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Review article

# Obesity, immunity and vaccination☆

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ABSTRACT

Vaccines are a fundamental tool in the prevention of infectious diseases. Following vaccination, a complex interaction takes place between the vaccine product and the recipient's immune system, the result of which is protection against the disease. High variability is observed in both individual and population immune responses to vaccination; at present, these differences are not well understood. Some well-studied receptor factors such as age, sex, genetics, immune history... however, others such as overweight and obesity are less well known. There is evidence that a very high body mass index is an important risk factor for infections in general and that fatty tissue has a clear role in modulating the immune system; suboptimal levels of vaccine seroconversion have also been observed in obese people. Throughout the document a review of the immunity and protection induced by various vaccines in overweight people is presented. Reactogenicity to vaccines in people is also being studied. Finally, the relationship between the microbiome, immunity and obesity, which is the subject of recent research, is exposed.



## Obesidad, inmunidad y vacunación

*Palabras clave:*
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RESUMEN

Las vacunas constituyen una herramienta fundamental en la prevención de las enfermedades infecciosas. Tras la vacunación tiene lugar a una compleja interacción entre el producto vacunal y el sistema inmunitario del receptor, cuyo resultado es la protección frente a la enfermedad. Se observa una elevada variabilidad en las respuestas inmunitarias a la vacunación tanto individuales como poblacionales; en la actualidad, estas diferencias no son bien comprendidas. Se conocen algunos factores del receptor bien estudiados como la edad, el sexo, la genética, el historial inmunológico... sin embargo, otros como el sobrepeso y la obesidad son menos conocidos. Existe evidencia de que un índice de masa corporal muy alto es un factor de riesgo importante para las infecciones en general y de que el

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tejido graso tiene un papel claro en la modulación del sistema inmunitario; también se han observado niveles subóptimos de seroconversión vacunal en personas obesas. A lo largo del documento se ha revisado la inmunidad y a la protección inducidas por diversas vacunas en personas con sobrepeso. Se estudia también la reactogenicidad a las vacunas en personas. Finalmente se expone la relación entre microbioma, inmunidad y obesidad que es motivo de recientes investigaciones.



## Introduction

Overweight and obesity is an ever-growing public health problem worldwide, affecting all age groups. Both are considered to be multifactorial diseases leading to excessive accumulation of fatty tissue. The World Health Organisation (WHO) currently estimates there are over 2500 million overweight adult people in the world, of whom approximately 650 million are obese.[1] Obesity worldwide has almost tripled since 1975. These figures led the World Health Assembly to declare obesity in 2004 as the epidemic of the 21st century. If current trends continue, projections indicate that by 2030 almost 40% of the world's population will be overweight and one out of every 5 individuals will be obese.[2] Although one of the objectives of the WHO for 2025 is to significantly reduce this rise and even invert it, the immense majority of experts on obesity consider this is hardly probable or improbable.

Regarding overweight and obesity in children and youth, figures are no more optimistic. Excess weight in the youngest population groups continues being considered one of the major public health problems, affecting both developed and developing countries, the latter being those which currently present with the fastest rise in figures.[3] In 2019, the WHO estimated that 38.2 million children under 5 were overweight or obese.

The problem of child-youth obesity is worrying because of its magnitude, but also because it tends to remain in adult life, which constitutes a major risk factor for suffering from other diseases.[4] Becoming obese in the second decade of life is a predictive factor for suffering from obesity in adult life. Being obese for a prolonged period is associated with a higher risk of cardiovascular diseases, inflammatory disease, diabetes, and cancer, among others.[5,6] Apart from a health problem, obesity has other social and financial implications which require appropriate consideration and planning.

Overweight and obesity are defined as an excessive accumulation of fatty tissue which is considered damaging to health. It may be measured by the body mass index (BMI) also known as the Quetelet index, which is calculated by dividing a person's weight in kilograms by their height in metres. The BMI classifies people into low weight (IMC $\leq$ 18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$), obese (30.0–34.9 kg/m$^2$) and severely obese ($\geq$35 kg/m$^2$).

At present obesity is considered a nutritional disorder with its origin in interaction between genetic, environmental, and behavioural factors, with the latter factor perhaps being the most important.[7] The result and sum of these factors has been that in the last 3 decades a sharp increase in overweight and obesity has occurred in the population of the European Union and on a worldwide level.

Today's association between obesity and the development of numerous chronic diseases is well established. Obesity is a clear risk factor for the development of multiple diseases such as type 2 diabetes, metabolic syndrome, cardiovascular diseases (mainly cardiopathies and strokes), high blood pressure and cancer (of the oesophagus, colon, breast—in postmenopausal women—endometrium and renal). It is also related to other health problems such as locomotor disorders, respiratory changes (asthma, infections), digestive disorders, psychological (lack of self-esteem, anxiety, depression) and indeed immunological disorders.[8] It is also a major factor, as has been reported, for infections in general and for the development of severe forms of COVID-19 in particular.[9]

## Obesity and the immune system

For many years fatty tissue was considered as a set of cells whose main function was to serve as a fat reserve. An inert tissue from an immune viewpoint. Only a short time ago, further functions were discovered for this tissue and among them, its role in modulation of the immune system.

Adipokines or adipocytokines are a set of immunomodulating molecules produced by fatty tissue.[10] Of these, molecules like leptin stand out (from the Greek *leptos* = thin). Discovered in 1949,[11] one of the most important functions of leptin is that it inhibits appetite. Its blood circulating levels are proportional to the amount of body fat. In other words, the greater the quantity of fatty tissue a person has, the higher the production of leptin.[12] The distribution of leptin through the blood flow leads to different effects. In the hypothalamus it induces synthesis and secretion of molecules that regulate appetite, such as anorectic peptides.[13] Another major effect of leptin is increasing metabolic rate and body temperature, reducing the production of fat (lipogenesis) and increasing its use (lipolysis).[14]

On the other hand, leptin also acts at immunologic levels, over-activating the immune response towards a pro-inflammatory profile. Thus, the greater the amount of body fat, the higher the amount of leptin and consequently higher inflammation.[15]

Another major adipokine is adiponectin. This molecule participates in the metabolism of glucose and fatty acids, increasing sensitivity to insulin, and thereby achieving that this hormone acts more appropriately.[16] It also plays a major role in the establishment of responses tending towards inflammation control.[17] In contrast to what occurs with leptin,

the circulating levels of adiponectin are inversely proportional to the percentage of body fat. Reduced concentrations of adiponectin are usually found in patients with obesity, type 2 diabetes mellitus or coronary arterial disease, and it may be indicative of a poorer prognosis of these diseases.

In view of the antagonistic role of both molecules, it seems obvious to think that obese people who present with a lower production of adiponectin, together with a higher production of leptin, will present with an imbalance towards the presence of pro-inflammatory responses. This may eventually lead to the stimulation of cytokine production of IL1β and IL6, which in turn may increase inflammation levels, reasoned by an increase in the production of acute-phase proteins such as C-reactive protein (CRP), serum amyloid A and hepcidin, among others. This type of inflammation is called low grade chronic inflammation, silent inflammation or metabolic inflammation.[18]

This metabolic inflammation which is common in obese people, is responsible for them having diseases such as type 2 diabetes, high blood pressure and hyperlipidaemia with hypertriglyceridaemia, *i.e.* metabolic syndrome.[19] It does not stop there. A metabolic inflammatory state significantly increases the risk of suffering from several types of allergies such as asthma, autoimmune diseases, several types of cancer, infections, or impaired vaccine responses.[20]

## Obesity and infection

As previously described, obese or overweight people not only present metabolic type changes but also immune type changes. These immune changes also lead to a higher susceptibility and/or severity of infections and poorer response to vaccines.

It has been known for decades that obesity produces changes in the functioning of the majority of immune cells, such as lymphocytes T, B and NK, and also that these patients have macrophages and neutrophils with a lower phagocytic capacity, plus lower intracellular microbicide activity.[21–23] These immune changes are a major and significant way of increasing the susceptibility to infections produced by all types of microorganisms and very particularly by viruses and bacteria,[24–26] with their role in parasitic infections and infestations being controversial.

Several studies report that obese people who are hospitalised are more susceptible to developing bacterial infections and their complications, such as pneumonias,[27] catheter-associated infections[28] and urinary infections,[29] which considerably increase the risk of death. Obese children have double the risk of suffering from severe respiratory infections when they are compared with children of normal weight. Several viruses such as the flu virus produce a higher morbimortality rate in obese individuals.[30–32] Infections are also one of the main causes of postoperative death in the obese patient. The risk of presenting with postoperative infections in patients with grade I obesity increases by 2, in those with grade II obesity this triples and in grade III obesity it is 4 times higher than those which present in people of normal weight.[33] Among the causes of this higher predisposition to get infections are the previously described immune alterations and low level of oxygenation of tissues in obese people, which means any wound healing is delayed or complex.[34] In sum, obesity is a relevant factor that changes body homeostasis, altering the immune-metabolic pathways and this produces an impaired protective response against infections.

## Obesity and response to vaccines

It seems obvious that obesity may interfere in the ability to bring about an effective immune response to infections and is also a major factor which correlates with the reduction of immune response induced by some vaccines.

BMI is an indirect measure used to identify individuals with a higher risk of weight-related health complications[35] and has also been used as an indirect measure of possible impaired vaccine immune response.[36,37]

The first studies to show possible association between obesity and an impaired immune response to vaccines was published in 1985, in a group of obese hospital workers who responded poorly to the hepatitis B vaccine.[38] Twenty-four years later, during the 2009 A/H1N1 flu pandemic, it was confirmed that the obese population were at greater risk of complications associated with this viral infection.[39]

Later studies, in the 21st century, determined that obese people vaccinated against tetanus,[40] or rabies[41] presented with a lower antibody response.

The significant differences described relating to immune response induced by certain vaccines between thin and obese individuals, suggest that medical problems and other types of problems relating to obesity or caused by it, could be the cause of suboptimal levels of vaccine seroconversion reported in these studies.

Considering that obese people present with too low a response to different vaccines maximum effort should be made to guarantee that this population group is protected to the best degree possible. If the daunting, rising figures of worldwide levels of obesity are observed, it seems logical to conclude that a high obesity-associated prevalence of vaccine efficacy failure will be the result. Epidemiologically, this is a relevant fact since the objective of obtaining favourable community protection and immunity rates are hindered in this population. There is therefore an urgent need to conduct further studies to better discover the immune response to different vaccines in obese populations.

### *Obesity and hepatitis B virus infection*

Obesity has been correlated with different diseases, among them non-alcoholic fatty liver disease (NAFLD) or steatosis. Steatosis is associated with liver inflammation, triggering hepatocellular cytotoxicity which can lead to hepatic fibrosis.[42] Since chronic infection by the hepatitis B virus (HBV) can eventually lead to cirrhosis, steatosis in addition to infection by this virus significantly increases the risk of chronic liver disease[43] and also hepatocellular carcinoma.[44]

Four years after the authorisation of the first vaccine against the HBV, Weber et al. conducted a study which showed the considerable reduction of anti-HB antibody protective levels, below 10 mUI/mL, which occurred 11 months

after vaccination in healthcare workers who presented with obesity.[38] Specifically, 55.7% of the people studied had negative results for anti-HB protective titres, with determination of a BMI ≥ 32.88 kg/m$^2$ as one of the highest risk factors to non-response to the vaccine. Given that all the patients received the 3-dose regime with an injection using a 2.5 cm needle, it was speculated that the injection site in the buttock could have played a role in the poor seroconversion of these obese individuals. It could have been the case that a shorter needle would have provoked low seroconversion by accidental inoculation of the antigen in the abundant fatty tissue of these individuals, instead of in the muscle. These same authors conducted a later study using a longer (3.75 cm) needle for the third dose, comparing vaccination in the deltoids to the buttock.[45] This new study reconfirmed the same: an inverse correlation between BMI and the degree of seroconversion. Thus, a BMI > 30 kg/m$^2$ is associated with a low seroconversion titre 17 months after vaccine administration. This research also showed that both age and BMI, but not inoculation site, were significant independent predictors of poor anti-HB antibody titres. Other studies conducted in obese or overweight suckling infants, teenagers and adults continued to show the same correlation between excess weight and impaired immune response to the vaccine.[46–48] The authors suggested that these impaired responses could play a key role in systemic factors related to obesity, beyond the inoculation site.[45]

In 1990, the first vaccines against hepatitis B, obtained from plasma, were replaced by 2 recombinant vaccines: RecOMBIVaX-HB™ and eNGeRIX-B™. Alarm bells again sounded when low titres of anti-HB antibodies were observed in obese people vaccinated with these new vaccines. It was also observed that a high percentage of obese healthcare workers vaccinated with these vaccines, developed anti-HB titres below the level considered protective (<10 mUI/mL).[49] Approximately 11% of people with a BMI between 25 and 35 kg/m$^2$ had a suboptimal response, with low antibody titres. In individuals with a BMI > 35 kg/m$^2$, the percentage of poor responders amounted to 61.5%, with the percentage of non-responders (without a detectable antibody titre) at 45%. These results became even more significant when they were compared with the level of seroconversion in people with a normal BMI, where only 4.3% of them were non-responders or responded poorly. These studies and other posterior ones continued showing obesity as a risk factor for the development of insufficient responses to the HBV vaccine.[50–53]

### *Obesity and the hepatitis A virus*

As with vaccination against hepatitis B, several studies have highlighted that obesity is associated with the induction of a low-level immune response with anti-hepatitis A vaccines. One of these research studies assessed the anti-virus antibody titre of hepatitis A (HAV) in people over 55 years of age, seven months after they had been vaccinated with a combined HAV/HBV vaccine. Again high BMI was identified as the most significantly correlated factor with low anti-HAV antibody titres.[54] Another study observed a slower kinetic antibody response to the anti HPV vaccine in overweight people, despite an increase in response after a second booster dose.[55] However, another study carried out some time after this, did not show any significant differences in the anti-HAV antibody titres among healthy and obese individuals, which suggests that obesity may not significantly affect the seroconversion of vaccination against hepatitis A in some population groups.[56]

### *Obesity and infection by the flu virus*

The main objective of anti-flu vaccination is to neutralise the protein of the haemaglutinin surface area (HA) of the virus. Although some controversy still exists, it is considered that those people who reach specific antibody titres against HA ≥ 1:40, detected using the haemagglutination inhibition trial (HAI), are protected against infection.[57] Obesity is considered as a high-risk factor for poor evolution of infection by the flu virus, especially due to the comorbidities which usually accompany it, in addition to chronic or metabolic cardiovascular diseases.[58,59] In the 2009 flu pandemic, it was observed that people who suffered from severe obesity (BMI ≥ 40 kg/m$^2$), were doubly likely to be hospitalised in the ICU compared with those who were not obese.[60] Regarding response against the flu vaccine, in 2012, Sheridan et al. described how obese people presented with marginally significant increase in antibody titres one month after flu B/Brisbane/60/2008 vaccination compared with those of healthy weight.[61] However, the same study indicates that an increase in BMI could have an inverse correlation with the antibody response 12 months after vaccination. Other research studies have shown that flu vaccine impaired responses in obese people would not differ statistically significantly.[62] Apart from producing specific antibodies, vaccination against flu also stimulates an immune response measured by T lymphocytes[63]; in obese people, this cellular response was represented by a lower percentage of CD8$^+$ activated T lymphocytes (CD8$^+$, CD69$^+$), a lower interferon production (IFN) and granzyme B (GrB) production, essential for the good functioning of these cells.[61]

### *Obesity and anti-tetanus vaccination*

It is currently accepted that anti-tetanus antibody titres ≥.1 UI/ml is a protective serological correlation and that titres >5 UI/mL indicate long-term protection.[64,65] One study carried out in children and adolescents aged between 8 and 17 years with a BMI > 29, reported a significantly lower seroconversion level after vaccination against tetanus than that of the children with a BMI with the ranges of normal. The mean titre of those with a higher BMI was around 2.6 ± .6 UI/mL, whilst the group with a normal BMI presented a mean titre of 4.2 ± .5 UI/mL.[66] In this same study the concentration of IL-6 (pro-inflammatory cytokine) was assessed, confirming that obese children and adolescents have higher levels than healthy controls. The study authors suggest that high IL-6 levels in obese children or overweight children could play a relevant role in the reduction of specific antibody levels against tetanus observed in their study.

### *Obesity and anti-rabies vaccination*

The protection correlation in the anti-rabies vaccination is established when antibody titres equal to or above

.5 UI/mL[67] are presented. The study conducted by Banga et al. in veterinary students describes that overweight students (BMI $\geq$ 25 kg/m$^2$) showed there was a higher probability of producing an inadequate response (lower) of specific antibodies when they were vaccinated against rabies.[68] This effect could also be observed in different animal species. For example, several studies have shown that larger breeds of dogs are a greater risk of developing inadequate antibody responses which do not reach the antibody titre considered to be protective.[69]

### *Obesity, COVID-19 and vaccination against SARS-CoV-2*

The current COVID-19 pandemic, caused by infection by the SARS-CoV-2 virus, has shown that there are certain population groups with a higher risk of developing serious disease and death. From the start there was evidence that older people were particularly vulnerable, and also those with diabetes mellitus or cardiovascular (including high blood pressure), respiratory or renal diseases. In COVID-19, obesity also constitutes a higher risk of suffering from more severe forms of the disease and a higher death rate.[70–72] The study by Simonnet conducted in France (2020), showed that the risk of invasive mechanical ventilation in patients with SARS-CoV-2 infection hospitalised in the ICU, was 7 times higher for those with a BMI > 35 compared with those with a BMI < 25 kg/m$^2$.[71]

Considering the results of the under response observed in numerous vaccines, we could speculate that obesity may also constitute a risk of presenting lower response to anti-COVID-19 vaccines. One recent study by Pellini et al. in 248 healthcare workers where they studied the titres of antibodies 7 days after the second dose with BNT162b2, determined that women, thin people and young people had a higher ability to develop better humoral immune responses compared with men, older people and overweight/obese people.[73] Although further studies are needed, these data may have major implications for the development of vaccination strategies compared against the COVID-19 pandemic, and particularly in obese individuals.[73]

### *Obesity and vaccination against tick-borne encephalitis*

Curiously, the study published by Garner-Spitzer et al., found that vaccination against tick-borne encephalitis (TBE) in obese people led to a specific antibody response which was higher than the control group, although later, 6 months after vaccination, there was a significantly faster reduction of these antibodies, which could have been related to a lower production of memory B cells.[74] This effect was positively correlated to high BMI, leptin levels and insulin levels. A greater frequency of systemic but nonlocal side effects were also observed regarding the vaccination of this group of people, which could be related to the before-mentioned metabolic inflammation which is characteristic of obesity.

## Obesity and vaccine reactogenicity

Some studies in recent years have suggested that the apparent increase of reactogenicity to vaccines in obese and overweight people could be more related to the vaccine administration route than to BMI. One study conducted in 2016 with the trivalent anti-flu vaccine administration stated that the frequency of reaction, both systemic and injection site, was statistically similar between the group of obese and overweight people compared with normal weight controls.[75] A study by Petousis-Harris suggests that babies and young people with a higher body mass index have greater probabilities of having injection site reactions with acellular whooping cough vaccines, possibly due to inadvertent subcutaneous administration.[76] In another study by the same author the possible "observational relationship" was assessed between BMI and reactogenicity produced by the meningococcal vaccine against serogroup B,[77] and they reached the conclusion that individual injection techniques were responsible for these reactions, with there being no relationship with the body mass of the vaccinated individual.

## The role of the microbiome in obesity and immunity

The study of obesity aetiology has come a long way, particularly since the detection of its preoccupying and growing current trend. Compared with recognised risk factors such as diet, lifestyle and socioeconomic and cultural level, the composition of intestinal microbiota has arisen as a relative new factor with an apparently more discreet and as yet little-known role. Everything we know until now suggests that the possible relationships between intestinal microbiota and obesity are complex and intricate.

Several studies in animals (usually mice) selectively colonised by certain bacteria, have led to the establishment of fairly specific associations between microbiota, immunity, inflammation and energetic metabolism. As a result, it is thought that microbiome and in particular the composition of intestinal microbiota could be one of the factors involved in the development of obesity.[78]

It is known that microbiota of most human populations comprises 5 *phyla* (*Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria* and *Verrucomicrobia*), and of these *Bacteroidetes* and *Firmicutes* comprise around 90% of the total bacterial species. In addition to bacteria, we should include protozoa, archaea, fungi, and virus.

Some of the mechanisms proposed by which intestinal microbiota could contribute to the pathogenesis of obesity and to related metabolic diseases are[79]:

1 The large number of bacteria which ferment the carbohydrates, which lead to an increase in biosynthesis rates of short-chain fatty acids (CCFA), providing an extra source of energy for the host, which eventually stores them as lipids or glucose. These CCFA, generated as subproducts of the metabolism of the intestinal microbiota, may stimulate B cell differentiation in plasmatic agents, the secretion of secreting IgA or inhibit IgE.
2 The increase of intestinal permeability to the bacterial lipopolysaccharides (LPS), leads to higher levels of systemic LPS which aggravate low grade inflammation and insulin resistance.
3 An increase in the activity of the intestinal endocannabinoid system.

In recent years it has been speculated whether the relationship between some of the bacterial components of the microbiota (*Bacteroidetes/Firmicutes*) is a contributing factor to the development of obesity. At present some scepticism remains regarding the role of the microbiota in the genesis of obesity in humans, since although some studies have described differences in its composition between obese and thin people, they are difficult to interpret because results often do not concur. Recent publications[80,81] on microbiome from a large amount of faeces simples found no association between BMI and the composition of microbiota. In said Análisis neither the *Bacteroidetes/Firmicutes* relationship nor the microbiota diversity were associated with obesity or BMI.

Notwithstanding, it is not really known whether intestinal microbiota play a significant role in the regulation and development of the immune system. The diverse constitution of the microbiota modulates the activity of the different types of immune cells. The microbiota may define the profile of the T $CD4^+$ T lymphocytes in the intestine and induce some types of regulatory T cells with anti-inflammatory functions.[82] As has been described throughout this review, obesity interferes clearly in the immune response to infectious agents and vaccines, but further understanding is required regarding interactions between the excess of metabolic anomalies relating to fatty tissue and the activity of immune cells. Although it is still not fully understood what the interrelationship between the immune system and the microbiota is, we cannot ignore that the microbiota is able to modulate innate and adaptive immune response to pathogens. In turn, the immune system facilitates tolerance to our own microbes (the billions of microorganisms which inhabit humans, collectively known as microbiome) from birth and throughout our lives, in symbiotic relationships.

Few studies in humans research the impact of intestinal microbiota in vaccine response.[83] These studies suggest that there is a relative predominance of *Actinobacteria* and *Firmicutes* associated with more powerful vaccine responses (humoral and cellular), whilst in contrast, the abundance of the *Proteobacteria* and *Bacteroidetes* groups are related to responses of lower intensity. However, it should be noted that for the moment these clinical studies were carried out in small samples and although it is therefore possible to know some indicative correlations of this association, broader studies are required.[84]

Research studies conducted in young adults and older people who received probiotics (*Bifidobacterium animalis* ssp. *lactis BB-12*® <nx *Lactobacillus paracasei* ssp. *paracasei*, *L. casei 431*®,[85] *Lactobacillus GG*,[86] *Lactobacillus plantarum CECT7315* <nx *CECT7316*,[87] *Lactobacillus*[88]), before and after receiving the inactivated flu vaccine showed specific antibody responses to the vaccine which were significantly higher compared with controls without probiotics.[85–88] The variability of probiotic organisms and the lack of knowledge over whether these really colonise the host, hinder interpretation of the results.

Studies based on the administration of antibiotics to improve the effectiveness of vaccines obtained no obvious results. Some research studies where antibiotics were administered before vaccination against poliomyelitis virus, rotavirus and flu found no improvements in the immunogenicity of these vaccines, compared with the controls without any antibiotic treatment.[89]

Despite increasing evidence of a connection between microbiota and the immune system, its impact in immunogenicity and efficacy of the different vaccines remains little known.[89]

## Conclusions

People who are overweight and especially obese people are more susceptible to infections in general and may respond inadequately to certain vaccines. Strategies to treat obesity and improve immunity in these individuals remains limited. These options include regular exercise, which has been proven to improve vaccine responses and general immunity in older adults,[90] changes to diet which have been effective in increasing innate and adaptive immune responses,[91] pharmacological treatment based on drugs such as paracetamol which blocks the prostaglandin E2 lipid inflammatory mediator and increases the function of innate immune system cells,[92] or metformin which reduces inflammation and increases the function of B lymphocytes both *in vivo* and *in vitro*.[93] Therefore, the development of effective strategies of intervention to reduce inflammation and increase immunity in people with obesity is an important step towards the prevention of infections in this vulnerable population group and an improvement in vaccination responses.

A personalised approach to vaccination with considerations of individual variables such as age, gender, vaccine biography, BMI, diet and other variables of recognised interest, is undoubtedly a decisive step towards the future in the advance towards protection of population groups against vaccine-preventable diseases.[89,94]

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The authors have no conflict of interests to declare.

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