Clinical Clues / *Klinik İpuçları*

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# Is There a Reliable Marker (Correlate of Immune Protection) for Disease Prevention? Laboratory-Clinical Evaluation

## Hastalıktan Korunma Konusunda, Güvenilir Bir Belirteç (İmmün Korunmanın Göstergesi) Var mıdır? Laboratuvar-Klinik Değerlendirme

Zeynep Gizem Ergün Özdel[1](İD), Mustafa Kemal Hacımustafaoğlu[2](İD)

[1] *Division of Social Pediatrics, Department of Child Health and Diseases, Uludağ University Faculty of Medicine, Bursa, Türkiye*
[2] *Division of Pediatric Infectious Diseases, Department of Pediatric Health and Diseases, Uludağ University Faculty of Medicine, Bursa, Türkiye*

***Question:*** *Is there a reliable marker (indicator of immune protection) for disease protection in a child who is reportedly vaccinated? How can laboratory-clinical evaluation be performed?* **Yasemin Alyay, MD.**

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### Answer (Zeynep Gizem Ergün Özdel, MD; Mustafa Kemal Hacımustafaoğlu, MD)

**Introduction and general information for the answer:** Serology is a laboratory method frequently used in the diagnosis of diseases by detecting antibodies that develop in infectious diseases. In addition to diagnosis, it can also be used as an indicator of immunity after some previous diseases or vaccination. After vaccination, antibodies are developed by the host immune system. These antibodies can be detected by serologic methods. Serologic responses (antibody development) can be used both for diagnostic purposes (as a laboratory marker or evidence of disease) and, in some cases, to demonstrate immune protection. A positive serologic test may support that the disease has been or is being underwent but may not always be considered as the evidence of immunity. To be considered as evidence of immunity, an antibody must have properties that block the microorganism (neutralization) or inhibit the pathogenetic process (e.g. binding to the cell and preventing cell entry and replication, facilitating efficient phagocytosis and killing, as in the case of opsonized antibodies).

In immunization, compatibility with protection (immune correlate of protection; ICP or correlate of protection; CoP) is defined as an immune marker/immune function that confers protection from a particular disease (the term of CoP will be used in this paper) (1-4). CoP is a term generally used to indicate the presence of immunological antibodies that provide/guarantee protection from disease (e.g. bactericidal or neutralizing antibody above the standard protective threshold or protective antibody concentration determined by ELISA). The presence of CoP detected by laboratory/serologic methods means that there is protection from the disease and that the risk of acquiring the disease is practically absent or very low. In simple terms, CoP is a laboratory/serology marker indicating immunity, which provides clinical protection from the disease. There are two types of CoP; mCoP and nCoP, both of which indicate correlate of immune protection (2,3,5).

**Correspondence Address / Yazışma Adresi**
**Mustafa Kemal Hacımustafaoğlu**
Division of Pediatric Infectious Diseases,
Department of Pediatrics,
Uludağ University Faculty of Medicine
Bursa-Türkiye
**E-mail:** mkemal@uludag.edu.tr

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a) CoP is defined as mechanistic CoP (mCoP), if it is achieved by a reliable standard method (e.g. neutralization for viruses, bactericidal and/or opsonizing antibody for bacteria) that directly and causally demonstrates protection. These methods, which directly demonstrate a neutralizing or bactericidal effect, are used in vaccine immunogenicity and clinical efficacy studies. However, because they are expensive, time-consuming, and require specialized techniques, they are not used to determine CoP in routine clinical practice.

b) CoP is defined as non-mechanistic CoP (nCoP), if CoP is achieved by a standard method that can indirectly demonstrate protection (e.g. a method that shows total antibodies assayed such as ELISA). However, in this case, the antibodies assayed by the ELISA method in question, must have shown similar or parallel efficacy to neutralization, bactericidal, and/or opsonizing antibodies in previous studies, or be a total antibody assay including these antibodies. For example, in some encapsulated bacteria such as pneumococci, *Haemophilus influenza* type b, and meningococci, CoP is defined as the protective antibody threshold above a certain level (1,4,5) (Table 1). If the patient has a serum bactericidal antibody assay (SBA) titer ≥1/8 (or >1/4) for encapsulated bacterial serogroups using complement (human or rabbit complement), this level of immunity is considered sufficient to protect against disease and is considered mCoP. However, not all antibodies detected by ELISA are bactericidal. Nevertheless, if the antibody level detected by ELISA in pneumococcal serotypes is ≥0.35 mcg/mL (nCoP), it is considered to be protective from invasive pneumococcal infections (since these antibody levels have been shown to parallel with bactericidal ≥1/8 SBA titer). Again, antibody levels ≥0.1 mcg/mL after conjugated *H. influenza* type b vaccination are considered to be CoP (nCop) (1-3,5). However, it should be kept in mind that higher titers may be required for protection against mucosal infections (such as AOM, sinusitis) and higher titers may be required for clinical protection in some serotypes (such as pneumococcal serotype 3) (1,6,7). However, since there is still no reliable data indicating that protective serologic titers measured by ELISA in meningococcal infections, ELISA antibody titers are usually not considered as a guide for CoP (8).

The protective antibody response in viral infections is neutralizing antibodies. Neutralizing antibodies are specific for viral antigen or epitope regions that play an important role in viral pathogenesis. In case of changes in specific epitopes in variant viruses that develop after mutation, the protective effect of neutralizing antibodies may decrease or disappear (1). Protective antibodies developed in bacterial infections are desired to be bactericidal and opsonizing. Bactericidal antibodies are evaluated by different methods (such as; SBA or opsonophagocytic antibody; OPA) which are usually not routinely tested. Antibodies measured by the more commonly used ELISA method (typically IgG, IgM, or total antibodies) may contain or reflect bactericidal (with high opsonophagocytic index) and protective antibodies, depending on the type of pathogen or infection. In some cases, however, it may not include truly protective antibodies, in which case it is not considered protective. For example, antibodies after pneumococcal or meningococcal vaccination can be measured by two different methods: Presence of bactericidal antibodies measured by SBA or OPA, directly indicates vaccine effect as CoP (mCoP) and is associated with protection. Total antibodies measured by ELISA do not all directly indicate bactericidal effect, but may indirectly support protection (CoP and nCoP) as they generally develop in association with bactericidal antibodies (2,3).

**Table 1.** Correlate of protection (CoP) after vaccination (modified from references 1 and 5)

| Vaccine | Immune Function | Protective Level |
|---|---|---|
| Tetanus | Toxin neutralizing Ab | ≥0.01-0.1 IU/mL* |
| Diphtheria | Toxin neutralizing Ab | ≥0.01-0.1 IU/mL* |
| Measles | Microneutralization | ≥120 mIU/mL |
| Rubella | Immunoprecipitation | ≥10-15 mIU/mL |
| Chickenpox | FAMA, gpELISA | ≥1/64, ≥5 IU/mL |
| Hepatitis A | ELISA Ab | ≥10 mIU/mL |
| Hepatitis B | ELISA Ab | ≥10 mIU/mL |
| Polio, inactive | Neutralizing Ab | ≥1/8 |
| Rabies | Neutralizing Ab | ≥0.5 IU |
| Pneumococcal conjugate vaccine | ELISA Ab | ≥0.35 µg/mL |
| Meningococcal | Bactericidal Ab | ≥1/4 (with human complement) |
| Lyme | ELISA Ab | ≥1400 U/mL |

*: >0.1 mIU/mL is associated with more definitive protection.

Antibodies with Fc-associated effector functions are antibodies that are recognized to have an active role in clinical (therapeutic) recovery and prevention. Their Fc-related effector functions include antibody-dependent cellular toxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). Among the four IgG subgroups, IgG1 and IgG3 are the IgG subgroups with the strongest Fc effector function. IgG1 is considered to be more effective because it has a longer half-life and is more stable than IgG3. If the antibodies that develop after infection are highly potent Fc-associated IgG1-type antibodies, it can be assumed that there may be better clinical protection (9).

A cellular immune response may also develop after natural infection or vaccination. Cellular response may be more important, especially in some infections (such as varicella). However, it is not always possible to measure this response with routine methods in practice. In cases where a protective serologic/antibody response develops in a host with a well-functioning immune system, it can be assumed that protective cellular immunity also develops in the background. In this framework, in an individual with a good immune system, generally speaking; for measles, rubella, smallpox, varicella, poliovirus, and hepatitis A; serological responses that develop due to disease or vaccination can generally be considered as CoP. Also, if serologic markers indicating CoP are present, the risk of disease development is considered to be absent or very low (5,10). Antibody levels of approximately ≥10 mIU/mL against hepatitis A are compatible with clinical protection and considered as CoP (nCoP). Furthermore, antibody levels much higher than this can be achieved with vaccination. After hepatitis B vaccination, antibody levels ≥10 mIU/mL by ELISA are considered CoP and are considered protective against clinical disease. With poliovirus vaccination (oral attenuated or inactivated vaccination), a neutralization titer of ≥1/8 or even ≥1/4 for all three types is protective, and these levels (CoP) are maintained almost lifelong with routine vaccination. For measles, a micro-neutralization titer ≥1/120 provides clinical protection. Antibody values ≥10 mIU/mL after rubella vaccination and by RIA or ELISA are considered CoP and have been found to parallel serum-neutralizing titer ≥1/8. After varicella vaccination, a neutralization titer of ≥1/8 provides clinical protection (CoP), and this level has been paralleled with antibody positivity (≥5 IU/mL) by ELISA (VZV glycoprotein). However, serologic CoP values for mumps are not clear. T-cell responses in mumps have also not been fully determined. Therefore, mumps cases may be observed in young adults despite vaccination (5,10-12).

As mentioned above, antibodies that develop after polio, measles, rubella, and varicella vaccines are protective in children whose routine vaccination schemes have been completed. These antibodies may decrease over time, but in a child with a normal immune system, protection from clinical disease can be provided with the support of adaptive cellular immunity, which we do not routinely measure (5,10,12).

With human papilloma virus (HPV) vaccination, antibodies develop at a much higher rate than with HPV natural infection, and antibodies protect against disease caused by the HPV types in the vaccine for many years. This protection has been demonstrated by clinical efficacy and effectiveness studies. However, a serologically determined standard CoP value has not yet been specified for HPV vaccines (5). For SARS-CoV-2 infection, an IgG antibody titer >500 BAU/mL or virus neutralization titer ≥1024 by ELISA measured for SARS-CoV-2 infection was found to be associated with clinical protection (CoP) (13).

CoP values are clearer for toxoid vaccines such as tetanus and diphtheria. For both, the measured serum antitoxin levels of ≥0.01 mcg/mL is considered to provide significant protection and ≥0.1 mcr/mL is considered to provide complete protection (5). In children whose vaccination schedules have been completed, these levels are considered to be reached (Table 1).

After a natural infection, the host develops an immune response, which often provides protection against the later disease. Vaccination aims to provide this protection without exposing the patient to the risk of disease. The different clinical endpoints targeted by vaccination, can be the prevention of infection, prevention of transmission, and prevention of disease. The primary endpoint targeted after vaccination is protection from clinical disease (disease prevention). Disease prevention can be partial prevention (incomplete), i.e. the disease is acquired but with a mild course. Or it may be complete protection, i.e. the disease does not develop even if it is mild after vaccination (14). It is also important that no subclinical or asymptomatic infection develops after vaccination and/or no transmission to others during this infection. This increases the success of the vaccine and contributes to the creation of herd immunity. In vaccinated person, the neutralization/control of the infectious agent before it can initiate the infection process and initial replication is known as sterilizing immunity. Sterilizing immunity plays an important role in vaccine-associated disease eradication by preventing both infection and transmission. It can be considered as the elimination of the pathogenic agent that will cause infection, with effective host resistance, at the place where it first enters, before it can infect cells and replication (15). Oral live attenuated poliovirus vaccines can be shown as an example of sterilizing immunity. In inactivated poliovirus vaccines, clinical disease is effectively prevented, but the advantage

of preventing infection and subsequent transmission in the gastrointestinal tract is not sufficient. Thanks to the success of vaccine immunization strategies, smallpox infection eradicated globally and the smallpox vaccine has been withdrawn from routine use. Today, provided that vaccination schedules are effectively completed, the vaccines such as the measles vaccine, hepatitis B vaccine, hepatitis A vaccine can be said to have additional infection and transmission preventive properties in addition to disease prevention.

However, in terms of infection, transmission, and disease occurrence, there may be a dynamic relationship between the amount of exposure to the agent and host characteristics (such as age, additional environmental or host-related factors, transient or permanent immune suppression), which may vary and may be temporal, and this situation can be characterized as *situation-related protection* (10,14). Therefore, even in a host with a good immune system, even with vaccination that provides protection against disease and even infection, in cases such as overdose or atypical (variant or mutated) pathogen entry into the body or decrease in host resistance due to different reasons (such as immunodeficiency, cancer patients receiving chemotherapy, transplant, immunosuppressive drug use), the expected CoP response may not be present and the CoP value may not guarantee protection from disease.

*In summary, as an answer to the question;* it can be said that in a child with a normal immune system, provided that the primary vaccination is completed in accordance with the rules, (such as measles, rubella, polio, chickenpox, hepatitis A, hepatitis B, HPV, tetanus, diphtheria vaccines), the child is not expected to have the relevant disease. Vaccinations should be completed to ensure protection in a child with incomplete vaccinations. In cases where vaccination or previous disease history is not clear, appropriate laboratory/serologic evaluation can be performed as mentioned above. If there is a level compatible with protection against disease (CoP), protection against disease is considered to be achieved.

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