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The complex link between immunization against childhood diseases and allergy

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Vaccines can be at the origin of allergic manifestations in susceptible children. Such manifestations include: immediate-type hypersensitivity (anaphylactic shock, rash or angioedema) within 1 h after the injection; semi-late hypersensitivity (local inflammatory lesion such as the Arthus phenomenon) a few hours after the injection; and delayed-type hypersensitivity (abscess or eczema at the site of the injection). Furthermore, early-life vaccinations have been implicated in the modulation of the immune system as they could promote the development of allergy by avoiding infections. However, most population-based studies have not found an increased risk of allergies in vaccinated children. Due to methodological problems in conducting the studies, further investigations are needed to better understand the phenomenon.

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The relationship between the immunization against childhood diseases and allergy is complex. On the one hand, some vaccines can be at the origin of allergic manifestations in susceptible children [1–6]. On the other hand, recent epidemiological data have shown that some childhood vaccinations intervene in the modulation of the immune system, by the promotion of particular lymphocyte subpopulations [7]. The latter phenomenon seems to depend on the window of exposure to immunization, among other factors.

Allergic reactions following childhood immunization

It is well documented in the medical literature that routine vaccination can result in allergic reactions [1–3], which are more or less dependent on certain components of the vaccines. However, as with any medication, vaccines can have side effects that are not allergic, such as fever, rash or local redness, or swelling. For example, the measles, mumps and rubella (MMR) vaccine can cause a rash that occurs approximately 7–10 days after administration of the injection; this is not an allergic reaction but a side effect of the MMR vaccine itself.

The allergic reactions reported after vaccination [6] are rare but not negligible and include the immediate-type hypersensitivity (anaphylactic shock, rash, angioedema or shortness of breath almost immediately or within 1 after the injection); semi-late hypersensitivity (local inflammatory lesion, such as the Arthus phenomenon a few hours after the injection, serum sickness or vasculitis); and delayed-type hypersensitivity (sterile abscess, eczema at the site of the injection and exacerbation of atopic dermatitis). The antigenic substances could be the vaccinated antigens (i.e., inactivated or live-attenuated microorganisms, viruses, antitoxins or purified antigens), the conservators (formaldehyde, mercurothiolate or phenol), the additives (aluminum hydroxide, dextran, glutamate, saccharose, lactose/maltose, human serum albumin or gelatine), the antibiotics (mostly neomycin), and various contaminants of the culture environment (i.e., egg proteins or propionolactone).

In theory, if an individual is allergic to eggs, then he/she may be allergic to egg-based vaccines, including the MMR [8], influenza, rabies, yellow fever [9] and tick-borne encephalitis vaccines. This is what was thought years ago and, consequently, many egg-allergic children did

not receive the MMR vaccine. However, it was finally recognized that very few egg-allergic children were actually allergic to the MMR vaccine [4,5,10,11]. Skin tests can be performed for the MMR vaccine itself. If, based on these tests, an egg-allergic child is not allergic to the MMR vaccine, then he or she can be vaccinated without any problem. Current expert recommendations are to vaccinate almost all egg-allergic children with the MMR vaccine, without any specific MMR allergy testing. However, this does not apply to other egg-based vaccines, such as the influenza virus vaccine [4,5,10].

The IgE-dependent allergic reactions to the gelatine [12–14] and the neomycin contained in MMR are more frequent than the allergic reactions related to the presence of egg proteins (negligible quantity) in this vaccine. Other gelatine-containing vaccines are those against chickenpox and Japanese encephalitis and, in Japan, associated vaccines including the diphtheria, tetanus, pertussis (whooping cough/*Bordetella pertussis*) and polio (DTP–polio)/Tétracoq [15]. Some of the reactions to these vaccines can occur in patients with a history of allergy to gelatine-containing food, but the diagnosis is based upon positive skin tests with the vaccine and gelatine. The allergological work-up includes immediate-reading skin-prick test with the vaccine (1:10) and intradermal reaction test (IDR) (1:100) [16,17] and skin-prick test with the gelatine (1:10) [16], and measurements of specific IgE for gelatine. These tests have a good diagnostic value but their predictive value remains controversial [18]. Current recommendations for the vaccination of children allergic to gelatine are to use a desensitization procedure, under medical supervision in a hospital or a medical center if the vaccine is considered essential.

Thimerosal, an organic compound with bactericidal and fungicidal action, may give mild local hypersensitivity reactions, including redness and swelling at the site of the injections. In 1999, concerns of toxicity associated with a possible rise in neurodevelopmental disorders among children vaccinated with thimerosal-containing vaccines [19], led the American Academy of Pediatrics and the US Public Health Service to issue a joint statement calling for its removal. Although there was no convincing evidence of a causal association [20], thimerosal is no longer used as a vaccine preservative in Europe and the USA, but is still used in other countries.

Some people are allergic to the diphtheria tetanus (DT) vaccine that is administered routinely during the first years of life. Other newer vaccines have been developed using the DT as a base. Such DT-based vaccines include the meningitis vaccines. Thus, an individual with an allergy to DT can, theoretically, be allergic to a DT-based meningitis vaccine. In addition, specific allergy testing for DT may be helpful. Various reactions of allergic aspect were also reported at the time of first vaccination or follow-up injections of DTP–polio/Tétracoq or Pentacoq vaccines. Associated vaccines, including DTP–polio/Tétracoq or Pentacoq, contain an important quantity of substances, such as anatoxins, bacterial polysaccharides, glycoproteins, which can activate the alternative pathway of the complement system, as well as the coagulation system and the kallikrein–kinin system.

This activation may result in increase of proinflammatory factors in the blood and induce the allergic reactions in the bronchial tree or the skin. As far as these associated vaccines are concerned, most of the children show a good tolerance of follow-up injections [21] and especially when these follow-up injections are made with the dissociated ingredients of the vaccines (DTP, polio, antihaemophilus), within an interval of a few days [22]. The rare anaphylactoid reactions after neonatal vaccination with BCG, related to the dextran contained in the Bacillus Calmette–Guérin (BCG) vaccine, are caused by the transplacental passage of maternal IgG anti-dextran. An anaphylactoid reaction was also observed in an adolescent after BCG revaccination [23]. Their diagnosis is based on the detection of the IgM/IgG antidextran antibodies in maternal blood or in the umbilical cord blood from the neonate a few weeks after the reaction. It must be noted that Holt *et al.* studied the efficacy of DTP vaccine in atopic and nonatopic children and found no significant differences in their specific antibody production [24].

In clinical practice, a physician should take a detailed personal and parental history, with detailed information about any symptoms that suggest allergy to egg proteins or gelatine, and about the type, severity and timing of any reaction to the previous injections of vaccines, should analyze the composition of the suspected vaccine and, finally, should calculate the risk and benefit of a follow up vaccination. Normally, the vaccination of allergic children should be performed under special precautions. For the atopics, two distinct situations must be considered: on the one hand, the problem of the vaccination of a subject (probably) allergic to one of the components of the vaccine, and, on the other hand, the risk of reactions related to environmental allergens, but triggered by the injection of a vaccine ('flash' phenomenon) [5].

If an individual is allergic to eggs, he or she should not receive the egg-based vaccine unless specific vaccine skin tests are performed by a specialist. For the prevention of reactions to egg protein-containing vaccines in children with severe IgE-dependent egg allergy, the immediate responses in skin tests with the vaccine have a good predictive value [25]. The prick test is pure or 1:10; the intradermoreaction 1:100. If skin tests are negative, the vaccine is well tolerated in almost all the patients, even if the prick test or the radioallergosorbent test (RAST) to the egg proteins is positive. Therefore, injection of the complete dose of the vaccine can be performed at the child's home or at the doctor's office. If skin tests are positive and vaccination is essential, injection of the vaccine should be performed using a 'desensitization' procedure, under medical supervision in a hospital or a medical centre. For example, a method of 'desensitization' for egg-containing vaccines is performed with injection of 0.05 ml of a 1:100 dilution, then after 15–20 minutes an injection of 0.05 ml of 1:10 dilution, followed by injections of the pure vaccine, in progressively increasing doses (0.05, 0.10 and 0.15 ml) at a 15–20 min interval, preferably to different injection sites and, finally, the rest of the vaccine. Only children with antecedents of anaphylactic reactions with cardiovascular signs after egg ingestion or

consumption of egg-containing food and children with active asthma (requiring a daily basic treatment) should be vaccinated in a hospital, under medical supervision and according to a particular protocol. Children with mild allergy to egg, translated by moderated signs, can be vaccinated without particular precaution [11]. An allergic reaction after vaccination against MMR justifies a specific allergologic exploration and contraindicates the second injection before carrying out a cautious evaluation of any potentially serious consequence of follow-up vaccination [26]. Nevertheless, a few cases of more or less severe anaphylactic reactions have been reported to patients without egg-protein allergy [27,28].

The 'flash' phenomenon is an aggravation of asthma and/or atopic dermatitis, after a decrease in the level of reactivity to environmental allergens, caused by exogenous factors, such as infections, biological and psychological stress, surgical interventions and vaccines. The most frequently accused vaccine is the one against the influenza virus. Evaluations of this vaccine's influence on bronchial reactivity, symptom scores and peak expiratory flow variability in asthmatic patients [29–31], have revealed that the vaccination of an asthmatic against the influenza virus, when carried out following the rules of good practice and in the right conditions, does not generate any significant immunological modifications, does not alter the respiratory functions and has no secondary effects [29,30,32,33].

The recommendations [34] concerning the right conditions of administering a vaccine include:

- Characteristics of the vaccine (degree of purity, limitations of the various vaccine associations);
- The timing (period of long and stable remission of asthma symptoms, spontaneous or with a long-term basic treatment, at distance from the periods of maximal exposition to allergens);
- Eventual increase of the antiallergic and/or antiasthmatic treatment;
- Systemic corticosteroids constitute a relative contraindication for vaccination, especially with live microorganisms;
- A well-tolerated hyposensitization does not contraindicate vaccination.

Influenza vaccination & asthma

There is controversy regarding the use of influenza vaccination [35–39], since it may precipitate an asthma attack in certain individuals. Furthermore, influenza viruses have been frequently associated with asthma hospitalizations. Evidence from recently published trials [30,40–42] and a Cochrane database systematic review [43], that aimed to assess its efficacy, indicates that there is no significant increase in asthma exacerbations after vaccination against influenza virus. However, uncertainty remains regarding the degree of protection that vaccination provides against asthma exacerbations related to influenza [36,42–44]. Therefore, prospective, randomized, double-blind and placebo-controlled trials are needed to confirm its efficacy, as well as to evaluate the direct and indirect benefits

in real conditions. Once relative data are collected and the true burden of complications is defined precisely, a clear evidence-based protocol should be designed in order to reassure doctors and parents of the importance, efficacy and safety of childhood immunization. A recent study comparing inactivated and live-attenuated influenza vaccines in USA children with asthma demonstrated superior protection by the latter. However, this indication has to be considered by the US FDA [45]. Studies on the efficacy and safety of influenza vaccines are useful because universal vaccination of all children will facilitate control of epidemic influenza and provide an infrastructure for the control of future influenza pandemics.

Early immunization as a modifier of the immune system

Concerns regarding allergic side effects of childhood vaccination and about a possible promotion of atopic diseases after immunization, have caused a loss of confidence in vaccines providing efficient protection against infectious diseases and have resulted in a decrease in vaccination rates [34,46]. Many parents and physicians wonder whether the current vaccinations of the child during the first years of life, are likely to modify the immune system and the risk of sensitization to environmental allergens and, therefore, to influence the risk of atopy.

Although there is not yet sufficient evidence on the role of routine vaccinations in the development of allergic sensitization and diseases, the 'hygiene hypothesis' suggests that excessive hygiene (many vaccinations, antibiotics) can increase the risk of development of allergic diseases by reducing the infectious risk, in particular the risk of viral infections, which are supposed to direct the immune system towards a humoral response of the Th1 lymphocyte type. However, live-attenuated vaccines might promote proliferation of Th1 lymphocytes, which would inhibit the response of the Th2 lymphocyte type and thus the production of Ig E, which characterizes the body's allergic response. More recent immunological concepts put the accent on the central role of regulatory T cells, controlling the responses of other immunocytes by secretion of cytokines and other mediators and their complex interactions. Their activity appears to be essential not only for the maintenance of immunological tolerance but also in the control of all physiological immune responses whether against normal self-proteins, microbes or cancerous cells.

Whereas there are few experimental data on the effects of vaccines on the development of the allergic response (the production of IgE), a lot of epidemiological studies have investigated the relationship between vaccinations and atopic dermatitis, rhinitis and/or asthma [7,47,48]. Most of these studies have biases such as their retrospective design, with an important variation of vaccination patterns, schedules and types of vaccines, the diversity of the studied populations, the insufficient number of subjects, and the low numbers of nonvaccinated individuals (TABLE 1). Furthermore, potential confounders have rarely been taken into account in these studies.

Table 1. Studies relating different vaccines with allergy .

Study	Population	Vaccines studied	Relation	Comments	Ref.
Alm <i>et al.</i>	295 children from anthroposophic families and 380 control children	BCG Other vaccines	0 +	Atopy estimated by SPT and RAST Possible interference of other factors	[49]
Kemp <i>et al.</i>	1625 children 5–16 years	DTP–polio	+	Questionnaires Small size of unvaccinated children	[50]
Hurwitz <i>et al.</i>	13,944 children 2 months–16 years	DTP/tetanus	+	Small size of unvaccinated children	[51]
Olesen <i>et al.</i>	9740 children 3–15 years	MMR	+	Questionnaires Effects on atopic dermatitis	[52]
Henderson <i>et al.</i>	10,000 unselected children 4 years	Pertussis	0	Birth cohort study	[53]
Stannegard <i>et al.</i>	6497 children 4–9 years	BCG	0	Questionnaires IDR (tuberculin PPD, <i>Mycobacterium avium</i> , <i>Mycobacterium scrofulaceum</i>)	[54]
Yilmaz <i>et al.</i>	736 children	BCG	0	Total IgE Tuberculin (PPD) test	[55]
Mohrenschlager <i>et al.</i>	1673 children 5–7 years	Early BCG Whole-cell pertussis	0 –		[56]
Maitra <i>et al.</i>	6463 children 7 years	Pertussis	0	Birth cohort study	[57]
Nilsson <i>et al.</i>	667 children 7 years	Pertussis	0	Follow-up of a randomized controlled trial Questionnaires, SPT	[58]
Annus <i>et al.</i>	979 children 10–11 years	Neonatal BCG	0	Questionnaires, SPT	[59]
Bager <i>et al.</i>	2000 women	BCG (age of vaccination 0–15 years)	0	Birth cohort study Telephone interviews, RAST	[60]
Gruber <i>et al.</i>	774 children 6 years	BCG	0	Prospectively followed birth cohort	[61]
Marks <i>et al.</i>	751 children 7–14 years	Neonatal BCG	0	Prospective study SPT, total IgE, RAST, spirometry, methacholine challenge	[62]
Koppen <i>et al.</i>	Review of epidemiological studies	All vaccines	0	Meta-analysis	[63]
McKeever <i>et al.</i>	29,238 children 0–11 years	All vaccines	0	Birth cohort Large longitudinal primary care data set	[64]
Anderson <i>et al.</i>	Children per center; median (range): 6–7 years: 2996 (1104–6533) 13–14 years: 3064 (1046–11,400)	DTP	–	154 ISAAC centers in 56 countries WHO database and local data on vaccination	[66]
Jedrychowski	1005 school children	Measles	–	3-year follow-up study	[67]

+: Positive relationship: lower vaccination coverage – fewer allergic manifestations.

0: No relationship.

–: Inverse relationship: vaccinated children – fewer allergic manifestations.

BCG: Bacillus Calmette–Guerin; DTP: Diphtheria, tetanus, pertussis; ISAAC: International Study of Asthma and Allergies in Childhood; MMR: Measles, mumps, rubella;

PPD: Purified protein derivative; RAST: Radioallergosorbent test; SPT: Skin-prick test.

Table 1. Studies relating different vaccines with allergy (cont.).

Study	Population	Vaccines studied	Relation	Comments	Ref.
Gruber <i>et al.</i>	1000 unselected children 5 years	Pertussis, MMR, influenza	-	Birth cohort Total IgE, SPT, RAST	[47]
Aaby <i>et al.</i>	400 children 3–14 years	BCG	-	SPT	[68]
Gruber <i>et al.</i>	38,808 children 6 years	BCG	-	For asthma but not for AD or allergic rhinitis	[69,70]
Bernsen <i>et al.</i>	1724 children of 700 families	Whole-cell pertussis	-	Possible confounders: other vaccine components (DT polio or other vaccinations)	[71]
Da Cunha <i>et al.</i>	1612 children 12–16 years	Neonatal BCG	-	Cross-sectional study Questionnaires	[72]
Martignon <i>et al.</i>	718 adolescents General population	Live attenuated vaccines (oral poliomyelitis, BCG)	-	Questionnaires All vaccines and their type (live, inactivated, attenuated) taken into account	[7]

+: Positive relationship: lower vaccination coverage – fewer allergic manifestations.

0: No relationship.

-: Inverse relationship: vaccinated children – fewer allergic manifestations.

BCG: Bacillus Calmette–Guerin; DTP: Diphtheria, tetanus, pertussis; ISAAC: International Study of Asthma and Allergies in Childhood; MMR: Measles, mumps, rubella;

PPD: Purified protein derivative; RAST: Radioallergosorbent test; SPT: Skin-prick test.

Positive relationship: fewer allergies following a lower vaccination coverage

Alm *et al.* found a significantly decreased prevalence of atopy (estimated by skin prick tests and RAST to common aero-allergens) in the children of families with anthroposophic life-style (RR = 0.62), with rural or semirural housing, big family size, frequent childbirth in residence, prolonged breast-feeding, diet with fresh and fermented food, limited smoking, and use of antibiotics and vaccinations limited to a bare minimum [49]. However, this decrease could be due to other factors than vaccinations. Some other cross-sectional retrospective studies indicated fewer allergic manifestations among children with lower vaccination coverage. In a study of 1625 children from New Zealand, aged 5–16 years, with a questionnaire completed by their parents (vaccines, atopy and history of infections), Kemp *et al.* did not find any correlation between atopy and the type and frequency of past infections, but noted a higher prevalence of atopy in children vaccinated with DTP–polio [50]. In a sample of 13,944 children, aged from 2 months to 16 years, in the USA, Hurwitz *et al.* found a higher relative risk for asthma and allergy (proved or presumed) in children vaccinated with DTP [51]. However, we should note that these two studies are hampered by the small size of unvaccinated subsamples. Olesen found a favoring effect, as atopic dermatitis increased following vaccination for measles, mumps and rubella or after measles infection [52].

No relationship

In a prospective study of 10,000 unselected children, followed from birth to the age of 4 years, Henderson *et al.* did not find any significant influence (positive or negative) of the pertussis vaccination on the frequency and the number of asthma/wheezing episodes [53]. Strannegard *et al.* found no significant relation

between atopy and vaccination with BCG, in a study undertaken in Sweden among 4–9-year-old children [54]. In addition Yilmaz *et al.* found no significant correlations between clinical history of atopy, total IgE and cutaneous reactivity with tuberculin purified protein derivative (PPD) in Turkish children vaccinated with BCG [55]. Similarly, in the MIRIAM study, BCG vaccination was not correlated to higher prevalence of asthma, allergic rhinitis, eczema or allergic sensitization at preschool age [56]. Other authors found no significant effect in atopy of vaccines for pertussis [57,58], BCG [49,59–62] and all vaccinations [63–65].

Inverse relationship: fewer allergies in vaccinated children

An international study relating national immunization rates in 56 countries to the prevalence of allergic manifestations in the corresponding regions found a negative association of DTP and measles immunization rates and IgE-mediated disease [66]. In the same direction, in a prospective cohort study of 1000 unselected children in Germany, followed from birth to the age of 5 years, Grüber *et al.* found that the cumulative doses of any vaccine given up to 5 years of age (pertussis, MMR, *Haemophilus influenzae*), was inversely related to atopic dermatitis and asthma prevalence and allergic sensitization rates (total IgE, skin-prick tests and RASTs to common allergens). The study concluded that children with a higher vaccination coverage seemed to be transiently better protected against development of atopy in the first years of life [47]. Similarly, in a 3-year follow-up study in Poland, Jedrychowski *et al.* showed that the risk of allergy and asthma in vaccinated children was approximately half of that in the reference group [67].

Aaby *et al.* measured the skin test reactivity to three allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and cockroach) in 400 African children, aged from 3 to 14 years,

and after adjusting for potential confounders found that BCG vaccination given early in infancy may prevent the development of atopy in African children [68]. A limitation of this study is the possible influence of the anthroposophic lifestyle of participating children.

Gruber *et al.* studied the correlations between the prevalence of the various atopic diseases and early vaccination with BCG of preschool children born in Germany and concluded that vaccination with the BCG slightly decreases the relative risk of asthma, but not of atopic dermatitis nor of allergic rhinitis, whatever the ethnic origin and the place of residence of the children [69,70]. Finally, in a prospective study of Australian children, Marks *et al.* explored the correlations between the prevalence of the various atopic diseases and neonatal vaccination by BCG [62]. They studied the relative risk of atopy, atopic dermatitis, allergic rhinitis, bronchial hyper-reactivity and asthma, according to the existence or the absence of neonatal vaccination by BCG and according to the family history of atopy and concluded that vaccination by BCG decreases the relative risk of asthma, but only in the children with parental history of allergy and, therefore, high atopic risk. Bernsen [71] and da Cunha [72] concluded that vaccination for pertussis and BCG, respectively, had a protective effect. In our study, after adjustment for sex, age, father's socioeconomic status and active smoking, adolescents having been vaccinated had a significantly lower risk of suffering from asthma or atopic diseases than nonvaccinated adolescents did [7]. The relationship did not depend on the disease against which the vaccine was used as prophylaxis, the observance of the vaccination schedule or the number of inoculations. However, a higher protection was observed in the case of live-attenuated vaccines (oral poliomyelitis and BCG). Although retrospective, the information collected in our investigation was based on the compulsory routine form filled by general practitioners or pediatricians of the individuals, which allowed knowing in detail the type of vaccination. These results, in agreement with previous ecological data, support the hypothesis that early vaccines could promote Th1 proliferation in response to the infectious agent contained in it, which inhibits the enhancement of atopic manifestations. As already underlined, 'not finding an increased risk' of allergies in vaccinated individuals is not the same as 'the nonexistence of any risk at all', and other studies are needed.

Conclusion

In conclusion, routine childhood vaccination has comparable efficacy in atopic and nonatopic subjects, and there is no convincing evidence that it promotes the development of atopy. Atopy may amplify the Th2-dependent regular response to some antigens contained in vaccines, but immunization does not further increase the risk for allergy. As the risks of not vaccinating seem to far outweigh the questionable risks of vaccine-induced allergy, guidelines for routine immunization programs should include atopic, as well as nonatopic, children. Moreover, vaccines against infections with potentially life-threatening or disabling risks are recommended to the allergic asthmatics. As most epidemiological data are retrospective and ecological, or

based on reports, it is essential to undertake prospective randomized studies of broad spectrum, with the participation of multiple centers and a rigorous standardization of the types of vaccines and the vaccinating methods, settings and schedules. For the purpose of correct randomization, we should deal with the ethical and legal problem of how to leave unvaccinated – and subsequently unprotected against various infections – a large part of the population.

Expert commentary & five-year view

Future challenges are to produce new vaccines that were impossible to develop so far, in order to prevent infectious diseases, neoplasms or to be used as new therapeutic options for autoimmune diseases and allergic disorders (desensitization). Multicenter randomized prospective studies of great amplitude, double-blind, placebo-controlled and effectuated with the same vaccines and standardized methods, are needed for the appropriate use of vaccination at the population level, allowing safety and efficacy.

Overcoming neonatal vaccination difficulties

Limitations of neonatal immune responses, including slower and weaker antibody responses, result from suboptimal interactions between antigen-presenting cells (APCs) and T cells, in addition to inhibitory influence of maternal antibodies, and could be overcome in the future by specific adjuvants/delivery systems ensuring optimal early-life immunogenicity and safety profiles.

Thymic vaccination, TLR & CpG ODN

The discovery of a new class of receptors, involved in recognition of patterns characteristic of groups of microorganisms (Toll-like receptors) elucidated the discriminating role of the innate immune system. Recent advances involving the structural basis of immune recognition have made feasible the selective processing and presentation of exogenous or endogenous antigens. In contrast with conventional vaccines which expand pre-existing peripheral T cells, thymic vaccination designs T-cell repertoires by utilizing peptides distinct from the antigen against which a T-cell receptor is directed.

Several prime-boost immunization strategies optimize the induction of strong effector and regulator T-cell responses with a new generation of T-cell-inducing vaccines. Selective use of synthetic oligonucleotides containing unmethylated CpG motifs as vaccine adjuvants can stimulate lymphocytes, natural killer cells and APCs to produce immunoglobulins, cytokines and/or chemokines and, therefore, significantly boost the immune response to coadministered vaccine antigens and improve vaccine efficacy.

Transcutaneous vaccinations & dendritic cell-targeting vaccines

Transcutaneous (patch-based) immunization has emerged recently as a new simple and safe method of vaccination that utilizes a wide variety of potent adjuvants that activate Langerhans cells in the skin, amplify their APC function and induce adaptive

immune responses towards infections. New vectors delivering signals that are capable of triggering dendritic cell maturation, will play a central role in the development of efficient vaccines.

Gene therapy & informatics

Biochemical, serological and microbiological methods have been used up to now to dissect pathogens and identify the components that are useful for vaccine development. New genomic approaches for vaccine development using nonconventional antigens, independently of their abundance and immunogenicity during infection, exploit nonconventional arms of the immune system, without the need to grow the pathogen *in vitro*, for example a new vaccine against serogroup B meningococcus. Armed with powerful informatics tools and extensive databases, including that of the human genome and complete genome sequences of the leading human pathogens such as *Mycobacterium tuberculosis*, vaccines developed in the next few years will prevent tuberculosis using hypotheses derived *in silico*. Other genetic tools are also available, enabling the transfer of DNA into *Mycobacteria* and their attenuation by the inactivation of genes (by allelic replacement), which provides a level of protection similar to that conferred by BCG. DNA vaccination effectively establishes long lasting cytotoxic T-cell memory and protection against tuberculosis. Moreover, genetic therapy could prevent infection and work as a therapeutic agent in infected individuals blocking reactivation of latent infection. Conventional drugs in association with gene therapy could also reduce the length of treatment.

Edible plant vaccines

On a different level, plants such as the potato provide economical protein expression systems and produce complex antibodies, including secretory IgA, as well as antigenic proteins for vaccine use that stimulate systemic and mucosal immune responses.

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Key issues

- There is a lack of sound evidence of a causal relationship between vaccinations and atopic diseases, and the potential vaccine-associated adverse effects are self-limited and not frequent.
- Vaccines may originate allergic manifestations in susceptible individuals. Immediate-type hypersensitivity is the most frequent manifestation.
- Most population-based studies have not found an increased risk of allergies in vaccinated children.

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