare service, was notified of serious hygiene and health problems from local practitioners, informed the Secretariat of State for Domestic Affairs or the Technical Office and, they if they could or wanted, responded appropriately. Once the typhus epidemics broke out, the Government convened a first meeting inviting representatives of the Italian Government i.e. Donato Ottolenghi, Director of the Institute of Hygiene at the University of Bologna, Gustavo Oreste, Provincial Physician at Forlì. Then, the Government appointed Professor Felice Pullè as Director of the Healthcare Office, later appointed Health Consultant of the Republic, assisted by Antonio Zappata (assistant at Ancona City Hospital), Cesare Nicolini (pharmacist) and by the Chief Nursing Officer of the "Ospedale della Misericordia Vio Cornacchia". Professor Pullé availed himself of the consultancy and advice of Professor Ottolenghi, who had dealt with the typhus outbreak in Cesena and of Brotzu, who was going to be appointed Chief Surgeon of the Healthcare Office that Professor Pullé was recommending to establish as soon as possible.

Figure 3. Marianna Anita Semprini, nurse in Riccione who came to San Marino to tackle the typhus epidemic, was infected and lost her life.

Four nurses (two men and two women) arrived from Riccione. One of them, Marianna Anita Semprini, was infected in the performance of her duties and lost her life because of typhus. Fig. 3

On February 26, 1925, the Senate posthumously awarded her a 3rd class Medal of Merit.

A second serious typhus epidemic hit the Republic again in 1943, 1944 and 1945. Luigi Pochettino described it in detail in his degree thesis at the Faculty of Medicine and Surgery at the University of Bologna in the 1944-45 academic year[38]. Pochettino provided the data concerning the cases of typhus and paratyphus B over the 1937/1942 period, as follows: 61 cases in 1937; 25 cases in 1938; 12 cases

[38] Luigi Pochettino, degree thesis: "Indagini epidemiologiche eseguite in occasione di due episodi epidemici di tifo addominale occorsi nel territorio della Repubblica di San Marina negli anni 1943 e 1944-1945." (Epidemiologic investigations carried out during the two abdominal typhus outbreaks in the territory of the Republic of San Marino in 1943 and 1944-1945).

in 1939; 16 cases in 1940; 15 cases in 1941 and 48 cases in 1942. The cases mentioned took place in the most rural area of the territory "and more precisely in a quite wide area including Domagnano, Ca' Giannino, Lesignano and Paderno and the territory between them.

"In the first days of July, 1943, suddenly and almost simultaneously, in different locations of the territory, a number of clinical cases of very high fever and general severe conditions took place. The fever increased rapidly but, in general, patients did not show gastro-enteric problems." All clinical investigations led to the identification of a typhoid infection. The number of infected subjects gradually increased reaching the peak of 15 cases on July 12 and other 15 cases on July 13. "Secondary infections followed reaching the number ascribable to the annual endemic outbreak within usual limits (normal, standard)."

In total, there were 233 sick people, of which two thirds hospitalized in specifically adapted isolation wards. Mortality was 7.3%, an incidence rate that Pochettino considered "relativity small despite the considerable seriousness of the outbreak". The most affected was the 5 – 35 age group and mortality rates were 10.1% (men) and 3.8% (women).

In 1944 and 1945, when San Marino was already invaded by thousands of refugees hoping to survive an unjustifiable bombing that caused a large number of deaths and injured persons, at the beginning of September 1944, also people with typhus and paratyphus began to arrive coming from Coriano, Riccione, Santa Maria in Cerreto, San Martino in Venti, Santa Cristina, Romini, Torriana, etc.

Pochettino wrote: "From this moment, the hygienic situation worsened so much to reach a stage which would not allow an effective control nor the possibility to take appropriate measures. From July 1st, 1944, to December 31, 1945, the total number of abdominal typhus cases and paratyphus B was totalled 514 typhus cases and 366 paratyhus cases. However, typhus represented the 58.4% and paratyphus the 41.6% of cases. Total mortality (typhus and paratyphus B) was 8%, i.e. greater than in the 1943 outbreak."

Continuing reading the thesis we learn that, during the 1943 epidemics, 152 patients and in 1944-45 more than 400 patients were hospitalised in the isolation ward of the Hospital.

This is a specific evidence concerning the Castello di Serravalle about the spreading of the Spanish flu that took hundreds of lives in San Marino in the Twenties: *"that sadly mourned the destruction of entire family groups."* An emergency shelter was established in the school building *"in the lazaret, there were beds and temporary sleeping platforms everywhere in the classrooms and corridors and the scent of disinfectant was all round…the assurances given by the physicians under the guidance of*

Arnaldo Rossi were not taken into account. They tried to explain that it was a bad flu indeed but not necessarily lethal…"[39]

In the Republic, Law 19 of May 27, 1943, made vaccinations against smallpox and diphtheria mandatory for all 2-year old children, with an anti-smallpox booster dose at 8 years of age.

In pre-vaccination times, the following diphtheria cases occurred:

1937: 36 cases with 2 deaths; 1938: 42 cases; 1939: 63 cases with 2 deaths; 1940: 33 cases; 1941: 21 cases; 1942: 27 cases with 3 deaths; 1943: 7 cases; 1944: 15 cases with one death and 1945: 12 cases with one death. Starting from 1946 there were no more deaths and cases decreased significantly up to a maximum of eight cases in 1947 and a minimum of zero cases in 1954 and 1956.40

In 1950, Enea Suzzi Valli and Leo Marino Dominici carried out an extensive study on the incidence of tuberculosis in San Marino.41 In the total absence of relevant documents, the study was based on the exam of the forms concerning deaths, starting from 1908, because very often before that year, the cause of death was not recorded. The study shows that the annual average mortality consequence of all forms of tuberculosis varied from a maximum of 19 deaths in 1918-1922 to a minimum of 10.2 deaths over the 1928-1932 period corresponding to 1.74% and 0.88% per 1,000 citizens. The average index throughout the entire 40-year period was 1.19%. Therefore: "Mortality due to tuberculosis from 1908 to 1947 shows a notable increase in the 15-year period 1913-1927 and another notably lower increase over the 1938-1947 decade. The castle most severely hit in the territory was Chiesanuova and the one with fewer cases was Faetano.

The Anti-tuberculosis Service was established in the Republic in 1837. The report sent by Enea Suzzi - the Public Health Inspector – to the Captains Regent on July 17, 1937, states:

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[39] Montanari Alba:"Olivara e dintorni" – San Marino – Edizioni GG Giorgio Gasperoni – 1996 – The chapter entitled: "Il lazzaretto".

[40] These information are provided in the study by Leo Dominici and Federico Micheloni: "Osservazioni sull'andamento della difterite nella Repubblica di San Marino in rapporto alla vaccinazione" – Extract from the magazine: "Igiene e Sanità pubblica" – Volume XIV – Issues ½ - January/February 1958.

[41] Enea Suzzi Valli – Leo Marino Dominici: "Incidenza della tubercolosi nella Repubblica di San Marino". 1- La mortalità per tubercolosi nel quarantennio 1908 – 1947" - Extract from the magazine: "Rivista Italiana d'Igiene" – Year X (1950) – No.3/4 – Pisa – Industrie Grafiche V. Lischi e Figli. 1950.

Enea Suzzi Valli – Leo Marino Dominici: "Incidenza della tubercolosi nella Repubblica di San Marino". 2- La morbosità per tubercolosi dell'apparato respiratorio nel decennio 1938-1947" - – Extract from the magazine: "Rivista Italiana d'Igiene" – Year X (1950) – No.5/6 – Pisa – Industrie Grafiche V. Lischi e Figli. 1950.

“As from the first of November of 1936, the mandatory notification of tuberculosis in its various forms, bound by an obligation of professional secrecy, was provided for. Since then, considering the only the tuberculosis form, which is the one that interests more and represents almost all of tubercular diseases, 50 cases were notified to this Office. Only after the Second World War the use of BCG vaccine spread (Bacillus Calmette-Guérin) in Europe and in the United States and, almost simultaneously, the antibiotic therapy with streptomycin.

The merit for discovering vaccination for preventing the transmission of infectious diseases goes to an English physician, Edward Jenner (1749-1823). He injected a child with purulent pus taken from the arm of a woman affected by vaccinia strain, the type of strain that infected bovines and in lighter form cattle handlers. The child became immunized from smallpox human form. Later, such medical practice was called “vaccination”.

The scientific community reacted to this new practice with a certain mistrust but very soon Jenner’s method spread throughout Europe.

REPUBBLICA DI SAN MARINO

SEGRETERIA DI STATO

Il governo, di fronte alle comunicazioni degli organi sanitari competenti che hanno segnalato la necessità di vaccino antipoliomielitico per prevenire il pericoloso morbo, constatate le difficoltà di approvvigionarsi del medicamento in Italia, ha svolto tempestive pratiche presso gli Stati Uniti d'America per ottenere un quantitativo di vaccino.

A pochi giorni di distanza dalle richieste sammarinesi il governo americano ha ufficialmente informato la Segreteria di Stato per gli Affari Esteri di aver disposto l'invio di c.c. 2.600 di vaccino Salk, dono della ditta ELI LILLY, che sarà trasportato d'urgenza dall'America a San Marino con mezzi aerei dell'esercito statunitense.

Nel dare la presente comunicazione, il governo sammarinese esprime al governo americano i sentimenti della più viva gratitudine per il generoso aiuto, che ancora una volta conferma i vincoli di amicizia e di solidarietà che legano la Grande Repubblica Stellata alla nostra piccola Terra.

LA SEGRETERIA DI STATO

Figure 4. Announcement of the arrival of the Salk vaccine against polio from America.

Then, great importance for the development of vaccines had Louis Pasteur (1822-1895). He was a distinguished investigator and scholar who studied cholera, anthrax and, especially, rabies.

It is precisely thanks to the vaccine against this viral disease that in 1886 Pasteur could explain the Academy of Sciences the brilliant result achieved by injecting the attenuated virus in 350 persons. One of the most important persons in immunization modern history surely was Albert Sabin, an American investigator and physician, of Polish origin, famous for his discoveries on poliovirus. In 1947-1950 in the US, he developed a technique for attenuating the virus in such a way as to obtain a vaccine that could be administered orally. The vaccine so obtained became the first global weapon against polio. Sabin never wanted to benefit economically from his discoveries and refused to patent them declaring that they belonged to children all over the world.

Vaccines were introduced in Italy at the end of 1800.

The first vaccination to be introduced was precisely the anti-polio vaccination made mandatory by the Crispi-Pagliani Law in 1888. In 1939, the vaccination against diphtheria became mandatory to children within the first two years of life.

Later, immunization general programmes for newborns were introduced, including: diphtheria, tetanus, polio, pertussis, rubella, measles, mumps, hepatitis B and haemophilus influenzae.

In the Republic of San Marino, only in 1938 the Public Health Inspector was delegated the choice and management of vaccinations. However, the provision making vaccinations compulsory was provided for by law[42]. In 1955, through the establishment of "ISS" (Istituto per la Sicurezza Sociale – Social Security Body), the "Ufficio di Igiene and Sanità" (Office of Public Health) maintained the definition of Government Office. It is still responsible for vaccination and recording infectious diseases. Only in 1967 this service became part of ISS then assuming responsibility on vaccination, through the "Servizio di Medicina Preventiva and Medicina di Base" (Preventive Medicine and General Medicine Service) later "Cure Primarie Salute Territoriale" (Territory Primary Health Care).

Finally, with Law No. 69 of May 23, 1995, Vaccination Regulations, the right to objection – including to mandatory vaccinations - of the subject to be vaccinated was recognised (or the subject's parents or guardians in case the subject is a minor).

In a little more than 100 years, we go from an age characterised by the request to access medical care to one in which it is necessary to provide for its denial. The history of vaccines is rich in outstanding clinical accomplishments and achievements but it has to be said that a limited number of episodes caused some adverse events. Today, there are many factors to be considered in deciding whether to vaccinate and, last but not least, the media factor.[43] Fair information, economic and insurance aspects, are only some of the factors that have taken hold of that world that once included only two words: medical care.

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[42] Mandatory vaccination against smallpox and diphtheria on May 27, 1943; mandatory vaccination against typhus and paratyphus on May 15, 1945; mandatory vaccination against polio on February 17, 1966; mandatory vaccination against pertussis on March 5, 1974; mandatory vaccination against measles and rubella on October 31, 1985; mandatory vaccination against pertussis, tetanus and hepatitis B on October 23, 1991; mandatory vaccination against polio, diphtheria, pertussis, tetanus and hepatitis B on October 24, 2005.

[43] It is estimated that about two million people refused vaccination in 2014-2015 as compared to previous years, after the press widely reported the hypothesis of a connection between flu vaccination and fatalities. The late confirmation on the safety of the vaccine to the general public could not prevent the increase in the number of deaths due to flu in that year.

REPUBBLICA DI SAN MARINO

UFFICIO DI IGIENE E SANITÀ

Sessione Primaverile di Vaccinazione Antivaiuolosa ed Antidifterica

Ad iniziare dall'anno corrente sono rese obbligatorie - ai sensi della Legge 27 Maggio 1943 - le vaccinazioni antivaiuolosa ed antidifterica per tutti i bambini nel secondo anno di età.

Pertanto tutti i nati nel 1942, e quanti non siano stati vaccinati in precedenza, devono essere presentati per le pratiche vaccinali associate nei giorni e nelle località sottoelencate. Nella prima seduta saranno eseguiti l'innesto vaccinico e la prima iniezione antidifterica; la seconda seduta è riservata al controllo della vaccinazione antivaiuolosa ed alla seconda iniezione antidifterica.

Sono esenti da entrambe le vaccinazioni, a giudizio di quest'Ufficio, i bambini che, per particolari condizioni di salute, non possono esservi assoggettati senza pericolo, e ciò fino a quando durano dette condizioni, e dalla vaccinazione antidifterica i bambini che hanno già sofferto la difterite, regolarmente denunziata all'Ufficio di Igiene.

È inoltre obbligatoria la rivaccinazione antivaiuolosa all'ottavo anno di età.

Le vaccinazioni sono gratuite. I certificati di subita vaccinazione e rivaccinazione antivaiuolosa e di vaccinazione antidifterica sono compresi fra i documenti prescritti dalla legge per la ammissione alle Scuole Primarie ed alle altre collettività infantili di qualsiasi genere.

Agli stessi obblighi sono soggetti **i bambini forensi sfollati in Repubblica,** i quali dovranno pertanto essere presentati per la vaccinazione associata unitamente ai Sammarinesi, onde quest'Ufficio possa a sua volta trasmettere le relative notificazioni ai Comuni di provenienza.

San Marino, 22 Aprile 1944 (1643 d. F. R.).

L'UFFICIALE SANITARIO GOVERNATIVO
E. Suzzi Valli

DIARIO DELLE VACCINAZIONI

	1ª SEDUTA riservata alla vaccinazione antivaiuolosa ed alla prima iniezione antidifterica	2ª SEDUTA riservata al controllo della vaccinazione antivaiuolosa ed alla seconda iniezione antidifterica
Città (Ospedale)	26 e 28 Aprile 1944 - ore 9	17 e 19 Maggio 1944 - ore 9
Borgo	29 " - " 10	20 " - " 10
Faetano	29 " - " 15	20 " - " 15
Acquaviva	27 " - " 15	17 " - " 15
Serravalle	26 " - " 9	17 " - " 9
Domagnano	26 " - " 15	26 " - " 15
Montegiardino	28 " - " 14	17 " - " 14
Fiorentino	28 " - " 16	17 " - " 16
Chiesanuova	28 " - " 17	17 " - " 17

Figure 5 Vaccination schedule showing session times for smallpox and diphtheria vaccination, 1944.

VACCINE- PREVENTABLE INFECTIOUS DISEASES

Today, vaccine-preventable infectious diseases still remain a serious public health problem because there are groups of non-vaccinated population and continuous circulation of many aetiological agents.

Poliomyelitis is an infectious disease caused by three intestinal viruses, spread by the faecal-oral route. Around 95% of people infected by the poliomyelitis virus are asymptomatic, however, all infected subjects transmit the virus in the environment via the faeces for a period of time. The number of polio cases decreased of more than 85% in little more than a decade. Thanks to vaccination, in 2002, Europe certified the polio-free status of its territory. However, the risk of re-importation of the polio virus in our country is related to maintaining appropriate vaccination coverage rates.

Diphtheria is a serious infectious disease caused by a toxin (Diphtheria toxin) secreted by a bacterium (Corynebacterium diphtheria). Diphtheria mortality rate is around 5-10% but in many cases, survivors suffer permanent damages to hearth, kidneys and nervous system. Disease outbreaks progressively decreased and almost disappeared in the late 1970's, after the vaccination against diphtheria had been carried out extensively in association with the vaccination against tetanus. The risk of reimportation of diphtheria in Italy from Eastern European countries still exists.

Tetanus is a serious infectious non-communicable diseases contracted through a toxin (Tetanus toxin) produced by bacteria (Clostridium tetani) that live in soil or animal intestinal tracts. Tetanus may be lethal in around 20-30% of the cases. In Italy, tetanus still affects several dozen subjects per year especially elderly women.

Pertussis is a disease caused by bacteria called *Bordetella pertussis*. It is one of the most contagious diseases known. In fact, a child with pertussis may spread it up to the 90% of non-immune children with whom he/she meets. To date, in Italy pertussis cannot be considered as a disease under control and the age group most affected is the 11-19 age range. The main aim of pertussis vaccination is to reduce if not eradicate severe pertussis in infants.

Hib (*Haemophilus Influenzae* type B) is a capsulated bacterium responsible for severe invasive diseases in children aged less than 5 years. Meningitis purulenta has a high mortality rate because about the 5% of the children (500 in 100,000) who contract this disease dies even if treated with antibiotics. Approximately 15-30% of the surviving children have permanent neurological damages such as blindness, deafness, mental intellectual disability and learning disabilities. As a consequence of the decline in infants' vaccination coverage ratio, invasive Hib severe new cases in children aged < 2 years were reported again.

Hepatitis B is a parenteral transmission disease because Hepatitis B (HBV) virus is transmitted to a subject through contact with the blood or other body fluids of an infected person. In our country, the results achieved in the last 25 years of general vaccination against HBV led to a significant reduction of acute disease and a marked decline of the prevalence in virus carriers from 3.5% of the Italian population when no immunization programs existed to a < 1% rate.

Measles is an important highly contagious viral disease transmitted through respiratory route. Measles encephalitis has a high mortality rate and surviving children may often suffer permanent brain damages or mental intellectual disability. It should be noted that from 3 to 10 children out of 100,000 die because of this disease. In 2002, a major epidemic of measles was reported in Italy, which affected more than 40,000 children, more than 600 children were hospitalised, 15 cases of encephalitis and 6 deaths were reported.

Rubella is a viral disease transmitted in airborne droplets when infected people sneeze or cough. Complications include: joint pain, thrombocytopenia (1 in 3,000) and encephalitis (1 in 5,000). At least in some areas of the country, the number of rubella cases declined significantly. Rubella in pregnancy often results in a congenital defect known as congenital rubella syndrome (CRS), more frequently when rubella is contracted during the first three months of pregnancy because it may result in miscarriage, serious foetal defects as deafness, intellectual disability, cataract and other malformations of the eye and heart defects. WHO has set the goal of a reduction in CRS cases to <1/100.000 live births.

Epidemic parotitis (Mumps) is a viral disease and complication can include: aseptic meningitis in up to 5 – 15% of cases, pancreatitis (4%), and inflammation of the testes (Orchitis) in 25 % of males after puberty and of the ovaries in 5% of the females. Parotitis is the first cause of acquiring hearing loss in children (3 in 100,000 in cases of disease).

Varicella is a widespread childhood infectious disease caused by the varicella- zoster virus (VZV). Complications can include pneumonia (23 in 10,000 cases), bacterial suprainfections, skin scars, arthritis, brain damage (more than 1 in 10,000 cases), thrombocytopenia, and cerebellitis. Complications occur more frequently in infants, adults and individuals with an impaired immune system.

Streptococcus pneumoniae (Pneumococcal bacterium) is the leading cause of community-acquired pneumonia (CAP: pneumonia acquired outside of hospitals). The term Invasive Pneumococcal Disease (IPD) is generally used referring to the most invasive and severe pneumococcal infections including bacteraemia, sepsis and meningitis. Pneumococcal diseases still are an important public health problem that cause high morbidity and mortality worldwide: 1.6 million deaths per year. The data of the monitoring system in Italy confirm that pneumococcal diseases highest incidence rates occur in ≥65 years and in the paediatric age groups.

Meningococcus (*Neisseria meningitidis*) is a bacterium widespread throughout the world: serogroups A, B, C, W135 and Y are often responsible for bacterial meningitis. Meningitis has a fatality rate of 10- 20%. The 20 % of persons develop permanent neurological sequelae. Instead, sepsis mortality rate is of 40%. Invasive meningococcal infections are more frequent in children aged less than 5 years but the disease affects also adolescents and young adults.

Human papillomavirus (HPV) infects anogenital mucosa, skin and respiratory tracts in most cases causing papillomas, precancerous lesions and malignant neoplasms. There are many types of HPV. 40 types infect anogenital tracts. The most common are HPV 16 and HPV 18, that are the main cause of cervical, vulva and vagina cancer in women, of penile cancer in men and of anus in men and women. Furthermore, HPV can also cause head and neck cancers. Instead, HPV 6 and HPV 11, are the most important factors in the development of anogenital condyloma in both genders. Cervical cancer is a global disease. In Italy, there are more than 2,000 cases every year. This figure becomes 40 times higher in the case of precancerous lesions that are normally detected at an early stage during the cervical cancer screening programme. Vulva, vagina and anus cancers have a low survival rate five years after diagnosis also because they are not included in early screening programmes. Anogenital condyloma is very frequent in Italy and 140,000 cases occur in men and women every year.

Influenza is a disease caused by influenza viruses that, every year, cause more or less important epidemics between December and April. Influenza annual epidemics are associated with high morbidity and mortality, affecting from 5 to 20% of the population every year. Every year, around 40,000 persons die for influenza-related causes. Up to 90% of these deaths occur in individuals over the age of 65 and in those with underlying chronic conditions. In fact, influenza can cause exacerbation of lung and heart diseases with consequent acute ischemic strokes, heart failures and cerebrovascular accidents or insult.

Rotavirus is an enterovirus mainly transmitted via fecal/oral route through close contacts or objects contaminated by infected faeces. Rarely, rotavirus can be transmitted by respiratory route. The infection affects the intestine causing gastroenteritis. There are several types of rotavirus, 5 of these, G1-G2-G3-G4-G9, are responsible for the greater number of gastroenteritis in Man.

Hepatitis A is an acute viral liver disease, particularly severe when affects adolescents or adults. Mortality rate is of about 0.3%, but increases with age (in individuals over the age of 40 is of about 2%).

Herpes Zoster (HZ), also known as “St. Anthony’s Fire”, is a common and debilitating condition caused by the reactivation of the Varicella Zoster Virus (VZV). Clinically it is characterised by severe neuropathic pain, erythematous vesicular lesions that typically occur only on one side of the body,

visceral complications including the increasing of cerebral ischaemic events. The form affecting the ophthalmic division of the trigeminal nerve, often referred to as ophthalmic HZ, represents the 10-20% of HZ cases. The risk for developing Herpes Zoster increases with age. In Europe, 1.7 million people are estimated to be affected by Herpes Zoster. The incidence of Herpes Zoster is similar worldwide. In Italy, a recent study has shown that 20.6% of patients with HZ was also affected by post-herpetic neuralgia (a chronic neuropathic pain) at 3 months with a negative impact on the quality of life.

AVAILABLE VACCINATION AND IMMUNIZATION SCHEDULE

"Immunization schedule" means the chronological order in which vaccinations have to be carried out. This Schedule is a useful guide for vaccination services health professionals, paediatricians, general practitioners and parents but, above all, represents a useful tool for implementing vaccination strategies.

The policy direction document prepared by the "Società Scientifiche Italiane" (Italian Scientific Societies) (SItI, SIP, FIMP, and FIMMG) in 2014 (Calendario per la Vita, Seconda Edizione, 2014), including the immunization schedule and the classification of available vaccines is available at: http://www.scienzainrete.it/files/calendario_per_la_vita.pdf.

Vaccinations included in the immunization schedule are free of charge and actively proposed to the target population. The vaccination programme includes all vaccinations useful for protecting from vaccine-preventable diseases all age groups – children, adolescents and adults. The Programme aims: to maintain and develop epidemiological surveillance activities of vaccine-preventable disease including through the enhancement and the connection to vaccination databases; to enhance the surveillance of vaccine-preventable diseases linking information flows with vaccination databases and the epidemiological surveillance with notifications from diagnostic laboratories; to ensure active and free of charge offer of priority vaccinations risk groups and develop initiatives for promoting the vaccination of health professionals and hard-to-reach groups; to design and implement actions for enhancing information and communication in order to promote the updating of the vocational education of health professionals and to disseminate the culture of vaccination prevention as citizens' responsible and informed choice; to ensure active and free of charge offer of priority vaccinations to the general population in order to attain and maintain needed coverage levels indicated below for preventing the spread of specific infectious diseases.

Available vaccines and recommendations for their use:

a. **DTP Vaccines.** Basic vaccination routine against Diphtheria, Tetanus and Pertussis consists of 3 doses at 3, 5 and 11-13 months of age. To maintain the efficacy of DTP vaccination, whose fourth dose was administered at 5-6 years of age, together with the fourth dose of inactivated polio vaccine (IPV), it is necessary to administer booster doses after a number of years.
b. **Enhanced-Potency and Inactivated Poliomyelitis Vaccine.** Today, all available vaccines in our country are enhanced-potency and inactivated vaccines. This vaccine should be administered by intramuscular injections according to a 5-dose cycle. The first three doses at 3, 5 and 11-13 months of age, always administering the combined hexavalent vaccine, and the fourth and fifth dose at 4-6, 18 years of age , preferably using the tetravalent combined vaccine

(DTPa/IPV up to 7 years of age and dTaP/IPV to children aged < 7 years).

c. **Vaccine against Hepatitis B.** The vaccination against the virus of Hepatitis B has to be administered through 3 intramuscular doses injected at 3, 5 and 11-13 months of age. As a rule, this vaccination is included into the hexavalent combined vaccine. Children of HBsAg positive mothers, instead, vaccination consists of 4 intramuscular doses: dose 1 within 12-24 hours from birth, dose 2 after a month, dose 3 after two months and the dose 4 at 11-12 months of age including in combination with other vaccinations.

d. **Vaccine against *Haemophilus influenzae* type b**. The vaccination against Haemophilus influenzae type b is actively offered to all newborns. The vaccine doses are 3 to be administered through intramuscular injection at 3, 5 and 11-13 months of age. In addition, this vaccination is included into the hexavalent combined vaccine. This vaccination is recommended to all subjects irrespective of their age at risk of contracting invasive Hib forms due to existing pathologies or predisposing conditions.

e. **MMR vaccine (measles, mumps, rubella) and trivalent MMR+V vaccine (measles, mumps, rubella and varicella)/Monovalent varicella vaccine.** Vaccination against measles, mumps, rubella and varicella can be carried out in childhood and administered concomitantly with a trivalent vaccine or separately with the MMR vaccine and the one against varicella. In both cases, vaccination consists of two doses: the first dose administered at 13-15 months of age; the administration of the second dose is considered indispensable for good immunization. It is appropriate to use vaccines that showed to be more effective in reducing breakthrough cases (rubella cases occur among persons who were administered the vaccine). The first dose of MMR+V can be administered concomitantly with meningococcal ACYW conjugate vaccine and the second dose of the DTPa/IPV vaccine. Vaccination against rubella in children consists in two doses of the MMR/MMR+V vaccine; the first dose administered at 13-15 months of age and the second at 5-6 years of age, possibly during the same session, with other vaccines (hexavalent, meningococcal B or meningococcal C/trivalent ACWY conjugate vaccine for the first dose, and DTPa/IPV for the second dose). As regards varicella, anamnestically negative children who are administered MMR+V vaccination at 5-6 years of age after having received a prior dose of MMR vaccine, it is recommended the administration of 1 dose of monovalent rubella vaccine to be carried out as soon as possible and, however, at earliest suitable opportunity at an interval ranging from 4 to 8 weeks from the first dose. Children anamnestically negative to varicella, who were vaccinated at 13 – 15 months of age only with MMR and not with MMR+V, as scheduled, may be vaccinated before 6 years of age, at the earliest suitable opportunity with a varicella monovalent vaccine and later, at 5 – 6 years of age with MMR+V vaccine. In the event of women of childbearing age, it is sufficient to recommend avoiding pregnancy within a month from the date of vaccination (and not 3 months as recommended a few years ago).

f. **Pneumococcal vaccine.** The availability of Pneumococcal conjugate vaccines (PCVs), before containing 7 strains and now 13 (PCV13) is a major step forward in the fight against children infectious diseases. The presence of polysaccharides conjugate of some of pneumococci currently more involved in paediatric diseases (19A, 1, 3, 5, 6A, 7) in the most recent vaccine

enables high efficiency against about 85-90% of the paediatric invasive pneumococcal diseases. The vaccine can be administered concurrently with the hexavalent or any other vaccine. The vaccine should be administered in 3 doses during the first year of life (at 3, 5 and 11-13 months of age). If vaccination begins in the second semester of life, 3 doses should be administered as well, at an interval of 6 – 8 weeks; two doses if the vaccination begins after reaching the age of 1; one dose if the vaccination begins after reaching the age of 2. Pneumococcal vaccination is recommended to all subjects, irrespective of their age, at risk of contracting the disease due to existing pathologies or predisposing conditions. Using PPV23 might provide a further protection in preventable cases of 13%- 25%. The use of PPV23 still remains important for an optimal immunization strategy for adults and elderly persons form both a public health and economic perspective. Summarizing, for adults we recommend the following: >50 years: PCV13 + PPV23 at an interval of at least 8 weeks; adults with chronic pathologies, 19-50 years of age: PPV23; immunocompromised subjects irrespective of their age: PCV13 + PPV23 at an interval of at least 8 weeks.

g. **Meningococcal C and ACYW135 vaccines.** The schedule used for the vaccination against conjugate Meningococcal C or ACYW135 quadrivalent conjugate vaccine provides for one single dose only after reaching the age of 1 (unless in the event of specific individual risk, for which limited to monovalent vaccine, the 3-dose schedule ay 3, 5 and 13 months of age). As with this schedule around 1 year of age hexavalent vaccinations against pneumococcus, measles, mumps, rubella, varicella, meningococcus C/ACYW135 quadrivalent and meningococcus B are provided for, it is recommended that during the first examination session (11 months of age) hexavalent + pneumococcus vaccinations are to be co-administered, for which is not indispensable to be 1 year of age yet, while during a second and third vaccination sessions, co-administration with other vaccines are permitted, at any interval, however, after 1 year of age. In addition to the vaccination of children within the first year of age, a dose should be provided to subjects aged 12.

h. **Vaccination against Meningococcus B** represents an ineluctable epidemiological, ethical and communication need. For these reasons, we recommend free of charge vaccination of all infants. The recommended vaccination schedule is, as follows (days are purely indicative and mentioned for clarity sake): hexavalent + pneumococcus at the beginning of the third month of life (61 days of life); meningococcal B vaccine after 15 days (76 days of life); meningococcal B vaccine after one month (106 days of life); hexavalent + pneumococcus after 15 days, at the beginning of the fifth month of life (121 days of life); meningococcal B vaccine after one month, at the beginning of the sixth month of life (151 days of life); hexavalent + pneumococcus at 11 months of age; meningococcal B vaccine at 13 months of age; meningococcal C vaccine, always after reaching the age of 1.

i. **Seasonal influenza vaccination.** Every year WHO indicate the composition of the new vaccine against seasonal influenza. The World Health Organization (WHO) estimates that vaccination against influenza prevents 70-90% of influenza cases in healthy adults; other data show that in a population of people aged 65 and over, the risk of hospitalisation due to pneumonia or influenza decreases by 27% and the risk of death by 48%. Where a good correspondence

between the composition of the vaccine and existing viruses exists, clinical trials estimated that the efficacy in health adults varies in a range between 70% and 90%. Active and free of charge priority vaccinations are provided to the general population in order to attain and maintain coverage levels indicated as needed for preventing the transmission of specific infectious diseases, that, in the case of influenza, is the vaccination coverage of 75% as a minimum attainable and of the 95% as optimal target of people aged 65 and more and groups at risk. Therefore, we recommend to lower the age to which the vaccination is offered before 60 years and then at ≥50 recommending to immunize all subjects, in such a way include the most part of persons at risk of this pathology based on a strategy, i.e. age, achieving greater protection for the population.

j. **Vaccination against Papillomavirus (HPV).** The vaccination against HPV is recommended to women and men for the prevention of as many HPV strains as possible i.e. the prevention of all HPV related conditions directly preventable through vaccination via an active and free of charge offer to girls and boys aged 12, with the possibility of using the vaccine from 9 years on. Furthermore, we recommend to extend the active and free of charge vaccination offer to one or more cohorts of young adults aged 18-25. The main 12-year age cohort is entitled to free of charge vaccination for life. Over 26 years of age, we recommend vaccination in sharing regime.

k. **Vaccination against Rotavirus (RV).** Considering the availability of effective and safe vaccines for the prevention of acute rotavirus gastroenteritis (RVGE) we recommend to offer this vaccine actively and free of charge, because of the substantial impact on health and relevant social cost of said gastroenteritis. There are two vaccines with different characteristics and schedules: 1) Vaccine containing live attenuated human strain. 2 doses are administered orally starting from <6 weeks of age with an interval of 4 weeks and can be administered simultaneously with other vaccines in the infant immunization programme. 2) Vaccine containing attenuated human and bovine parent rotavirus live strain. 3 doses are administered orally starting from 6 weeks of age with an interval of at least 4 weeks and can be administered concomitantly with other vaccines in the infant immunization programme.

l. **Vaccination against Hepatitis A.** The vaccine against Hepatitis A is strongly recommended where general epidemiological conditions are at risk and has to be administered to adults according to clinical recommendations based on their clinical, behavioural and occupational situation.

m. **Vaccine against *Herpes zoster*.** The single dose vaccine is recommended to prevent Herpes Zoster and postherpetic neuralgia (PHN) associated in subjects 50 years of age or older. Clinic efficacy of the vaccine against Herpes Zoster: sound efficacy and protection data even in the long term against Herpes Zoster and PHN. Epidemiological evidence confirms the increasing of HZ and PHN cases as persons get older starting from 50 years of age; 90% of patients with HZ are immunocompetent. We recommend to offer active and free of charge vaccination against HZ to one or more cohorts of subjects aged between 60 and 70 years and to all those subjects over 50 with chronic pathologies such copd (Chronic Obstructive Pulmonary Disease), diabetes and cardiuvascular diseases in order to reduce their frailty and improving

their quality of life both through an "age-based" strategy and through a complementary "risk-based" strategy.

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Luisa M. Borgia visited Websites indicated in in the document on
May 14, 2016

National Bioethics Committee of Republic of San Marino –
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