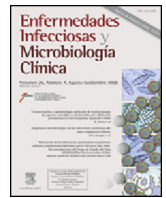




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Review article

Is it ethically acceptable to invite a pregnant woman to enrol in a clinical trial with Tdap if it could entail not being vaccinated with Tdap before delivery[☆]

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ABSTRACT

Pertussis incidence has increased in recent years, especially among infants aged <2 months. A number of Spanish regions have started a vaccination programme with Tdap vaccine to all pregnant women in the third trimester of pregnancy. An observational study has shown that this strategy reduces the number of cases of pertussis by 90% in infants aged <2 months. Mathematical models showed that a cocooning strategy (i.e. vaccination of the mother at immediate postpartum, and other adults and adolescents who have close contact with the newborn and caregivers) will reduce the incidence of pertussis by 70% in infants aged <2 months. It is intended to conduct a clinical trial in which 340 pregnant women will receive Tdap vaccine, whereas another 340 pregnant woman will be vaccinated soon after delivery. Vaccination with Tdap will be offered to all partners and caregivers of the newborn. After assessing both the ethical and scientific reasons supporting the trial, it is concluded that it is ethically and legally acceptable to invite pregnant women living in communities where Tdap vaccination has been implemented to participate in the trial.

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¿Es éticamente aceptable invitar a una embarazada a participar en un ensayo clínico con dTpa si ello pudiera conllevar no vacunarse con dTpa antes del parto?

RESUMEN

La incidencia de tos ferina ha aumentado últimamente, afectando especialmente a lactantes menores de 2 meses. Varias comunidades autónomas han iniciado un programa de vacunación con dTpa a todas las mujeres gestantes en el tercer trimestre de embarazo. Un estudio observacional ha mostrado que esta estrategia reduce la incidencia de tos ferina en lactantes <2 meses en un 90%. Modelos matemáticos indican que la estrategia del nido (vacunar a la madre en el posparto inmediato y a los adultos y adolescentes convivientes y cuidadores del recién nacido) reduce en un 70% la incidencia de tos ferina en niños <2 meses. Se pretende realizar un ensayo en el que 340 gestantes serán vacunadas con dTpa mientras otras 340 lo serán en el posparto inmediato; a todos los convivientes y cuidadores del recién nacido se ofrecerá vacunarse con dTpa. Tras analizar las razones científicas y éticas del ensayo, se concluye que es ética y legalmente aceptable ofrecer la participación en este ensayo a gestantes que viven en comunidades donde se les ofrece vacunarlas con dTpa.

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Palabras clave:

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Introduction

A re-emergence of pertussis has recently been observed, with most reported cases occurring in children between the ages of 1 and 2 months. In Spain, the incidence of pertussis peaked in 2011 between 600 and 700 cases/100,000 births,¹ before a vaccination campaign against tetanus, diphtheria, and acellular pertussis (Tdap) was initiated, which was administered to children at 2, 4, and 6 months. 3281 cases were reported in Spain in 2011, of which 49% were confirmed or probable cases.¹ Between 1997 and 2011, based on the Minimum Basic Data Set, the mean incidence rate for hospitalisations in children under one year of age was 115 cases/100,000 births, most (72%) in children under 2 months at a rate of 83 cases/100,000 births; during these 15 years, 37 children died, all under the age of 2 years.² What typically happens is that the newborn's environment infects the infant. One family member is the primary case (source case of the infection) for between 27% and 88% of pertussis cases in infants.^{3,4}

Several strategies are recommended to protect the infant, either through systematically vaccinating adolescents and adults, or through the cocooning strategy – vaccinating the mother and those in close contact with the infant, whether family members or not. Both strategies present difficulties in terms of logistics and acceptability. The cocooning strategy has been demonstrated to be effective in epidemic outbreaks,⁵ although one recent study – with a very small sample – did not demonstrate any benefits.⁶ This strategy can be applied correctly in periods between outbreaks,^{7,8} and is recommended in Australia, Canada, Germany, France, Switzerland and the United States.³

In 2011, the U.S. Advisory Committee on Immunisation Practices (ACIP) recommended vaccinating pregnant women in the third trimester of pregnancy with the aim of protecting the infant.⁹ Anti-pertussis antibodies are passively transferred across the placenta from the mother to the foetus after the mother is vaccinated against tetanus, diphtheria and acellular pertussis (Tdap)^{10–13}; these have a half-life of 6 weeks,¹⁴ a key window for protecting the as-yet unprotected infant.

Very limited data indicate that there are high antibody titres in newborns at 2 months of age, and that at 4 months the infants whose mothers were vaccinated with Tdap had antibody titres similar to infants with unvaccinated mothers.¹⁵ An observational study conducted in England showed that pertussis vaccination in pregnant women was 90% effective in infants under 2 months.¹⁶

ACIP recommends vaccinating all pregnant women in the third trimester of pregnancy, ideally between weeks 27 and 36. This should be complemented with the cocooning strategy, if possible vaccinating all those who will be in close contact with the baby who have not previously been vaccinated with Tdap, at least, 2 weeks in advance of the baby's probable birth; if a pregnant woman has not been vaccinated with Tdap, either before or during the pregnancy, it should be done immediately after giving birth.^{9,17} The American College of Obstetricians and Gynaecologists,¹⁸ as well as renowned experts from 5 Spanish medical societies,³ subscribe to this recommendation in all its terms.

Vaccines with tetanus toxoid (T and Td) are well tolerated in pregnant women and do not affect either the mother or the newborn.¹⁷ Fewer data are available on the Tdap vaccine, but those available do not reveal any unusual adverse reaction patterns.^{15,17,19}

Tdap vaccination in pregnant women in Spain

Several Autonomous Communities, including Catalonia, the Canary Islands, the Valencian Community, Extremadura and the Basque Country, have implemented Tdap vaccination in pregnant

Table 1

Main characteristics of the Tdap-(Boostrix)-047 clinical trial sponsored by GSK.

Design	International, multicentre, cross-over, placebo-controlled, observer-blind trial
Primary objective	To demonstrate that the immunogenicity of a single dose of <i>Boostrix</i> produces higher antibody titres (measured in GMC) in the cord blood than those of the control group. It will be considered a positive outcome if the lower limit of the 95% CI of the GMC (Tdap Group divided by the Control Group) for the three types of antibodies (anti-PT, anti-FHA, and anti-PRN) is >1.5
Sample size	680 pregnant women between the ages of 18 and 45 years distributed into 2 groups of 340 each
Administration of the vaccine and the placebo to the mothers	Between weeks 27 and 36 of the pregnancy, one group will receive a dose of <i>Boostrix</i> and the other, the control group, a dose of placebo (saline solution). During the first 72 h after birth, the control group will receive a dose of <i>Boostrix</i> , while the <i>Boostrix</i> group will receive a dose of placebo. All those in close contact with the newborn (adolescents and adults) will be offered the <i>Boostrix</i> vaccine (cocooning strategy)

anti-FHA: anti-filamentous haemagglutinin; anti-PRN: anti-pertactin; anti-PT: anti-pertussis toxin; GMC: geometric mean concentration of antibodies; 95% CI: 95% confidence interval.

women between weeks 27 and 36 of their pregnancy, without making any mention of the cocooning strategy. The goal is to reach 50% coverage or higher.^{20,21} It was observed in Michigan (U.S.) that only 35% of women who were offered no-cost vaccination agreed to be vaccinated.²² In England, the vaccination programme acceptance rate in pregnant women approached 60%.¹⁶

Tdap clinical trial in pregnant women

It is proposed to conduct a clinical trial–Tdap-(Boostrix)-047–in a population which has not been previously studied. The only clinical trial conducted to date was carried out with the vaccine *Adacel* (from Sanofi Pasteur) in 48 women (33 received *Adacel* and 15 placebo) with positive, albeit preliminary, results.¹⁵ Although the composition of *Triaxis* (from Sanofi Pasteur MSD)–name of *Adacel* in Spain–differs slightly from that of *Boostrix* (GSK), both vaccines are marketed and present similar efficacy and safety profiles. Aside from the mentioned placebo-controlled clinical trial,¹⁵ the geometric mean concentration of only one antibody type has been determined (anti-pertussis toxin antibodies) in two observational studies with no control group,^{11,12} as well as the geometric mean concentration of the antibodies against three antigen components of *B. pertussis* contained in *Boostrix* in prospective observational studies with a control group in a very small number of pregnant women.^{10,13} Table 1 summarises the main characteristics of the proposed study. It can be observed that the geometric mean concentration of antibodies against the three antigen components of *B. pertussis* in *Boostrix* will be determined in the 640 cases participating in the trial.

Ethical and scientific considerations of the trial

Some clinics and public health specialists are of the opinion that the proposed trial should not be conducted in Communities in which the healthcare authority offers no-charge Tdap

vaccination to pregnant women. They argue that if pregnant women are offered the Tdap vaccine, they should not invite them to put off vaccination within the campaign in order to enrol in the trial. Is this the correct stance from an ethical perspective?

This question is posed assuming that the clinical trial has been approved by the pertinent independent ethics committee and authorised by the Spanish Agency of Medicines and Medical Devices.

The situation the trial proposes is as follows:

- a) Tdap vaccination in pregnant women is intended to protect the infant during the first 2–3 months of life. The benefit, therefore, is for the child. Unlike the ACIP recommendations, the Autonomous Communities' vaccination programme does not include the cocooning strategy.
- b) Healthcare authorities such as those in Catalonia and the Valencian Community have proposed vaccination coverage goals of a minimum of 50% of pregnant women in the first year of the programme, which implies that they estimate that there will be thousands who will not agree to be vaccinated while pregnant. It is highly probable that no women will be vaccinated in the days after the birth, since the Communities' vaccination programmes do not envisage such a possibility. That the vaccine is free is far from being a determining factor in general acceptance of Tdap vaccination among pregnant women. The available data range between 35%²² and nearly 60%.¹⁶
- c) The clinical trial intends to prove that maternal antibody transfer to the foetus in the group receiving the Tdap vaccine is superior (at a predetermined limit) to maternal antibody transfer in women who were not vaccinated while pregnant. Half of the women who agree to participate in the trial will receive the Tdap vaccine as if they agreed to be vaccinated in the vaccination campaign. The other 50% of the pregnant women in the trial will receive the Tdap vaccine within the first 72 h after birth. Furthermore, *everyone* who will be in contact with the newborns of *all* the women participating in the trial will be offered the Tdap vaccine (cocooning strategy). That is, all the participating women will be vaccinated according to the ACIP recommendations, both pregnant and postpartum women.¹⁷
- d) In Spain, pertussis incidence is highest in children between 1 and 2 months of age, and in 2011 reached 600–700 cases/100,000 births.¹ More detailed and more recent (2011–2014) data available from the Valencian Community for infants up to 2 months of age indicate that the pertussis incidence rate is between 260 and 680 cases/100,000 births, between 82% and 100% of cases were admitted, equivalent to between 28 and 83 cases/year with a hospital stay of 10–12 days and with a mortality rate between 0 and 3 cases/year; the pertussis incidence rate in children between 3 and 12 months of age varied between 43 and 113 cases/100,000 population.²⁰ The data from Catalonia—a community in which around 80% of the cases and epidemic outbreaks reported in Spain in 2011 occurred¹—indicate that in that year an incidence rate of 469 cases/100,000 children under the age of one year was reached.²¹
- e) The risk of children under the age of 2 months developing pertussis can be reduced by 90% if the vaccine is administered to their mothers during the third trimester of pregnancy.¹⁶ It is not known if administering a Tdap dose to those in contact with the child, in addition to the mother, would obtain an additional reduction (and by how much) in the newborn risk rate. Administering Tdap to women in the immediate post-partum period also involves a significant reduction in the risk of children <12 months developing pertussis. According to ACIP's mathematical model, this reduction in risk is equivalent to 60% of the effect of vaccinating pregnant women.¹⁷ Furthermore, other models have estimated that correctly implementing the cocooning

strategy can reduce cases of pertussis in infants <3 months of age by up to 70%.^{23,24}

With these data, the following *more unfavourable* theoretical scenario can be assumed regarding the risk faced by the participants in the proposed trial. The type (having pertussis) and magnitude (that it might or might not require hospitalisation) of the risk is shared by *all* the infants in the trial. Only the expected incidence of onset will differ in each group. Thus, the maximum incidence rate in infants younger than 2 months of age of 700/100,000, the 90% reduction of this rate if the vaccine is administered to pregnant women, and the 70% reduction if not administered to pregnant women but the cocooning strategy is correctly followed, would give incidence rates of 70/100,000 and 210/100,000, respectively; i.e. 0.7/1000 and 2.1/1000, respectively. Taking the pertussis incidence rate in infants born from vaccinated mothers as a reference (0.7/1000), 714 women would have to be vaccinated in the post-partum period (and those in close contact) for an additional case of pertussis to occur in an infant.²⁵ Note that the trial is to enrol 340 women in the group receiving the vaccine in the immediate post-partum period.

- f) Rid et al.²⁶ created a method to systematically assess risks in clinical research. A scale of the magnitude of harm in 7 situations was established, from insignificant harm (e.g., a bruise) to catastrophic harm (e.g., death), in relation to risks of daily life related to playing sport and travelling in a car. Thus, for example, playing football entails a 1/10,000 risk of suffering a complete ligament tear, and travelling in a car a 1/1,000,000 risk of death.²⁶ Acknowledging that the risk from the trial is that the infant will develop pertussis, it is concluded that the risk of all the infants whose mothers participate in the trial (between 0.7/1000 and 2.1/1000) would be equivalent to the risk of suffering harm of a moderate magnitude (e.g., a bone fracture) in daily life (sport and driving); that is around one case/1000.²⁶
- g) As is well known, the basic ethical principles for all research in human subjects—respect for persons, beneficence and justice—were established by the Belmont Report.²⁷ Twenty years later, Emanuel et al.²⁸ established the 7 ethical requirements that must be met by all research with human subjects, based on the principles in the Belmont Report, but expanded, especially in the social aspects of research. As observed in Table 2, the proposed trial meets the applicable requirements.

The scenario that poses the ethical problem is whether a pregnant woman who has been informed that a Tdap vaccination programme has been started in her community can be invited to participate in a clinical trial that, in itself, meets the applicable ethical (and scientific) requirements for all research in human subjects. That is, the ethical problem would not be brought up in a community in which no-cost Tdap vaccination is not offered to pregnant women.

Clinical trials posing an ethical conflict similar to the proposed trial

The scenario posed by the Tdap-(Boostrix)-047 trial is very unusual in clinical research. It did occur, however, in the exploratory trial by Munoz et al.¹⁵, which was conducted between October 2008 and May 2012. Given that ACIP has recommended Tdap vaccinations in pregnant women since June 2011,⁹ this means that there were pregnant women who agreed to participate in this trial after the recommendation was already in force. Aside from this case, as the beneficiary of the vaccination is the infant, there are two situations in which it can be argued that they share certain similarities with the situation of the proposed trial, in

Table 2Ethical requirements that must be met by all research with human subjects, according to Emanuel et al.²⁸

Requirement ²⁸	Justifying ethical values ²⁸	How they are met in the Tdap (Boostrix)-047 trial
Social or scientific value	Scare resources and nonexploitation	Answers several scientifically valid and as yet unanswered questions, which would help ascertain the reason for the good effectiveness results obtained in the study by Amirthalingam et al. ¹⁶
Scientific validity	Scare resources and nonexploitation	The design, methods, and procedures ensure its scientific validity. Approval by the IECs will be a clear indicator that the trial's objective, methods and procedures are scientifically appropriate
Fair subject selection	Justice	The sample of participating pregnant women will be obtained from among those who meet the screening criteria and are cared for in the participating hospitals, with no discrimination whatsoever
Favourable risk–benefit ratio	Nonmaleficence, beneficence, and nonexploitation	The T, Td, and Tdap vaccines have been administered to thousands of pregnant women without any significant risks having been observed for either the mother or the child; all the women will receive a dose of Tdap during the pregnancy or immediately after birth; all the adults and adolescents in close contact with the newborns will also receive a dose. The decrease in the pertussis incidence rate in infants with both vaccine strategies is highly significant, and in the worst scenario according to observational data ¹⁶ and mathematical models, ^{23,24} is expected to be around 0.7–2.1/1000 births
Independent review	Public accountability; minimising influence of potential conflicts of interest	The trial protocol will follow the usual ethical/administrative review in Spain, so it will require the IECs of the involved hospitals and AEMPS to approve it before it is implemented. Approval by the IECs will be a clear indicator that the trial's objectives, methods and procedures are scientifically, ethically and legally appropriate
Informed consent	Respect for subject autonomy	Only women who have given their written informed consent after having read the patient information sheet and having spoken with the investigator will participate
Respect for potential and enrolled subjects	Respect for subject autonomy and welfare	The participants will have the right to leave the trial without having to give any reason, they will be informed of any new information they should know if it could influence their decision to continue to participate in the trial, ²⁹ they will be informed of the results obtained and their data will be kept strictly confidential at all times, according to good clinical practice standards.

AEMPS: Spanish Agency of Medicines and Medical Devices; IEC: independent ethics committee; Tdap: vaccine against tetanus, diphtheria and acellular pertussis; T: vaccine against tetanus; Td: vaccine against tetanus and adult diphtheria.

clinical research conducted in children who are not sufficiently old enough to give their assent, i.e., who are not yet 7 years old.³⁰

The first scenario is that posed by trials in which the immunogenicity and reactogenicity of pentavalent (DTaP-HBV-IPV) or hexavalent (DTaP-HBV-IPV/Hib) vaccines administered to children at 2, 4, and 6 months of age along with a vaccine against meningococcal C conjugate with a non-toxic variant of the diphtheria toxin (MenC-CRM),³¹ or against meningococcal C conjugate with tetanus toxoid (MenC-TT),³² or against meningococcal C and *H. influenzae* (Hib-MenC).³³ Since the beginning of the 21st century, the first dose of a vaccine against hepatitis B has been administered to newborns before they are discharged from hospital in several Autonomous Communities. As the trial's vaccine administration schedule consisted of 3 doses at 2, 4, and 6 months, the children to be included in the study should not receive the first hepatitis B vaccine as established by the Autonomous Community vaccine schedule. To conduct the trial, the investigators had to inform the mothers about the trial immediately after giving birth and obtain their consent for their children to participate in the trial and to not receive the first dose of the hepatitis B vaccine as established by the vaccine schedule. It is evident that, due to the mechanisms of transmission, the risk of a newborn becoming infecting with the hepatitis B virus is much lower than with *B. pertussis*, although, as has been seen, the risk of an infant in the trial developing pertussis is very low. The example is valid for the analysis since it is the mother who decides to postpone a scheduled vaccination for her child.

The second scenario is clearly different, but poses a situation that has a similar characteristic to the case at hand. They are both clinical trials in chronic diseases in which the patients are being treated with standard therapy. In these cases, if the efficacy of a new drug or a new treatment regimen is being investigated, it is common for the patients to undergo a short screening or wash out period, in which they do not receive the active medication—if anything, they

can only receive rescue medication in situations of clear need—and during that period they usually receive a placebo. After this period the patients are randomised to the experimental group or to the control group (in which they will receive either active therapy or placebo). In these cases, vaccination is not postponed, but rather a medication that the patients were receiving is withdrawn for a period of weeks or even months. Thus, for example, it is common for hypertensive children between 1 and 6 years of age participating in clinical trials to have a one-week screening period with one week of placebo,^{34,35} which can be followed by another 14 days of placebo before receiving active medication.³⁴ In one of the most important trials studying hypertension control in children with chronic kidney failure, one third of the participants was kept with no antihypertensive treatment for a minimum of 2 months, before being randomised to an active therapy.³⁶ Similarly, children with mild asthma between 2 and 6 years of age participating in clinical trials usually undertake a screening period lasting between 2 and 4 weeks before being randomised to one of the treatment groups.^{37,38} In one such trial, one group received a placebo for 12 weeks³⁷ or 24 weeks.³⁸

There are, undoubtedly, multiple reasons why some parents authorise their sick children to undergo short periods of time without receiving an active treatment. Parents' decisions about the potential participation of their children in a clinical trial are influenced by their perceptions of the well-being, low level of risk, and safety of their children in the trial, as well as the potential benefits to their children, the family and other children, if the trial has minimal impact on their routine care or offers enhanced care, and the practical aspects of their participation.^{39,40} Although the risk of all the above-mentioned clinical trials was minimised as much as possible, the risk perceived by the parents—and by the population in general — is usually lower if the children continue with their usual treatment than if they are included in a clinical trial. In fact,

laypeople make the error of thinking that the healthcare authority only authorise new drugs that are very effective and that have no serious adverse effects,⁴¹ even though, in fact, many patients are subjected to low-value interventions.⁴²

Doctor–patient relations and the Tdap-(Boostrix)-047 trial in Autonomous Communities that vaccinate pregnant women with Tdap

The valid relationship model between physicians and patients in the West until the last decades of the 20th century was based on the physician seeking the *well-being* of his/her patient under the premise of a moral principle of beneficence. In this relationship, well-being is defined by the physician without giving much thought to the patient's opinion. Thus, this relationship is known as "paternalistic".

Following the development in the United States of the theory of informed consent from a legal perspective,⁴⁴ the rights of patients began to be forged in the United States, and later in several European countries over the last three decades of the 20th century.⁴³ Thus, the doctor–patient relationship began to change in the 1970s: physicians started to lose the decision-making power that they had over patients and that they had enjoyed for centuries, making way for the establishment of a more equal relationship in which patients and their doctors made informed decisions by consent.⁴³

In Spain, the General Health Act of 1986 solidified the change in the doctor–patient relationship by sanctioning the patients' autonomy—and, as a result, the need to obtain informed consent,—against the paternalistic model of the past.⁴⁵ In 1997, the Oviedo Convention, endorsed by the Council of Europe, established that all interventions may only be carried out after obtaining the free and informed consent of the person affected.⁴⁶ The basic law regulating patients' autonomy establishes that patients, after receiving the pertinent information, have the right to freely decide between the available interventions and they can even refuse to receive treatment, except in cases established by law.⁴⁷ This is why all healthcare professionals must respect the decisions made freely and voluntarily by patients. Therefore, all patients have the right to be respected, and to have their decisions respected, and that their decisions be made under informed consent. This is a free and express authorisation for a certain diagnostic, preventive or therapeutic intervention to be performed, including as part of research.⁴⁴

Spanish legislation, therefore, decrees that the doctor–patient relationship must be established within a framework in which the patients' values and preferences must be taken into account by healthcare professionals and that, in case of discrepancies, the patients' decision will prevail over that of any other consideration. This means that ethically and legally, a physician should not "decide for" their patient under any circumstances, except those provided for by law. Therefore, in the case at hand, physicians who inform pregnant women about vaccinating against pertussis with Tdap should not under any circumstances omit information about the clinical trial, since to do so would be to make a decision that does not apply to them. It should be the pregnant woman who decides, once appropriately informed, whether or not to participate in the trial or whether to be vaccinated within the programme or not be vaccinated at all.

Furthermore, physicians should not presume that the fact that the vaccination programme is ongoing means it is an insurmountable obstacle for recruiting trial subjects. It has already been seen that there are many and varied reasons why mothers or fathers authorise their very young children to participate in clinical trials. Moreover, it is interesting to observe that there is no basis for the

common belief among some physicians that asking the parents of a child who could potentially participate in a clinical trial overwhelms them.³⁹ The possibility that there are mothers who do not want to be vaccinated within the vaccination programme but who will want to participate in the trial due to its perceived benefits, should not be ruled out *a priori*.

Conclusion

The ultimate objective of ethics is to train people capable of making autonomous and responsible decisions.⁴⁸ In light of the legal (and ethical) principle of respect for persons that establishes that it is the person who should decide—with the assistance of the healthcare professional—which diagnostic, preventive and therapeutic interventions they will undergo, it does not appear that at the present time there is space for the classic paternalistic attitude of physicians in their care activity. Therefore, in order to respect the wishes of their patients, physicians who practice in Communities that have implemented Tdap vaccination in pregnant women must inform them of the existence of the trial so that, after finding out about its risks, benefits, requirements and drawbacks, they can make a rational decision about their potential participation in the trial. Any other attitude adopted by the healthcare professionals would be paternalistic and, therefore, wrong, since it would ignore the patient's values and preferences, which should always be respected.^{49–51}

A pregnant woman in a Community where the Tdap vaccine is offered at no cost and where the trial is being conducted has the right to know about the three choices available to her: be vaccinated within the programme, participate in the trial, or to not be vaccinated or participate in the study. This right should not be violated by a paternalistic attitude by physicians who refuse to participate in the trial—and who therefore cannot offer this possibility to their patients—understanding that it is a third-party—the healthcare authority—which, by having implemented the programme, prevents the patient *de facto* from making a decision—whether or not to participate in the trial—that only she should be able to make. In this scenario, the physician is in breach of their responsibility, which is no other than to appropriately inform why it is important to be vaccinated and about the possibility of participating in the trial.

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Conflicts of interest

The author declares that there are no conflicts of interest.

References

1. Grupo de Trabajo Tos Ferina 2012 de la Ponencia de Programa y Registro de Vacunaciones. Revisión del programa de vacunación frente a tos ferina en España. Comisión de Salud Pública del Consejo Interterritorial del Sistema Nacional de Salud. Ministerio de Sanidad, Servicios Sociales e Igualdad; 2013.
2. Fernández-Cano MI, Armadans-Gil L, Alvarez-Bartolomé M, Rodrigo-Pendás JA, Campins-Martí M. Hospitalización por tos ferina en España (1997–2011). *Enferm Infecc Microbiol Clin.* 2014;**32**:638–42.
3. Campins M, Moreno-Pérez D, Gil-de Miguel A, González-Romo F, Moraga-Llop FA, Arístegui-Fernández J, et al. Tos ferina en España. Situación epidemiológica y estrategias de prevención y control. Recomendaciones del Grupo de Trabajo de Tos ferina. *Enferm Infecc Microbiol Clin.* 2013;**31**:240–53.
4. Moraga Llop FA, Iglesias Griñant S, Martínez Gómez X, Codina Grau G, Gorritz Hernando P, Campins Martí M. Tos ferina en el lactante, ¿quién lo contagia? *Vacunas.* 2012;**13**:88–94.
5. Rosenblum E, McBane S, Wang W, Sawyer M. Protecting newborns by immunizing family members in a hospital-based vaccine clinic: a successful Tdap

- cocooning program during the 2010 California pertussis epidemic. *Public Health Rep.* 2014;129:245–51.
6. Healy CM, Rench MA, Wootton SH, Castagnini LA. Evaluation of the impact of a Pertussis Cocooning Program on infant pertussis infection. *Pediatr Infect Dis J.* 2015;34:22–6.
 7. Frère J, de Wals P, Ovetchkine P, Coïc L, Audibert F, Tapiero B. Evaluation of several approaches to immunize parents of neonates against *B. pertussis*. *Vaccine.* 2013;31:6087–91.
 8. Hayles EH, Cooper SC, Wood N, Sinn J, Skinner SR. What predicts postpartum pertussis booster vaccination? A controlled intervention trial. *Vaccine.* 2015;33:228–36.
 9. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoids, and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months – Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR.* 2011;60:1424–6.
 10. Leuridan E, Hens N, Peeters N, de Witte L, van der Meeren O, van Damme P. Effect of a prepregnancy pertussis booster dose on maternal antibody titers in young infants. *Pediatr Infect Dis J.* 2011;30:608–10.
 11. Healy CM, Rench MA, Baker CJ. Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants. *Clin Infect Dis.* 2013;56:539–44.
 12. Vilajeliu A, Goncé A, López M, Costa J, Rocamora L, Ríos J, et al. Combined tetanus-diphtheria and pertussis vaccine during pregnancy: transfer of maternal pertussis antibodies to the newborn. *Vaccine.* 2015;33:1056–62.
 13. Abu Raya B, Srugo I, Kessel A, Peterman M, Bader D, Gonen R, et al. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels – a prospective study. *Vaccine.* 2014;32:5787–93.
 14. Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine response. *J Infect Dis.* 1990;161:487–92.
 15. Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA.* 2014;311:1760–9.
 16. Amirhalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet.* 2014;384:1521–8.
 17. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoids, and acellular pertussis vaccine (Tdap) in pregnant women – Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR.* 2013;62:131–5.
 18. Committee on Obstetric Practice. The American College of Obstetricians and Gynecologists. Committee Opinion, No 566, June 2013 [consulted 29 Jun 2015]. Available from: <http://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co566.pdf?dmc=1>
 19. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ.* 2014;349:g4219.
 20. Servicio de Salud Infantil y de la Mujer. Servicio de Vigilancia y Control Epidemiológico. Dirección General de Salud Pública. Conselleria de Sanitat. Generalitat Valenciana. Vacunación de las embarazadas en la Comunidad Valenciana. Protejamos a los lactantes frente a la tos ferina [consulted 29 Jun 2015]. Available from: <http://www.matronas-cv.org/categorias-principales/noticias-y-eventos/i/19936/78/vacunacion-de-las-embarazadas-frente-a-la-tosferina-en-la-comunidad-valenciana>
 21. Agència de Salut Pública de Catalunya. Programa de vacunacions. Vacunació de les dones embarassades contra la tos ferina a Catalunya. Gener 2014. Generalitat de Catalunya [consulted 29 Jun 2015]. Available from: <http://canalsalut.gencat.cat/web/.content/home.canal.salut/professionals/temes.de.salut/vacunacions/documents/arxiu/vac.tos.ferina.embarassades.170114.pdf>
 22. Housey M, Zhang F, Miller C, Lyon-Callo S, McFadden J, Garcia E, et al. Vaccination with tetanus, diphtheria, and acellular pertussis vaccine of pregnant women enrolled in Medicaid – Michigan, 2011–2013. *MMWR.* 2014;63: 839–42.
 23. Van Rie A, Hethcote HW. Adolescent and adult pertussis vaccination: computer simulations of five new strategies. *Vaccine.* 2004;22:3154–65.
 24. Forsyth KD, Wirsing von König CH, Tan T, Caro J, Plotkin S. Prevention of pertussis: recommendations derived from the second Global Pertussis Initiative roundtable meeting. *Vaccine.* 2007;25:2634–42.
 25. Sedgwick P. Number needed to harm. *BMJ.* 2011;342:d281.
 26. Rid A, Emanuel EJ, Wendler D. Evaluating the risks of clinical research. *JAMA.* 2010;304:1472–9.
 27. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report Of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Fed Reg* 1979; 44: 23192–7.
 28. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA.* 2000;283:2701–11.
 29. Dal-Ré R, Avendaño C, Gil-Aguado A, Gracia D, Caplan AL. When should re-consent of subjects participating in a clinical trial be requested? A case-oriented algorithm to assist in the decision-making process. *Clin Pharmacol Ther.* 2008;83:788–93.
 30. Modi N, Vohra J, Preston J, Elliott C, van't Hoff W, Coad J, et al. Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees. *Arch Dis Child.* 2014;99:887–91.
 31. Tejedor JC, Omeñaca F, García-Sicilia J, Verdaguer J, van Esso D, Esporrín C, et al. Immunogenicity and reactogenicity of a three-dose primary vaccination course with a combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-*Haemophilus influenzae* type B vaccine coadministered with a meningococcal C conjugate vaccine. *Pediatr Infect Dis J.* 2004;23:1109–15.
 32. Tejedor JC, Moro M, Ruiz-Contreras J, Castro J, Gómez-Campderá JA, Navarro ML, et al. Immunogenicity and reactogenicity of primary immunization with a hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-*Haemophilus influenzae* type B vaccine coadministered with two doses of a meningococcal C-tetanus toxoid conjugate vaccine. *Pediatr Infect Dis J.* 2006;25:713–20.
 33. Tejedor JC, Moro M, Ruiz-Contreras J, Castro J, Gómez-Campderá JA, Navarro ML, et al. Immunogenicity and reactogenicity of primary immunization with a novel combined *Haemophilus influenzae* Type B and *Neisseria meningitidis* Serogroup C-tetanus toxoid conjugate vaccine coadministered with a Diphtheria-tetanus-acellular Pertussis-hepatitis B-inactivated poliovirus vaccine at 2, 4 and 6 months. *Pediatr Infect Dis J.* 2007;26:1–7.
 34. Flynn JT, Meyers KE, Neto JP, de Paula Meneses R, Zurowska A, Bagga A, et al. Efficacy and safety of the angiotensin receptor blocker valsartan in children with hypertension aged 1 to 5 years. *Hypertension.* 2008;52:222–8.
 35. Schaefer F, van de Walle J, Zurowska A, Gimpel C, van Hoeck K, Drozd D, et al. Efficacy, safety and pharmacokinetics of candesartan cilexetil in hypertensive children from 1 to less than 6 years of age. *J Hypertens.* 2010;28:1083–90.
 36. ESCAPE Trial Group. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med.* 2009;361:1639–50.
 37. Wasserman RL, Baker JW, Kim KT, Blake KV, Scott CA, Wu W, et al. Efficacy and safety of inhaled fluticasone propionate chlorofluorocarbon in 2- to 4-year-old patients with asthma: results of a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol.* 2006;96:808–18.
 38. Brand PL, Luz García-García M, Morison A, Vermeulen JH, Weber HC. Ciclesonide in wheezy preschool children with a positive asthma predictive index or atopy. *Respir Med.* 2011;105:1588–95.
 39. Shilling V, Williamson PR, Hickey H, Sowden E, Smyth RL, Young B. Processes in recruitment to randomised controlled trials of medicines for children (RECRUIT): a qualitative study. *Health Technol Assess.* 2011;15:1–116.
 40. Hoberman A, Shaikh N, Bhatnagar S, Haralam MA, Kearney DH, Colborn DK, et al. Factors that influence parental decisions to participate in clinical research: consenters vs nonconsenters. *JAMA Pediatr.* 2013;167:561–6.
 41. Schwartz LM, Woloshin S. Communicating uncertainties about prescription drugs to the public: a national randomized trial. *Arch Intern Med.* 2011;171:1463–8.
 42. Schwartz AL, Landon BE, Elshaug AG, Chernew ME, McWilliams JM. Measuring low-value care in Medicare. *JAMA Intern Med.* 2014;174:1067–76.
 43. Gracia D. Fundamentos de bioética. 2ª ed. Madrid: Editorial Triacastela; 2007.
 44. Simón P. El consentimiento informado. Madrid: Editorial Triacastela; 2000.
 45. Ley 14/1986, de 25 de abril, General de Sanidad. BOE núm. 102 de 29 de abril de 1986 [consulted 29 Jun 2015]. Available from: http://www.boe.es/diario_boe/txt.php?id=BOE-A-1986-10499
 46. Convenio relativo a los derechos humanos y la biomedicina. BOE núm. 251, de 20 de octubre de 1999 [consulted 29 Jun 2015]. Available from: <http://www.boe.es/buscar/doc.php?id=BOE-A-1999-20638>
 47. Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica. BOE núm. 274, de 15 de noviembre de 2002 [consulted 29 Jun 2015]. Available from: http://www.boe.es/diario_boe/txt.php?id=BOE-A-2002-22188
 48. Gracia D. The many faces of autonomy. *Theor Med Bioeth.* 2012;33:57–64.
 49. Consejo General de Colegios Oficiales de Médicos. Código de Deontología Médica. Guía de ética médica. Julio 2011 [consulted 29 Jun 2015]. Available from: https://www.cgcom.es/sites/default/files/codigo_deontologia_medica.pdf
 50. Asociación Médica Mundial. Declaración de Lisboa sobre los derechos del paciente. Redacción revisada. Santiago, Chile. Octubre 2005 [consulted 29 Jun 2015]. Available from: <http://www.wma.net/es/30publications/10polices/l4/index.html>
 51. General Medical Council UK. Good medical practice. 2013 [consulted 29 Jun 2015]. Available from: http://www.gmc-uk.org/guidance/good_medical_practice.asp