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Immunization practices in athletes

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Summary. *Introduction:* Immunization practices of athletes is a topic of growing interest in preventive medicine. Several reasons contribute to support such statement including: the demonstrated decrease of the immune response of athletes, the recent increase in vaccine-preventable diseases, the increasing mobility of professional athletes and coaches and sports doctors' frequent lack of awareness of on the issue of athletes' immune prophylaxis. *Results:* This review offers a concise and schematic framework to the immunization practices in athletes, based on the most recent scientific evidences and the vaccine schedules proposed by international organizations and scientific societies including the recent "Life Vaccination Schedule" proposed by four Italian Scientific Societies and Professional Associations. *Conclusion:* vaccination in athletes, if correctly managed, represents a powerful, costly and long lasting tool for athletes sport teams. (www.actabiomedica.it)

Key words: vaccination, recommendations, primary prevention, communicable diseases, athletes, sports

Introduction

Immunization practices among athletes is a topic of growing interest in preventive medicine. Several reasons contribute to support such statement and deserve investigation and multidisciplinary collaborations. They include:

a) the recent increase in vaccine-preventable diseases (VPD) (1) and
b) the reported need of immune prophylaxis in major international events (2, 3);
c) the importance of athletes' physical wellness, and their frequently being involved in competitions and trainings close in time;
d) the globalizations of sport events and the increasing mobility of athletes whose performances often take place in regions at high risk for certain infectious diseases;
e) the particular immune response of athletes;
f) the lack of awareness of coaches and sports doctors on the issue of athletes' immune prophylaxis.

This review offers a concise and schematic framework of the immunization practices in athletes, based on the most recent scientific evidence (4-8, 26) and on the vaccine schedules proposed by international organizations and scientific societies including the recent childhood, adult and elderly people vaccination schedules proposed by the Italian Society of Hygiene, Preventive Medicine and Public Health with the collaboration of the Italian professional Associations of General Practictioners and Pediatricians Scientific Societies (6).

Sport and the immune system

The immune system protects the human body against foreign pathogens through early responses (natural immunity) and late responses (acquired immunity).

Natural (or innate) immunity has non-specific effect against the pathogens and it is early activated (approximately within 12 hours) by the contact with the pathogen.

Natural immunity consists of several components:
- epithelia and the antimicrobial substances they produce;
- neutrophils, macrophages, phagocytic and cytotoxic cells and natural killer cells;
- complement proteins and inflammatory mediators;
- cytokines and chemokines: molecules that regulate the different steps of the innate immunity.

The acquired immunity is activated afterwards (from 24 hours onwards) by the contact with the pathogen, it is highly specific and confers immunological memory. It consists of two arms: humoral immunity, mediated by antibodies produced by B lymphocytes and cellular immunity (or cell-mediated), mediated by T lymphocytes (T helper and T cytotoxic).

Natural and acquired immunity are often synergic: in fact, on one side, the natural response leads and defines the nature of the acquired response; on the other side, the acquired response often uses innate response's mechanisms to eliminate the pathogens.

Intense exercise (either acute or chronic) alters the functions and quantity of both innate and acquired immune system's circulating cells (e.g. neutrophils, monocytes and NK cells) (4, 10, 11). In fact, during intense exercise, an initial lymphocytosis (mostly T cells, but also B cells) is observed. It is proportional to the intensity and the duration of the training and it is followed by a subsequent lymphocitopnenia (lymphocytes' level is below the level of pre-exercise) during the early stages of the recovery phase. The recovery phase lasts around 24-72 hours; after that, the number of lymphocytes is equal to the one observed during the pre-exercise phase. T and B lymphocytes' production and circulation is modified in response to increasing training also for well trained athletes. The reason of the observed decrease in the acquired immune response during intense physical exercise seems to be related to an increased release and circulation of stress hormones (cortisol and catecholamines) and to the cytokines-mediated alteration of the balance pro/anti-inflammatory activity.

The interaction between endocrine factors and the immune system, as previously mentioned, occurs during sessions of intense training. In such situations a catecholamines' release is observed as well as an increase of circulating immune cells. The catecholamines' release, as an acute effect, stimulates the production of inflammatory components.

The above-described pro-inflammatory reaction is followed by an increased cortisol release which has an opposite effect of mitigating the ongoing inflammatory reaction.

For this latter reason, during intense physical exercise a depression of the immune system in the post-exercise phase is observed. In addition, the human body response's to physical stress leads to an increase of circulating lymphocytes "suppressor (CD8 +)" which have high cytotoxic activity (10, 12, 13).

With regard to natural immunity, intense or prolonged exercise does not destroy the NK cells, but it temporarily transfers them to so called "tanks" sites (e.g. the walls of peripheral veins) as a result of catecholamines exercise-induced activity and the activation of adhesion molecules.

The above-described alteration of both the immune responses (mostly the acquired) following intense training and competitions is called "open window" (14-19) and it is responsible for a higher risk of infection for athletes when exposed to microorganisms. Furthermore, intense exercise causes a decrease in saliva secretion and release of IgA with a subsequent increased risk of upper respiratory tract infections (20).

The extent of the decline of the immune response in relation to exercise is influenced by several variables such as age, sex, duration and intensity of exercise. In addition, other risk factors such as biological, physical and psychological stress can influence neurological and endocrine factors responsible for immune response parameters' control.

There are other underlying conditions that might contribute to an increased susceptibility to infections:
- High respiratory rates occurring during exercise and the subsequent dryness of the oral mucosa as well as the increased viscosity of mucus lead to a reduced nasal and trachea clearance.
- Muscles' micro traumas cause the increase of the expression of C-reactive protein and of other factors which lead to a leukocyte sequestration at the site of trauma and to the release of free radicals (21).

- During epidemic periods, the use of swimming pools, changing rooms, gyms increase the risk of contagious.
- The practice of outdoor sports, with cold and rain, and the subsequent body surface's cooling might contribute to increased susceptibility.

In this context, vaccination might be a safe prophylaxis' method and an effective primary prevention approach as long as implemented in the framework of appropriate vaccination settings (23, 24).

The choice of proper vaccines is important to reinforce the immune response in athletes. In fact, it has been proved that during the "open window" phase, athletes' response to vaccination might be sub-optimal due to the above described temporary decrease in immune system activity.

Recommendations on vaccination cycles

WHO, publish a current recommendations for children and adolescents' immunization (25). These recommendations are periodically updated to better guide different countries policies. They must be adapted in different regions according to: the epidemiology of different infectious disease, the individual susceptibility, the local socio-economic and health conditions, the economic resources and, last but not least, the different health policies' priorities. In Italy, the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI) (6), with the collaboration of the Italian Federation of General Practitioners (FIMMG), of the Italian Federation of Pediatricians Doctors (FIMP) and of the Italian Society of Pediatrics (SIP) developed a proposal for a unique vaccination schedule for all ages, called "Immunization schedule for the life" (6). The proposal follows WHO recommendations and the best available scientific evidence.

The document produced by the SItI, the FIMMG, the FIMP and the SIP (6) defines the age, the numbers of doses, the time intervals between doses and estimates the minimum and the optimal immunization coverage rates needed to control the different vaccine-preventable diseases. In addition, for each vaccine recommendations are provided in order to: i) obtain and maintain age-specific minimum immunization coverage rates, ii) guide in different clinical, occupational and travelling settings.

Immunizations for athletes

Athletes should undergo the recommended childhood immunizations and they should be carefully monitored at the time of sport activity enrollment on the base of clinical anamnesis and childhood immunization history. In addition, athletes should be target of annual influenza immunization campaigns for two main reasons: i) because of the sharing of overcrowded environments and ii) because of the advantages of a healthy status for the performances.

Influenza is an epidemic infectious disease with pandemic potential, caused by virus type A (78%), B (20%) and rarely C (2%). Primary prevention of influenza is obtained with immunization. The vaccine is usually trivalent and protects against at least two circulating influenza A virus and one influenza B virus. In case of epidemics where the type of virus is known, a monovalent vaccine is added to the trivalent vaccine. That was the case in the 2009-2010 season with the offer of the monovalent anti A (H1N1) virus. The available vaccines are killed vaccines, split vaccines, viruses and subunits. During the influenza season, for adults who have been previously vaccinated, one single dose per year is sufficient, for first-time vaccinated adults, a second administration after 4 weeks is recommended (but not strictly necessarily). The average protective effect of trivalent vaccine is around 90% for influenza B virus and 70% for influenza A virus. The vaccine protection against influenza lasts generally for only one season. It is therefore recommended to repeat influence vaccine the beginning of every epidemic season. The best time to administer flu vaccination in northern emisphere is the fall, from mid October until December. In Italy, as in other European countries, influenza vaccination is recommended for people aged over 65 years, for people of all ages with chronic conditions and for certain professional groups. An yearly guidelines of the Ministry of Health provides recommendations for age-specific vaccine administration (27).

Sport-specific immunizations

The countries different immunization policies have implications in the sector of professional sports. With the globalization, the presence of athletes coming from different countries with different immunization policies has increased in sports clubs. This situation makes it essential to sports clubs to conduct a careful immunization history for all their athletes, in particular, for those athletes who come from countries where childhood vaccination cycles are not regularly implemented.

The young athlete recruited by a sport club should undergo, if he/she has not done it before, an adequate immunization coverage for all VPDs recommended during childhood and adolescence with particular reference to hepatitis B and tetanus. Although there are no specific recommendations for athletes involved in different sports, it is reasonable to assume that some sports activities have higher infectious disease risk factors that must be taken into account when managing the athlete's immunization scheme.

For athletes who have potential contacts with soils contaminated with tetanus spores and who are at risk of lesions (horse racing, cross country, played on sports fields, etc.), a rigorous tetanus prophylaxis with immunization and boosters is essential. Tetanus is an acute non contagious infectious disease, caused by *Clostridium tetani*, a spore-forming and anaerobic bacillus that releases specific neurotoxin.

The active immunization against tetanus is carried out with vaccine made of a tetanus toxoid. Vaccine efficacy is obtained with three doses of vaccine, the second after 6-8 weeks from the first, the third within a year from the second. The way of administration is intramuscular or subcutaneous. The serological response is measurable and a threshold of 0.01 UI/mL is conventionally used as indicator of effective antibody response. Such threshold is reached with the second dose of vaccine in 99% of cases. Boosters are recommended every 10 years to individuals already vaccinated. Vaccination does not influence the environmental circulation of *C. tetani*, and therefore not vaccinated or not correctly vaccinated subjects are at risk of infection (23, 24). In Italy, since 1963, with the law n. 292, vaccination against tetanus has been mandatory for the military, for children at the age of 2 (with the subsequent Law n. 419 of 20/03/1968 for children at the age of one), and for all members of the Federations Olympic Committee.

For athletes who have close personal contacts and are at high risk of cuts or wounds (wrestling, football, basketball, soccer, etc.) the full course of vaccination against hepatitis B is needed (27). With regard to primary prevention of infection, in 1982 the first vaccine against HBV became available, derived from the plasma of infected patients. Since 1986 a recombinant vaccine has been made available, obtained by recombinant DNA technology. The administration of the vaccine is in three doses, with a 0-1-6 vaccination schedule (the second dose after a month from the first and the third after six to twelve months after the first). A 0-1-4 schedule might be used to obtain a quicker protective action. There is no incompatibility with other forms of immunization (28, 29); therefore it should be considered as part of wider immunization programme. To verify the continuous protective effect of the immunization over time it is necessary that the antibody titer is maintained above 10 IU. Vaccination against hepatitis B is mandatory in Italy since 1991 by Law n. 165 with which it was established to immunize all infants from the third month of life to twelve years old. In 2003, complete immunization coverage of all subjects in the first 24 years of age was obtained (the so called "immune welding"). Therefore the problem of HBV immunization should today persist only for Italian athletes with more than 33 years old and for foreigners ones. Hepatitis B immunoglobulins administration is recommended as post-exposure prophylaxis for a more rapid induction of immunity (DM 07/04/1999) (27).

For indoor sports where close contact between athletes is common (wrestling, gymnastics, etc.) and for outdoors sports played in cold and wet seasons, vaccinations against airborne diseases (e.g. pneumococcal) should be prioritized. The vaccination against pneumococcal infection should be associated, in situations of increased individual or environmental risk, with influenza vaccination (5-30). It gives 5 year protection and boosters are needed afterwards. Pneumococcal infection caused by *Streptococcus pneumoniae* is the most common cause of community-acquired

pneumonia. Antibodies persist for 5-10 years and it is therefore recommended revaccination after 5 years.

Unlike hepatitis B, that does not require booster doses, the other above-described infections (tetanus, influenza, and pneumococcus) need periodic boosters. For this reason, sports clubs should investigate and report the exact history of vaccination of their athletes as well as implementing efficient prophylactic programs with periodic immunization cycles in order to maintain good immune performances.

Vaccination in travelling athletes

Sport clubs should not forget to consider other at risk conditions for athletes such as travelling for competitions and trainings in areas endemic for specific infectious diseases which are not present in the athletes' country of origin or where they live. When travelling for important sport events it is advisable for athletes to undergo an immunization prophylaxis specifically targeted on the country of destination according to WHO's guideline and Italian recommendations. Such prophylactic approach should be in line with the already existing recommended behaviors for general international travelers (e.g. yellow fever, vector borne diseases, cholera, typhoid fever, Hepatitis A and meningococcal meningitides).

Yellow fever is a vector-borne transmitted infections (vector: insect phlebotomist) caused by yellow fever virus.

It is an endemic disease in urban and forest regions of tropical and subtropical Africa and South America (Bolivia, Brazil, Colombia, Ecuador, Peru, Venezuela, Guyana, Argentina, Paraguay and Panama); the risk of acquiring the disease depends on several factors such as the traveler's immune status, vector's density in the environment, duration of exposure, the visited area (increased risk for rural areas as compared to urban ones) and the period of the year.

Risk of infection is 10 times higher in Africa as compared with South America; in East Africa the risk of transmission is seasonal and is higher between July and October. In Brazil the risk is higher between January and March. The vaccine can be administered after 9 months of age in a single dose; the protection begins 10 days after inoculation and lasts for over 10 years. However, for international travelers often visiting endemic areas, boosters every 10 years are recommended. The simultaneous administration of other vaccines is possible, but in different sites of inoculation. Some countries require mandatory vaccination certificate to enter their territory (32, 33). In Italy, the vaccination ia available in the immunization centers of the Ministry of Health (present in international airports) or at the Local Health Units (ASL) identified by local health authorities, in accordance with international norms.

Among the fecal-oral transmitted diseases which are highly endemic in extra-European countries, it is important to mention cholera, an acute bacterial disease of the intestinal tract caused by *Vibrio cholerae*. Vaccination is an effective tool of primary prevention for all people and, in particular, for athletes that travel to endemic areas for training and competitions.

Two vaccines are available: 1) the vaccine WC/rBS, oral vaccine obtained by recombinant DNA techniques, 2) the vaccine CVD 103, oral vaccine, currently not registered worldwide. Both vaccines, made from O1 biotypes do not protect against biotype O139. The vaccine WC/rBS requires two doses at a interval of 1-6 weeks with a booster dose after 2 years for adults and after 6 months for children aged 2 to 6 years. In addition, the oral vaccine WC/rBS also protects against diarrheal diseases caused by traveler enterotoxigenic *E. coli* (33).

Another bacterial disease fecal-oral transmitted is **typhoid fever** caused by *Salmonella* Typhi and paratyphi. Vaccination against typhoid fever is also recommended when traveling in endemic areas such as Asia, Africa, Central America and South America.

Two vaccines are available for travellers: 1) the oral typhoid vaccine, made from live microorganisms. Its protection lasts for 2 -3 years, but its effectiveness is compromised by Sulfonamides and mefloquine. 2) the Vi capsular polysaccharide vaccine made from *S.* Typhi's capsular polysaccharide highly purified. It is administered intramuscularly in a single dose with boosters every 2 to 3 years.

The oral vaccine is recommended for subjects aged >3 months and its schedule consist of a caspula or sachet administration per day taken before meals for three alternate days. The Vi polysaccharide vaccine is less immunogenic as compared to the oral vaccine.

Other recommended vaccine for athlets spending time in areas endemic for hepatitis A (Asia, Africa, Central and South America, countries of Eastern and Southern Mediterranean basin), is the vaccine against **Hepatitis A**. It is a fecal-oral disease frequently contracted by people travelling in countries where the disease is endemic. From the preventive point of view, there are several vaccines, consisting of inactivated virus which provide protection from infection after 14-21 days. Vaccine against Hepatitis A can be administered simultaneously with other vaccines. The schedule involves the administration of 2 doses. The immunity lasts for at least 10 years after the vaccination schedule completion. Hygiene standards are of fundamental importance for the prevention of fecal-oral infections (personal hygiene, washing and cooking of vegetables, shellfish, etc.). There is no treatment against hepatitis A, the disease can rarely progress leading to physical debilitation and often making it necessary the cessation of any type of sports activity and professional sport competitions). Therefore, immunization against HAV is essential to preserve the health and athletic performance of athletes frequently travelling to endemic areas. A double protection strategy can be adopted associating HAV vaccination with HBV vaccination in case a subject has not already been vaccinated against HBV. Such strategy is possible using a combined vaccine, recommended from the age of 16 onwards; the standard primary vaccination in adults consists of three doses, with a 0-1-6 month schedule. In case of anticipated traveling a 0-7-21 days schedule can be used.

Meningococcal meningitis is an acute bacterial disease, airborne transmitted and caused by the meningococcus *N. meningitidis*. Meningococcal meningitis is widespread around the world, but the sub-Saharan Africa has been for years an area of high incidence and where frequent epidemics still occur. The main form of prevention is immunoprophylaxis. Currently available vaccines consist of purified polysaccharides of meningococcal, available in monovalent, bivalent and quadrivalent form. It is recommended to administer meningococcal vaccine, intramuscularly in athletes who often stay in crowded places during races, training retreats, etc.. Immunization schedule consists of a unique dose subcutaneously or intramuscularly administrable after the age of two. The protective effect lasts for at least three years with 85-100% efficacy.

Special circumstances

There are special circumstances sports club and societies must be aware of in order to protect athletes' health status and where clubs have to cooperate with local Health authorities both of the country of origin and the country hosting sports events. Such circumstances include infectious diseases' outbreaks. In the past, several episodes were reported of outbreaks occurred during sports events. For example, the measles outbreaks occurred in Switzerland and Austria in 2008 and the infestation of ticks in Austria during the European Football Championship 2008. On this special occasion the Austrian and Swiss Ministries of Health (2, 35) prior to the beginning of the Championships, enacted a specific alert on the epidemic situations and recommend an immunization prophylaxis against tick-borne encephalitis and measles. The Italian Ministry of Health (41) acknowledged the alert in accordance with international standards and local regulations. It informed the citizens through messages addressing regional health, tourism and sport authorities and decided - in agreement with the Italian Olympic Committee - to give the vaccine against tick-borne encephalitis to athletes. They also recommended measles vaccination to athletes, supporters and visitors in age group 15-30 who were not immune.

Another example is the pandemic H1N1 influenza during the Olympic Games in Vancouver in 2010. The European Centre of Disease Prevention and Control (ECDC) published on its website an article titled *"Going to the Games? Do not forget your gear"* that included a list of preventive measures and recommended influenza vaccination to limit the risk of influenza infection and control the pandemic.

Immunization management for professional athletes

The aim of athletes' immunization is not the eradication of the infections but the protection of at risk subgroups of the population. For this reason it is

important to correctly select the best time for immunization practices, avoiding times when athletes suffer from a reduced immune response, with particular reference to post-competition or intense training, where the "open window", could negatively affect the immune response.

Furthermore, it is important to remember that some vaccines may cause some side effects, including mild local reactions at the injection site due to irritant substances (e.g. swelling, redness and soreness), up to a fever, headache, lymph nodal swollen and asthenia. Such adverse reactions, in association with the administration of the vaccine, might reduce athletes' performances in terms of physical strength and efficiency. It is therefore recommended to vaccinate athletes during periods free from trainings and competitions except in case of urgent need of immunization (e.g. accidental contact with the pathogen or an unexpected competition in area at risk).

Conclusions

This review underlines the importance of immunization practices to ensure the total well-being of the athletes who practice sports and in particular in the the professional sector. The existence of immunization practices should not negatively influence the implementation of the recommended behavioral preventive measures, that can be very effective if rigorously applied following the existing guidelines (6).

Taking into consideration that not always infectious diseases' treatments are available and that physical and physiological recover might be slow, it is of fundamental importance that doctors and staff in charge of athletes' health monitor each athlete specific situation and advice on optimal preventive measures, in particular in situations considered at risk and in case of incomplete childhood immunization.

In addition, to counterbalance the growing phenomenon of the vaccine hesitancy, efforts should be devoted to plan and implement effective information and communication interventions to promote immunization among healthcare professionals and to increase among the athletes the demand for immunization (37, 28)

The situations proposed in this review are guidelines to raise awareness on the fact that an adequate immunization schedule can guarantee a better quality of life and better sport performance for athletes this being a great advance for both athletes themselves and their clubs.

Practical implications

- Vaccination in athletes is essential for the prevention of infectious risks.
- Athlets should be monitored when enrolled in a team on the base of clinical anamnesis and childhood immunization history.
- The best time for immunization practice should be selected.

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