Legal Aspects of Informed Consent in Clinical Research: the Case of Vaccinations in the International Legal Framework

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ABSTRACT: Informed consent is an essential prerequisite in clinical trials. The goal of the informed consent process is to provide appropriate information, so that the potential participant can make an informed decision about whether or not to enrol in a trial. Information must concern the explanation of the research status, its objectives, a description of benefits and risks, alternative treatment that may be available, and the subject's rights and responsibilities. After a review of the main regulatory instruments on informed consent, the article analyses the EU regulatory framework for vaccines. In a second part, the issue of voluntariness and validity of informed consent in case of compulsory vaccination is discussed, through an examination of selected national rules (France, Spain, Italy, and Germany).

KEYWORDS: Informed consent; clinical trials; law; vaccines; public health and human rights

SUMMARY: 1. Informed consent in phase 1-4 clinical trials – 2. Informed consent in clinical research: hard law measures – 3. Vaccine trials in European legal framework – 3.1. Mandatory vaccination and ethical issues: the case of compulsory vaccination in France, Germany, Italy, Spain.

1. Informed consent in phase 1-4 clinical trials

Communication of risks and benefits is a fundamental aspect of the informed consent process in clinical trials in order to guarantee an informed decision making by the potential participant. The assessment of the risks and benefits comprehension is for this reason a critical component of regulatory requirements for clinical trials conduct. The Clinical Trial Regulation[1] introduced different risk categories for clinical trials.

Since 1940s, the scientific community has drawn up a distinction in phases of clinical research, which is accepted by European laws. The initial stage is defined "preclinical" research, not done with people, but it involves laboratory studies (in vitro) and tests on animals. This step of the study includes an investigation of the possible toxic and/or teratogenic effects. Functions of the physiological sys-

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[1] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials in medicinal products for human use and repealing Directive 2001/20/EC.

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tems are investigated, and the investigator must provide a general pharmacological characterization of the drug, with particular reference to adverse reactions (Pharmacodynamics). After preclinical studies that provide evidence of safety, the substance is at first tested in trials involving healthy human volunteers. In phase 1-4 clinical trials the efficacy of an investigational product is explored in a patient population which has been selected according to inclusion and exclusion criteria.

Depending on the phase and the object of the clinical trials, the level of risk and its communication change. Anyhow, informed consent must be obtained before procedures and treatments are performed.

In Phase I, the patients involved have significant possibilities to experiment serious side effects[2]. They must be adequately informed before they consent to participate. The duty of investigators to inform in this stage is very strict. Phase I studies assess the safety and tolerance of a drug. This initial phase of testing includes a small number of healthy volunteers (20 to 100). The study is designed to determine the effects of the drug on humans including how it is absorbed by the subject. In this step side effects are analysed. The process of patient recruitment and informed consent is governed by laws to ensure the rights, safety, and well-being of participants. Previously the Directive 2001/20/EC[3] and then the Regulation (EC) No. 536/2014 established that it is necessary to make provision for the monitoring of adverse reactions occurring during the clinical trials using Community surveillance procedures, in order to ensure the immediate cessation of any clinical trial in which there is an unacceptable level of risk. Legal requirements are honesty regarding the nature of participation in clinical research and honesty regarding the level of the risk. Science and experimentation must demonstrate formal, ethical and methodological correctness. Patients involved in the clinical trial must represent the future category of subjects to whom the drug can be administered, but women and children are usually excluded from this phase of experimentation. The Regulation (EU) No 536/2014 on clinical trials of medicinal products for human use introduced requirements for taking account of gender in trials, but the procedure is to involve only men in the first phase of clinical trials, with particular attention to life expectancy, performance status and organ function. Concerning the inclusion criteria to participate in a clinical trial, the European Parliament, with the resolution of 14 February 2017 on promoting gender equality in mental health and clinical research (2016/2096(INI)), calls on the Member States, when applying Regulation (EU) No 536/2014, to use a methodological approach for clinical trials. This approach would guarantee an adequate representation of men and women.

Phase II is needed to confirm drug has therapeutic effect, to determine optimal dose, to determine correct frequency dosing. This second phase involves up to several hundred patients. Most phase II studies are randomized trials where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. Often these studies are "blinded": neither the patients nor the researchers know who has received the experimental drug.

[2] B. Goetz Karen, M. Pfleiderer & c. K. Schneider, *First-in-human clinical trial with vaccines – what regulators want*, in *Nature Biotechnology*, 2010, pp. 910-916.

[3] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the application of good clinical practice in the conduct of clinical trials with medicinal products for human use.

Phase III compares the effects of a new treatment with standard treatment, finding out efficacy of the drug and effects or risks and safety in the long term. It is required a large number of volunteers/ patients (several hundred or thousand) to provide significant clinical and statistical power. Concerning phase II and phase III of clinic trials, gender and age-related aspects are not addressed and there are no specific legal provisions about obtaining informed consent in these steps.

Phase IV of clinical trials studies the drug after it has received a Product Licence – drug marketed. From Clinical Trials Regulation's perspective, the studies of this stage are "non-interventional" that investigate various aspects of drug use including efficacy and safety under real life conditions. Pharmacovigilance is the field of public health research that studies the effects of medicinal products in large populations. The specific objective of this stage is to evaluate drug's long-term effectiveness and impact on a patient's quality of life. In this sense, pharmacovigilance is non-interventional research. The informed consent is also necessary for non-interventional studies. The content of informed consent in phase IV of clinical trials is different compared to that of earlier phases, but participant's participation remains informed and voluntary.

The European legal framework of pharmacovigilance for medicines for human use marketed within the EU is provided for in Regulation (EU) No. 726/2004[4], as amended by Regulation (EU) No. 1235/2010[5], and in the Directive 2001/83/EC[6], as amended by Directive 2001/84/EC. Title IV of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use contains the provisions applied for the authorisation for the manufacture of medicinal products as part of the requirements needed for the application for a marketing authorisation. The marketing authorization rules guarantee the quality assessment. The competent authority of the Member State issues manufacturing authorization. Pharmacovigilance in also governed by Commission Implementing Regulation (EU) No. 520/2012[7].

This body of legislation aims to strengthen public health through improved prevention, detection and assessment of adverse reactions. New legislation for pharmacovigilance is supported by a new guidance on good pharmacovigilance practices (GVP), a new set of guidelines for the conduct of pharmacovigilance in the EU. The pharmacovigilance legal requirements and GVP apply to all medicinal products authorised in the EU, whether centrally or nationally authorised. While risk proportionality underpins the new legislation, the requirements are generally the same for different types of product. Pharmacovigilance is an essential part of pharmaceutical product development and commercialization. All safety aspects must be monitored properly through a systematic approach. Benefit and risk must be continually assessed as more is learned about the product through its use. Informed consent, in phase IV, essentially comprises a data privacy clause, there are no additional diagnostic

[4] Regulation (EU) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

[5] Regulation (EU) No. 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use.

[6] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[7] Regulation (EU) No. 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council.

tests or invasive procedures. The patients should report adverse drug reactions directly to the national competent authorities.
These legal requirements concerning clinical trials established by the aforementioned European laws apply for clinical trials in general and thus also for vaccine trials, although they are not specific for vaccines.

2. Informed consent in clinical research: hard law measures

The principle of informed consent is declared, at international level, in the Convention on Human Rights and Biomedicine (Oviedo, 1997)[8], that represents a milestone in the protection of human rights in biomedical field. The content of the Oviedo Convention is supplemented by various Additional Protocols, such as Additional Protocol concerning biomedical research (2005)[9], with a view to protecting human rights and dignity in the specific field of biomedical research. Chapter II (articles 5 to 9) addresses the need for informed consent before any biomedical intervention. Refusal to give consent or the withdrawal of consent to participation in research must not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care. The Convention provides particular protection of people who are not able to consent, due to either their age (minors) or their mental incapacity (article 6), and of people who have a mental disorder (article 7). Research on pregnant or breastfeeding women is covered by the Protocol (Chapter VI). Article 18 describes the conditions in which research on pregnant women may be undertaken.
At European level, the analysis of hard law measures starts from the Directive 2001/20/EC of 4 April 2001 ("the Clinical Trial Directive"), that legally ensured the implementation of the principles of good clinical practice in clinical trials on medicinal products in Europe. Several articles in the Directive provided guidance regarding the protection of clinical trial subjects. With specific regard to informed consent, article 3 of the Directive provided for legal guarantees. Participants must give a written consent (or oral if he/she is unable to write) after being informed of the significance, nature, implications and risks of the clinical trial. The National transpositions by the Member States, in compliance with the directive, showed the importance of understanding the informed consent process as a whole, and the right of participants to have sufficient information about the research and any risks they may encounter. A common element in any transposition law regarding clinical trials on human beings was the requirement of proportionality. This principle, along with that of prevalence of the subject's welfare over the interests of science and community, could be found in the Council of Europe's Convention on Human Rights and Biomedicine and in the 2001/20/EC Directive. However, the transposition of the Directive across EU countries has led to uneven application. For this reason the Clinical Trial Directive has been replaced by the Clinical Trials Regulation to minimize the scope for regulatory au-

[8] THE COUNCIL OF EUROPE, *Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on human rights and biomedicine*, Oviedo, 4 April 1997. Available at: https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164.
[9] THE COUNCIL OF EUROPE, *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research*, Strasbourg, 25 January 2005. Available at: https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/195.

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tonomy at national level and to make Europe competitive in research, ensuring the production of reliable and robust, high-level scientific data, ensuring patient safety[10].

The Clinical Trials Regulation replaces the Clinical Trials Directive, but although the Regulation entered into force on 16 June 2014 the timing of its application depends on the development of a fully functional EU clinical trials portal and database. The entry into application of the Regulation is currently estimated to occur by the next year. As observed in the preamble of the Regulation, in a clinical trial is necessary to give a primary position to the rights, safety, dignity and well-being of subjects. The new Regulation does not substantially change the rules on the protection of individuals and informed consent introduced by Directive 2001/20/EC; some provisions are reformulated and/or synthesized to facilitate their understanding. Unlike Directive 2001/20/EC, the new Regulation specifically regulates cases where, due to the urgency conditions, it is not possible to obtain free and informed consent beforehand. Article 29 of the Regulation sets forth the general framework for informed consent. Informed consent must include: the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial; the subject's rights and guarantees regarding their protection, in particular his/her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification; the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; the possible treatment alternatives, including follow-up measures, if the participation of the subject in the clinical trial is discontinued. Information must be comprehensive, concise, clear, relevant, and understandable to any person, provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned. The article also provides for an interview with an investigator. During the interview, special attention must be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information. The Regulation provides for specific attention for vulnerable subjects: article 31 provides particular conditions for clinical trials involving incapacitated subjects; article 32 of the Regulation provides a specific discipline for clinical trials involving minor, specifying that the primary condition for the conduct of a clinical trial involving a minor is the presence of a direct benefit; article 33 provides for specific provisions for pregnant or breastfeeding women participating in clinical trials. Finally, article 34 gives the possibility for Member States to organize a further protection for certain subjects in a situation of institutional or hierarchical dependency likely to inappropriately influence their consent ("persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, or persons in residential care institutions").

Some Member States, such as Spain and France, have already adopted implementation measures in order to adapt their national legislation to the Regulation (EU) 536/2014. France adopted two decrees on 17 November 2016 in order to adapt its national legislation to the CTR[11]. Spain issued a De-

[10] M. GEHRING, R.S. TAYLOR, M. MELLODY, B. CASTEELS, A. PIAZZI, *Factors influencing clinical trial site selection in Europe: the Survey of Attitudes towards Trial sites in Europe (the SAT-EU Study)*, in *British Medical Journal*, 1.

[11] The first decree (Decree concerning Research Involving Humans No. 1537 of 16 November 2016) focuses on "research involving the human person" and produces many changes, also regarding the role of the national commission for research. The second decree (Decree No. 2016-1538 of 16 November 2016) focuses on the rules regarding contracts for clinical studies for commercial purposes conducted by sponsors in public health

cree to adapt at the future application of CTR and to develop those aspects, which the regulation leaves to national legislation[12].

3. Vaccine trials in European legal framework

Vaccine trials fall within interventional research and they are not "low interventional studies" with minimal risk. Healthy volunteers are the target population for vaccine trials and this requires special carefulness concerning benefit/risk assessment. The fact that such trials involve healthy subjects determines two consequences: a stringent stress on safety both in clinical trials and in clinical practice, and a more rigid regulation concerning informed consent. A rigorous regulatory procedure must therefore be ensured to evaluate quality, efficacy and safety. In vaccine trials, there are: a pre-clinical development, carried out in lab assays and on animals; a clinical development that covers three or four stages. The Clinical development is built on rigorous ethical principles of informed consent from volunteers, with an emphasis on vaccine safety as well as efficacy.

Phase I clinical trials are small-scale trials to assess if a candidate vaccine is safe in humans and what immune response it evokes. Risk assessment in first-in-human trials for vaccine is specifically regulated by the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (EMA, Committee for Medicinal Products for Human Use (CHMP) 2007, first revision 2017)[13]. For sponsors, relevant risk assessment for first-inhuman clinical studies means careful design and conduct of studies that reduce potential risk to humans.

Phase II refers to the initial trials examining effectiveness in a limited number of volunteers (usually between 200 and 500); the focus of this phase is vaccine safety, side-effects and the immune response.

Phase III trials are intended for a more complete assessment of safety and effectiveness in the prevention of disease in a large group of people.

Phase IV trial are optional studies that drug companies may conduct after a vaccine is released. This stage aims to detect rare adverse effects as well as to assess long term efficacy.

Within the European Union human vaccines are regulated by European Medicines Agency (EMA)[14].

All manufacturing information including tests for safety, purity, and potency for a particular product is regulated under a Good Manufacturing Practices (GMP) Directive 2003/94/EC[15] and Regulation

establishments. These two decrees complete a government Order dated 17 June 2016, which implemented the law no 2012-300, dated 5 March 2012, on research on human persons. The Ordinance concerning Research Involving Humans (2016/800), dated June 16 2016, amended the Public Health Code.

[12] The RD 1090/2015 provides for that to obtaining and content of informed consent shall follow the provisions of Article 29 of CTR, as well as Articles 8 and 9 of Regulation Law 41/2002, of 14 November. The person participating in the trial, particularly people with special vulnerability will be informed of the access routes to the usual clinical practice for their pathology.

[13] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf (last visited 28/04/2019).

[14] https://www.ema.europa.eu/en (last visited 28/04/2019).

[15] Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (GMP)

(EU) No. 1252/2014[16]. The GMP requires, in general, that medicines are of consistent quality, appropriate for their intended use and that the requirements of the marketing authorisation or clinical trial authorisation are met.
Directive 2001/83/EC and Regulation (EU) No 726/2004[17] constituted the EU regulatory framework for the manufacture, authorization and distribution of veterinary medicinal products. The Regulation (EU) No 726/2004 established a European Medicines Agency that provide regulatory authorities with the mandate to promote and protect public health by authorising the use of safe and effective vaccines and by continuously assessing their benefit and risk profile following the granting of marketing authorisation.
Recently, the regulatory framework has been reviewed by Regulation (EU) 2019/6 of the European Parliament and of the Council on veterinary medicinal products, in order to harmonize the legislative provisions of the Member States. The regulation, which is mandatory in all its elements and directly applicable in all Member States, will enter into force on the twentieth day following its publication in the Official Journal of the European Union and will apply from 28 January 2022.
During the 64th session of the WHO Regional Committee for Europe has been adopted the European Vaccine Action Plan 2015–2020 (EVAP), that imagine a Europe free from vaccine-preventable diseases, where all countries have an equal access to vaccines and immunization services[18].

3.1. Mandatory vaccination and ethical issues: the case of compulsory vaccination in France, Germany, Italy, Spain

The European regulatory framework does not regulate whether vaccines are mandatory or recommended, and the Member States remain free in their decision[19].
However, the EU's role in health policy is limited, because National governments are responsible for deciding how to organise their health service. The European regulatory framework does not regulate whether vaccines are mandatory or recommended[20], and the Member States remain free in their decision. Thus, National Health Services of most European countries have different vaccination systems, different vaccine recommendations and different schedules of vaccine administration.
In the EU, Austria, Cyprus, Denmark, Estonia, Finland, Germany, Ireland, Lithuania, Luxembourg, the Netherlands, Norway (EEA and Schengen), Portugal, Spain, Sweden and the United Kingdom have no obligation to vaccinate The other countries have an obligation to vaccinate with between 1 vaccine (Belgium) and 12 (Latvia). With 11 compulsory vaccines, France would be one of the most constraining countries.

[16] Regulation (EU) No. 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use.
[17] Regulation 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
[18] https://www.who.int/ (last visited 28/04/2019).
[19] For knowing vaccine schedules in all countries of the European Union: https://vaccine-schedule.ecdc.europa.eu/ (last visited: 30/04/2019).
[20] https://ec.europa.eu/health/vaccination/overview_en (last visited 28/04/2019).

The Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishes a European centre for disease prevention and control. This is an independent agency, a Community source of scientific advice, assistance and expertise from medical, scientific and epidemiological staff acting on behalf of Member States' authorities responsible for human health (article 9). Regulation (EC) No 851/2004[21] mandates the European Centre for Disease Prevention and Control ('ECDC') to support the prevention and control of communicable diseases and foster the exchange of best practices and experience with regard to vaccination programmes[22]. In addition, the ECDC coordinates data collection, validation, analysis and dissemination at EU level, including on vaccination strategies. The European Centre for Disease Prevention and Control (ECDC) established network of experts working in the field of immunisation: Vaccine European New Integrated Collaboration Effort (VENICE)[23], with the objectives of collecting, sharing and disseminating information on national immunization programmes and for improving the overall performance of the immunisation systems in the EU/EEA Member States. The European Centre for Disease Prevention and Control (ECDC), in the *guide Let's talk about prevention. Enhancing childhood vaccination uptake. Public Health Guidance*, 2016, identifies ways to help healthcare providers and encourage all parents to get their children protected by vaccination, particularly those in population groups whose children are currently non and undervaccinated. The guide underlines that vaccines are safe and effective and highlights the balancing of benefits and risks for different diseases. There is no reference to informed consent form but the guidance provides a detailed information on benefits and risks of different vaccinations.

Although vaccination policy is a competence of national authorities, the European Commission supports EU countries to coordinate their policies and programmes[24]. In 2014, the Council of the European Union in the Conclusions on vaccinations as an effective tool in public health[25], invited member states to:

- continue to improve epidemiological surveillance and evaluation of the situation concerning communicable diseases in their territories, including diseases preventable by vaccination;
- continue to improve national vaccination programs and to strengthen national capacity for carrying out evidence-based, cost-effective vaccination, including the introduction of new vaccines where considered appropriate;
- continue to develop plans and standard operating procedures in collaboration with the ECDC and the WHO to ensure a timely and effective response to vaccine-preventable diseases during outbreaks, humanitarian crises and emergencies;

[21] Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European Centre for Disease Prevention and Control.

[22] https://ecdc.europa.eu/en/home (last visited 30/04/2019).

[23] VACCINE EUROPEAN NEW INTEGRATED Collaboration Effort (VENICE), *Report on Adult Vaccination Strategies and Vaccine Coverage in Europe,* 2010. Available from: http://venice.cineca.org/.

[24] To learn about vaccine policy of all European countries: https://www.efvv.eu/ (last visited 28/04/2019).

[25] THE COUNCIL OF EUROPE, *Council conclusions on vaccinations as an effective tool in public health*, Brussels, 2014. Available at: https://www.ifa-fiv.org/wp-content/uploads/2015/12/EU-Health-Council-Conclusions-on-Vaccination_Dec-2014.pdf.

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- continue to develop comprehensive and coordinated approaches within vaccination programs, following the Health in All Policies approach creating synergies with broader health policies and pro-actively working with other preventive sectors;
- ensure transparency with regard to the post-marketing evaluations of vaccines and of studies on the impact of vaccination programs in order to provide reliable information for both governments, medicines regulators and manufacturers;
- actively offer appropriate vaccination to population groups considered to be at risk in terms of specific diseases and consider immunization beyond infancy and early childhood by creating vaccination programs with life-long approach;
- work with health professionals on risk communication in order to maximize their role in informed decision making;
- inform the population in order to raise its trust in vaccinations programs, using appropriate tools and communication campaigns also by engaging opinion leaders, civil society and relevant stakeholders (e.g. academia).

As seen in the previous paragraphs, one of the premises for informed consent is voluntariness, but with obligatory vaccination, providing consent could become only a formality or a legal fiction. Therefore, in the case of obligation, voluntariness could be lacking and thus from an ethical and legal perspective, the informed consent is invalid. In the case of a vaccination obligation, a clash between individual's rights and public safety becomes apparent. On the one hand individual autonomy and on the other the need to protect public health protection through obligatory vaccinations[26]. For obligatory vaccinations, there is a paradoxical situation where parents/guardians of children who are to be vaccinated need to sign an informed consent form despite a vaccination obligation. In 2014, the WHO issued a document, titled Considerations regarding consent in vaccinating children and adolescents between 6 and 17 years old, in which it underlines that formal consent can be gathered with opt-in procedure (health authorities inform the parents about the vaccination and written consent from the parent is required to opt-in, i.e. give permission for the older child/adolescent to be vaccinated) or opt-out procedure (a written form is used to allow parents to express non-consent or refusal to vaccination of their child).

Refusing to sign informed consent and therefore refusing to subject the child to vaccination would have legal consequences.

Legal consequences differ from country to country. In some cases, they could be very strong, including pecuniary penalties, difficulty to attend public schools, or even penal consequences for the parents.

The Council of Europe in the Conclusions on vaccinations as an effective tool in public health (2014), recognizes that while vaccination programs are the responsibility of individual Member States and that various vaccination schemes exist in the EU, efforts to improve vaccination coverage may also benefit from cooperation within the EU and from improved synergies with other EU policy areas, having special regard to the most vulnerable populations identified in the different regions and individual Member States of the Union and to increasing mobility.

[26] A. ZAGAJA, *Informed Consent in Obligatory Vaccinations?,* in *Medical Science Monit*or, 2018, 1.

In France, with regard to vaccines in clinical practice, on June 2017 the Health Minister announced plans to move from three (diphtheria, tetanus and poliomyelitis) to eleven mandatory vaccines, in order to prevent the expansion of certain diseases. These additional eight vaccines – pertussis (whooping cough), Haemophilus influenzae B, hepatitis B, meningococcus C, pneumococcus, measles, rubella and mumps – were only recommended, but Loi n° 2017-1836[27] makes them mandatory since 2018.

Information and consent of parents is always required also if vaccines are mandatory.

Parents who fail to get their children inoculated could face up to six months in prison and a higher fine. Among legal consequences, unvaccinated children in France could be not allowed at any preschool (nursery, daycare, kindergarten) and school grade.

In the German law there are no mandatory vaccinations, but there are strongly recommended vaccinations. Annually the commission for immunization ("Ständige Impfkommission STIKO") publishes its recommendations. Most ministries for health of the 16 federal states assume these without alteration. In exceptional situations the Ministry of Health of the Federal Republic of Germany or the local federal governments are authorized by legal decree to oblige parts of the population to be vaccinated. Provided that an infectious disease with serious clinical end arises and epidemic sprea-ding is estimated (Infectious Diseases Protection Law: Infektionsschutzgesetz - IfSG). The Fundamental Right of being physically unscathed may be limited. Following this law, certain employers are authorized to collect informations about the immune status of employees (e.g. in hospitals) to decide about an occupation or its kind. No legal regulations exist for mandatory vaccination when visiting kindergarten, school or university. If somebody caught an infectious disease or is suspicious of having caught it or of being infected, health institutions may forbid to go to kindergarten or school.

In Italy, ten vaccinations (diphtheria, tetanus, pertussis, poliomyelitis, haemophilus influentiae B, hepatitis B, measles, rubella, varicella and mumps) are mandatory for children since 2017 (Law 119/2017[28]). Parents have to present their vaccination certificates at school and each Region must provide additional recommended vaccinations for free. Schools have to notify the local health agencies (ASL) when parents fail to present the necessary vaccination documents. The decision n. 5/2018 of the Constitutional Court determined that the Law 119/2017 is compliant with the Italian Constitution and that regulatory intervention is not unreasonable, given the current state of epidemiological conditions and scientific knowledge. It aims to protect individual and collective health on the basis of the duty of solidarity in preventing and limiting the spread of certain diseases. The Constitutional Court considered inter alia that all vaccinations made mandatory were already planned and recommended in the national vaccination plans and funded by the State. Furthermore, the shift from a strategy based on persuasion to a compulsory system is considered justified in the light of the gradual decline in vaccination coverage.

Fines up to five hundred euros are imposed for families that fail to vaccinate their children, but penalties must be preceded by the meeting between health authorities and families in order to inform them about the vaccination program. The lack of vaccination implies the exclusion only from nursery

[27] LOI n° 2017-1836 du 30 décembre 2017 de financement de la sécurité sociale pour 2018, JORF n°0305 du 31 décembre 2017.

[28] Italian Law 119/2017 – GU Serie Generale n. 182 del August 5, 2017.

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school and kindergarten. For defaulting of 6-16 year olds will start the recovery process that, in the negative case, culminates with the financial penalty. Information and consent acquisition of parents is however required also if vaccines are mandatory.

In Spanish legislation, vaccines are subject to the general rules for medicinal products for human use. Spain has no mandatory vaccines whilst pressure from health authorities is very high. Vaccine uptake between children is around 95 percent and it is around 40 percent between adults and elderly. Un-vaccinated children in Spain are allowed at any preschool (nursery, daycare, kindergarten) and school grade, but sometimes private schools would not admit unvaccinated children.

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