Drug Safety 2005; 28 (9): 743-752
0114-5916/05/0009-0743/$34.95/0

When Should Vaccination Be Contraindicated in Children?

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Abstract

No child should be denied immunisation without serious consideration given to the consequences. In the past, many contraindications to vaccination were based on theoretical concerns. These concerns often assumed an immunoallergic mechanism for adverse reactions, whereas many such events are often due to other causes. Other contraindications were based on evidence of excess risk, but this risk was not always balanced against the higher risk of disease. Therefore, contraindications often varied between countries and over time.

In recent years, the widespread availability of less reactogenic vaccines and the common use of combined preparations have prompted a review of contraindications in many countries. Accumulated experience worldwide has allowed the list of conditions that contraindicate vaccination to be reduced. The international consensus now is that there are very few situations in which a child should not be immunised and the only true contraindication applicable to all vaccines is a history of anaphylaxis to a vaccine component or following a previous dose of the vaccine. Health professionals should feel confident in accepting national recommendations and, if in doubt, should refer children for an expert opinion, rather than deny a child protection against a serious infection.

There are very few situations in which a child should not be immunised. Although contraindications to immunisation vary according to national policy, there is a consensus that the only true contraindication applicable to all vaccines is a history of anaphylaxis to a vaccine component or following a previous dose of the vaccine (table I).[1-4] There are other situations in which vaccination is not contraindicated but in which a clinical judgement is needed before vaccination can proceed. Such precautions require an assessment of the potential benefits and risks of vaccination to the individual and may result in a temporary deferral or in offering immunisation under controlled circumstances.

Contraindications and precautions are often confused. Historically, many false contraindications have been passed from practitioner to practitioner, resulting in children being unnecessarily denied immunisation without serious consideration of the long-term implications, both for the child and for the community. Vaccine providers often have substantial knowledge gaps about contraindications and vaccines are frequently not given because of misconceptions about what truly contraindicates a vaccine.[6,7] As more becomes known about the safety and efficacy of each vaccine and the individual patient's reactions and responses to them, many previous recommendations about when and to whom vaccines should not be given are being reconsidered by experts and advisory groups.

The purpose of this review is to discuss the rationale for past and current contraindications, the

Table I. Summary of contraindications to vaccination by country as stated in national immunisation guidance

Vaccine	Australia[2]	Canada[4]	US[3]	UK[1,5]
All vaccines	A known anaphylactic sensitivity to any component of the relevant vaccine Anaphylaxis following a previous dose of the vaccine	Anaphylactic reaction to previous dose of vaccine Anaphylactic reaction to a constituent of a vaccine	Permanent contraindications: severe allergy to a vaccine component or severe allergic reaction following a prior dose of vaccine	A confirmed anaphylactic reaction to a previous dose of the same vaccine[1] or a confirmed anaphylactic reaction to a vaccine component[1]
DTP-containing vaccines (DTwP or DTaP)	Encephalopathy within 7 days, defined as severe acute neurological illness with prolonged seizures and/or unconsciousness and/or focal signs that are not due to another identified cause Immediate severe allergic or anaphylactic reaction to vaccination with DTP	As above	Encephalopathy within 7 days of pertussis vaccination	As above
Live vaccines	Live vaccines should not be administered to immunosuppressed individuals regardless of whether the suppression is caused by disease or treatment (the exception is MMR, which should be administered to HIV-infected individuals provided that the immunosuppression is not severe)	Severe immunodeficiency	Temporary contraindication: immunosuppression	'Special risk groups' defined and described individually[5]

DTaP = diphtheria-tetanus-acellular pertussis; **DTP** = diphtheria-tetanus toxoid-pertussis; **DTwP** = diphtheria-tetanus-whole cell pertussis; **MMR** = measles-mumps-rubella.

evidence to support this rationale and the current consensus on the appropriate management of individuals in each category. The review will cover only those vaccines used in the routine childhood schedule of most developed countries.

1. A History of Reactions to a Vaccine or a Vaccine Component

Reactions to vaccines can be caused by the vaccine antigen itself, by a chemical component included in the final formulation or by impurities derived from the manufacturing process. Reactions may be immune-mediated or due to a direct toxic effect of the vaccine. They may also be due to vaccinator technique. Failure to distinguish the mechanism and nature of each reaction has often led to confusion about contraindications.

Toxin-mediated reactions usually occur within 24 hours of the immunisation and resolve within a couple of days. They may cause a local inflammatory reaction at the injection site or a systemic reaction such as a fever. For live vaccine viruses, however, reactions are usually caused by viral replication and are usually similar to the natural infection, occurring many days or even weeks after immunisation. Systemic events that are reported within 48 hours of receipt of live virus vaccines, such as those for measles-mumps-rubella (MMR), are highly unlikely to have been caused by the vaccine. Immune-mediated reactions vary both in the symptoms exhibited and the timing of onset of symptoms (table II).

Most vaccine reactions do not involve an immuno-allergic mechanism[8] and, therefore, there is no reason to assume that such reactions would predispose to a future immediate life-threatening reaction such as anaphylaxis. The main rationale for not vaccinating someone who has had a local or systemic reaction to a previous dose is that the reaction may recur and be even more severe. However, for live virus vaccines the risk of reactions declines with each dose, as prior immunity would prevent significant viral replication. In addition, for many vaccines, evidence of the safety of revaccination in those with a history of a reaction has now been established. Careful history taking, therefore, should enable distinction between different forms of

Table II. Immune-mediated vaccine reactions

Type of reaction	Timing	Nature	Mechanism
Type I: anaphylaxis and other immediate hypersensitivity reactions	Generally occurs immediately or within a few hours following immunisation	Characteristic signs of anaphylaxis include: pallor, tachycardia, oedema, laryngeal spasm and wheezing, hypovolaemic shock and hypotension Milder forms of immediate hypersensitivity reaction include: urticaria, facial swelling and wheezing (but without circulatory collapse)	Caused when antigen binds to IgE antibodies on mast cells and basophils, causing release of mediators such as histamine. This usually requires sensitisation from prior exposure to the antigen for the formation of the IgE antibodies
Type II: interaction of antibody with normal tissue antigens	Reaction may take 2–3 weeks to develop in a naive individual but occur within a few days on re-exposure	Autoimmune reaction, e.g. idiopathic thrombocytopenia (see section 4.2)	These could theoretically occur if an antigen or other vaccine component shares a common epitope with a host tissue antigen. This may then cause the antibodies induced by the vaccine to react with that tissue
Type III: Immune complex-mediated hypersensitivity (Arthus) reaction	Reactions occur within a few hours following immunisation and peak 1–2 days later	Local inflammatory reactions, e.g. redness and swelling at the injection site are the most common form of immune-mediated vaccine reaction Generalised Arthus reactions (serum sickness) after vaccination are extremely rare but can cause arthritis, rashes and renal damage	Localised reactions occur when the vaccine antigen combines with IgG antibody leading to a deposition of antigen-antibody complexes on the walls of blood vessels Generalised reactions can be caused by systemic formation of antigen-antibody complexes, which are then deposited in joints, skin and kidneys
Type IV: cell-mediated/delayed type hypersensitivity	Reactions within 48 hours if previously exposed. Longer in naive individuals	Skin manifestations such as dermatitis and rash	Occurs when antigen-specific T lymphocytes are activated by the vaccine, causing lymphokine release and macrophage stimulation

immune-mediated and other reactions and in many cases will allow vaccination to be completed.

These considerations have become even more important since the development, introduction and widespread use of combination vaccines. It is often difficult to attribute reactions to a specific component and the consequences of withholding vaccination for all the antigens in each combination are more serious. Because of the absence of a quality assured and licensed supply of single components, it is important to carefully assess the withholding of protection against other diseases to children who are deemed unable to receive one antigen in a combined vaccine. Robust evidence of risk is, therefore, required before any reaction should be considered as an absolute contraindication to completing a standard schedule.

1.1 Anaphylaxis to Previous Vaccination

Anaphylaxis following vaccination is extremely rare. A US study identified only five cases of potentially vaccine-associated anaphylaxis in 7.5 million doses of vaccine given (0.65 cases/million doses).[9] However, since such a reaction is likely to recur on re-exposure to the antigen, severe anaphylaxis following vaccination is a contraindication to a further dose of the implicated vaccine in many countries.[1-4]

1.2 Anaphylaxis to a Vaccine Component

Known anaphylaxis to components of vaccines is also often cited as a contraindication. Vaccine components include the vaccine antigen, residual animal proteins, preservatives, stabilisers, adjuvants and antimicrobial preparations. However, the evidence about allergy to vaccine components is extremely limited as specific allergies are often not recognised prior to vaccination and most anaphylaxis following vaccination occurs in individuals without a prior history. Based upon this limited evidence, vaccines are contraindicated in individuals who have previously experienced a severe allergic reaction, such as anaphylaxis, to a vaccine component.[1-4] However, in some instances where evidence in relation to the safety of specific vaccines in individuals with allergies to components has become available, such contraindications have been removed. Allergy to egg

protein is one example where empirical evidence exists to guide policy.

The most common animal protein allergen in vaccines is egg protein. This is found in vaccines prepared using embryonated chicken eggs. Both influenza and yellow fever vaccines contain multiple proteins derived from egg white and yolk and are currently contraindicated in children with a history of anaphylactic reaction to egg or egg protein. The measles and mumps viruses used in MMR vaccine are cultured in chick fibroblasts and could potentially contain egg antigens. In reality, the amount of egg in the MMR vaccine is extremely small[10] and the incidence of true anaphylaxis in children with known egg allergy is unclear. However, large case series reviews[10] and studies[11,12] worldwide have concluded that reactions following MMR vaccine in egg-allergic children are rare and are not fatal. Most of the rare severe reactions to MMR that have occurred have been in children who are not allergic to egg[13] and are thought to be due to an unrecognised allergy to other components of the vaccine such as gelatin or neomycin.[14,15] Both of these components are present in MMR vaccine in much greater amounts than egg protein.

Based on the evidence discussed, egg allergy is not cited as a contraindication to MMR vaccine in many countries' vaccine recommendations. Despite this, many physicians remain very cautious in their recommendation of MMR for children who have previously reacted to egg and this has resulted in unnecessary deferral or exclusion of this vaccination. MMR vaccine may be given under hospital supervision, so that any resulting anaphylactic reaction can be promptly treated.[14] The UK guidelines state that this is only recommended for children where there is major concern,[5] such as those with a history of cardiorespiratory reaction to eggs.

1.3 Non-Immediate Hypersensitivity Reactions to Vaccine Components

A history of non-anaphylactic, non-immediate hypersensitivity reactions to vaccine components was often previously cited as a contraindication to vaccination. The rationale for this was the theoretical concern that re-exposure to that antigen could lead to a life-threatening reaction such as anaphylaxis. However, most hypersensitivity reactions are mild and self-limiting. The most common reaction to neomycin, for example, is a delayed skin reaction.[16] Similarly reactions to thiomersal[17] and aluminium[18] tend to be local, delayed skin reactions. As there is no evidence that such reactions predispose individuals to anaphylaxis or predict a subsequent anaphylactic response, previous localised reactions to thiomersal, neomycin or aluminium are not considered valid reasons to withhold vaccines containing these components.[18-20]

Where an individual with a clear history of hypersensitivity to a vaccine component requires vaccination, it may still be possible to vaccinate them. This decision should be made after careful exploration of the nature of the allergy and the history of exposure to the antigen.[21] For each individual, the relative balance of the benefits and risks should be assessed and may depend upon their prior vaccination status and likelihood of exposure. Where there is considered to be a risk of an allergic reaction but protection from infection through further immunisation is still required, vaccination under controlled circumstances should be considered.

1.4 Severe Systemic Reactions to Pertussis Vaccination

Previously, if a child developed a generalised reaction following immunisation with diphtheria-tetanus-whole cell pertussis (DTwP) vaccine such as a high temperature, convulsions or prolonged inconsolable or high-pitched screaming, it was assumed that the pertussis component was the most likely cause. This was based on evidence that febrile reactions to DTwP were more common than those observed after diphtheria-tetanus (DT) alone.[22,23] Such reactions appeared to increase in frequency with dose[24-26] and age.[27,28] Therefore, children who suffered systemic reactions to DTwP were often recommended to have DT alone for subsequent immunisation.[5,29] However, febrile reactions to whole cell pertussis vaccines are attributable to the direct effect of endotoxin[30] and this mechanism is probably also responsible for other systemic reactions including hypotonic-hyporesponsive episodes (HHEs), convulsions and screaming. From the experience of re-immunising children who have had systemic reactions (such as HHEs) in several countries,[31-33] there is now good evidence that these

individuals can safely receive pertussis-containing vaccines without any major problems. Although the data are reassuring with respect to using whole-cell pertussis vaccine again in such children,[32] acellular pertussis vaccines that have lower reactogenicity profiles are usually preferred where they are available.

The recent introduction of combination vaccines containing acellular pertussis for primary immunisation in many countries has also prompted a review of contraindications. Acellular pertussis vaccines are associated with a significantly lower rate of local reactions, HHEs, convulsions and screaming than whole cell preparations[34,35] and rates of reaction with such vaccines are similar to those following DT alone.[36,37] There is no justification, therefore, for completion of vaccination with DT alone and recommendations have now been changed in many countries. The development of a severe general reaction (high fever, screaming, convulsions and HHEs) following immunisation is no longer considered a contraindication to further pertussis immunisations in most countries.[1-4] Experience in Canada[38] has shown a marked decline in adverse reactions since the switch to acellular vaccines and no increase has been observed since the change in recommended contraindications. This evidence suggests that recurrence of severe reactions is extremely rare with acellular vaccines.

1.5 Severe Local Reactions to Vaccinations

Local reactions are fairly common after many routine vaccines. It was previously assumed that most local reactions were immune-mediated and would increase in severity with successive doses. Because of this and concern that local reactions might predispose an individual to a subsequent systemic reaction, in many countries a history of a severe local reaction to a vaccine would contraindicate further doses.[5]

As local reactions occur with greater frequency in children receiving DTwP compared with DT vaccines[22] and as rates of local reactions to DTwP increase with each dose,[24] such reactions previously used to contraindicate further whole cell pertussis vaccination in the UK. To complete protection against whooping cough, acellular pertussis vaccines that have a lower rate of local reactions following infant vaccination than whole cell preparations were recommended.[5] However, local reactions are usually self-limiting and do not seem to correlate with systemic reactions such as fever.[27] In the US, therefore, even when whole cell pertussis vaccines were still in use, such reactions did not contraindicate revaccination with DTwP.[39] With the introduction of infant vaccination with diphtheria-tetanus-acellular pertussis (DTaP), where rates of local reactions are low and similar to those with DT alone,[36,37,40] local reactions also no longer contraindicate further DTaP vaccination in the UK.

For some vaccines, such as for *Haemophilus influenzae* type b and meningitis C, local reactions are generally mild[41] and do not seem to recur.[42,43] Therefore, local reactions to these vaccines should not normally contraindicate further vaccination. For other vaccines, such as those containing tetanus toxoid, more severe local reactions have been commonly observed. Although previous studies[44] suggested that redness and swelling at the injection site is more common in those with high pre-existing antibody levels, subsequent studies[27,45,46] have shown no consistent correlation. In addition to this, follow up of patients with a history of previous local and systemic reactions to tetanus toxoid showed no adverse reactions to re-vaccination between 1 and 5 years later.[47] Thus, local reactions to most vaccines should not contraindicate further vaccination with that antigen, although where the reaction was severe advice about the number and timing of doses should be taken.

2. A History of Neurological Conditions

2.1 Pre-Existing Neurological Conditions

In the past neurological conditions were often considered contraindications to vaccination with pertussis. The avoidance of pertussis vaccination in children with underlying neurological conditions, including convulsions, was based on evidence that diphtheria-tetanus-pertussis (DTP) vaccines containing whole cell pertussis did lead to an increased risk of febrile convulsions[23,48] and that this risk was increased in children with a history of convulsions.[49] It was, therefore, postulated that this type of reaction could lead to a worsening of any underly-

ing condition. However, follow up of children who have febrile convulsions following DTP vaccination shows no adverse outcomes[50] and the risk of febrile convulsions from whooping cough itself is likely to be significantly greater.[51] Experience suggests that no major problems occur when children with a history of convulsions are vaccinated with DTP[52-55] and such conditions are now considered only as precautions. Risk of febrile reactions can be further reduced by the use of vaccines containing acellular pertussis and by giving advice on the prophylaxis and management of fever.

Children with stable pre-existing neurological conditions such as spina bifida should be immunised according to the recommended schedule. With respect to vaccinating children with current neurological deterioration, the main concern has been to avoid wrongly attributing any worsening of the condition to the vaccine. To avoid this, deferral of immunisation is usually recommended in the UK until the cause is identified or the condition has stabilised.[1]

2.2 Neurological Conditions Following Vaccination

In addition to children with underlying conditions, those children who develop neurological conditions following vaccination have often been denied further pertussis immunisation. This relates to concern from the early 1970s that pertussis vaccine may cause encephalopathy and, therefore, that a second dose of vaccine could lead to a deterioration of that condition. Research suggested that pertussis vaccine may be responsible for such conditions, but at a very low rate (approximately 1 in 300 000 doses).[56] In Australia and the US, therefore, 'encephalopathy not attributable to another identifiable cause' occurring within 7 days of pertussis vaccination is included in their list of contraindications.[2,3] Subsequent review of the data on pertussis vaccine and severe neurological illness has concluded that even this low risk may be incorrect. In 1994, the US Institute of Medicine review concluded that the available evidence was "insufficient to indicate a causal relationship between DTP and permanent neurological damage".[57] In light of this low or absent risk and the well substantiated risk of pertussis infection itself,[51] in Canada and the UK neurological illnesses occurring after pertussis vaccine are not absolute contraindications to further vaccination. Where such cases occur in the UK, deferral of vaccination is recommended whilst investigation of other possible causes is undertaken.[1] Vaccination can then be completed once the condition has stabilised.

3. A History of Immunodeficiency

Immune dysfunction due to disease or medical treatment affects the immune response to varying degrees and this will determine the safety and efficacy of certain vaccines in immunocompromised children. Inactivated vaccines can (and should) be given to immunocompromised children, but the response may be suboptimal and may depend on the stage of their treatment. Severe complications (such as disseminated bacilli Calmette-Guérin [BCG] infection or vaccine associated paralytic polio) can follow live vaccinations in immunocompromised children and such vaccines are, therefore, contraindicated in severely immunosuppressed individuals.[5,58]

Severe immunosuppression can be the result of conditions such as congenital immunodeficiency, HIV infection, malignant disease, organ or bone marrow transplantation or treatments such as chemotherapy, radiation or prolonged high dose corticosteroids. Not all live vaccines are contraindicated for all conditions and in certain circumstances they are recommended (see sections 3.1 and 3.2). Live vaccines should also not be ruled out completely for children with these conditions as it may be possible for such vaccines to be given before treatment is commenced or once they have completed their treatment and a sufficient time period has lapsed for the vaccines to be safe and effective. Therefore, before considering vaccination for children with immunocompromising conditions, the degree of their immunosuppression should always be determined by their specialist and the options for vaccination discussed. The decision to give or withhold a vaccine should be considered on a careful, case-by-case review of the benefits and risks.

3.1 Corticosteroid Treatment

The recommendations vary from country to country with respect to the dose and duration of administration for oral or rectal corticosteroids that

contraindicate live vaccination. This may be because the exact amount of systemic corticosteroids needed to suppress the immune system is ill-defined.[59] A dosage of 2 mg/kg/day is considered to be sufficiently immunosuppressive to question the use of live vaccines where it has been given for more than 1 (UK,[5] Australia[2]) or 2 weeks (US[3] Canada[4]). Topical and inhaled corticosteroids are not thought to be immunosuppressive and are, therefore, not a contraindication to live vaccinations.

3.2 HIV Infection and Measles-Mumps-Rubella Vaccine

Although live vaccines are contraindicated for most immunocompromising conditions, the MMR vaccine is recommended for children with HIV infections who do not show evidence of severe immunosuppression (as ascertained through their CD4 lymphocyte count[60]) since they are at increased risk for severe complications from measles infection.[13,61]

3.3 Contacts of Immunosuppressed Individuals

It is important to ensure that the family and close contacts of the immunocompromised child are fully immunised to provide indirect protection to the child by reducing their chances of exposure. This can be done safely and effectively with the majority of vaccines. However, where oral polio vaccine is still available, there is a risk of transmission of the vaccine viruses to immunocompromised children. Inactivated polio vaccine should, therefore, be given to the close and household contacts of these children.[62] MMR vaccine viruses are not transmitted to contacts[5,13,58] and the transmission of varicella vaccine virus is very rare.[63,64] These two vaccinations are, therefore, strongly recommended for all family members and close contacts of vulnerable children.

4. Other Precautions for Routine Vaccines

A precaution is a condition in a patient that may increase the chance of a serious adverse effect or that may compromise the ability of the vaccine to produce immunity. A vaccination may need to be deferred when a precaution such as short-term immunocompromising treatment or acute illness is present. However, in some circumstances a vaccination may be indicated if, after careful assessment, the benefit for the individual from the vaccination is judged to outweigh the risk.

4.1 Acute Illness

Minor infection is not a reason to postpone immunisation. Although one study[65] found that infants with colds are less likely to seroconvert after measles vaccination, subsequent studies have concluded that seroconversion to MMR is not significantly affected by the presence of a concurrent or recent respiratory tract infection[66] and that MMR vaccine is both safe and efficacious in children who present with mild illness.[67] Illnesses such as respiratory tract infections, otitis media and diarrhoea are so common in children that postponing vaccination because of minor illness could result in many children missing out on vaccination altogether. However, vaccination should be postponed in children experiencing moderate or severe acute illness until they have recovered. This is to avoid imposing vaccine reactions on an unwell child or wrongly attributing progression of symptoms to vaccination.

4.2 Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) has been reported following administration of MMR vaccine. This is a rare adverse reaction – the absolute risk is estimated to be 1 in every 22 300 doses given.[68] The precise mechanism of the reaction is unclear and the risk of recurrence is not known. If the mechanism is a type II hypersensitivity reaction, then a theoretical risk of a second episode exists. The risk of ITP following natural rubella infection is estimated to be approximately 1 in 3000 cases[68] and thus in susceptible children the risk of disease far outweighs the risk of revaccination. Vaccine-associated cases of ITP also tend to be milder than those occurring naturally. Serological testing is, therefore, recommended for all children who have experienced an episode of ITP within 6 weeks of their first dose of MMR. The vaccine should then be given to children who are seronegative to any antigen on the grounds that the beneficial protection

against wild virus infection outweighs the theoretical possibility of a recurrence of ITP.

5. Discussion

The current list of contraindications to vaccination in the UK, Australia, the US and Canada (table I) is shorter than the list of contraindications recommended by the WHO in 1988.[62] However, some European countries are still using more extensive lists of contraindications that may discourage high coverage of immunisation.[69] The use of an extensive list of contraindications in the Russian Federation was thought to be a major cause for the re-emergence of diphtheria in the 1990s.[70] Since then, efforts have been made to reduce the false contraindications that were previously applied.

Both contraindications and precautions are described in detail in national immunisation guidelines and product information. However, recommendations on contraindications to specific immunisations often differ between expert advisory committees and those of the vaccine manufacturer. Whereas an expert advisory committee aims to safely and effectively vaccinate as many children as possible, advice in a manufacturer's product information may be more cautious, particularly since licensure of their product is based mainly on pre-licensing studies in healthy children. The UK now states that where the recommendations of the Joint Committee on Vaccination and Immunisation (JCVI) differ from the manufacturer's summary of product characteristics, the recommendations of the JCVI should be followed.[1] It is hoped that in this way, unnecessary contraindications and precautions will no longer stand as barriers to immunisation. Health professionals can then follow advice in accordance with national policy that has taken into account both the risks of withholding and of giving a vaccine.

Many specialist advisory clinics have been set up to advise parents and immunise children with complex histories. This helps to avoid children missing out on immunisation because of physician wariness about immunising or re-immunising such children. Until healthcare professionals become confident in the revised recommendations that most children can be safely re-vaccinated, these specialist clinics will provide the means to ensure that children are given the opportunity to be fully protected.

6. Conclusions

No child should be denied immunisation without serious thought to the consequences.[5] Ongoing exchange of information between countries and constant surveillance of adverse events following immunisation will add to the evidence base for expert advisory groups. This information is vital to reassure healthcare professionals that previously held contraindications have been sufficiently investigated to warrant dismissal. Such professionals should feel confident in accepting these new recommendations for immunisation and be reassured that they are doing their best to protect their patients.

Acknowledgements

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study.

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