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Pediatric Vaccine-Induced Antibody Thresholds: Rethinking Pre-Immunosuppression Serologic Testing and Revaccination Implications

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Guests: Dr. Megan Culler Freeman from the Department of Pediatrics, Division of Infectious Diseases, at the University of Pittsburgh Medical Center (UPMC) Children's Hospital of Pittsburgh and Dr. Sarah Wheeler from the Department of Pathology at the University of Pittsburgh and Clinical Immunopathology at UPMC.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

Childhood vaccines are probably not the highlight of any kid's visit to the doctor, but they provide robust protection against pathogens likely to be encountered later in life. Most of the time, vaccines are given without any follow-up testing to determine whether vaccination was successful. However, in some cases, vaccine serological testing may be required if proof of vaccination is needed, but one's vaccination record cannot be located or if the child is scheduled to undergo immunosuppression to treat a medical condition. In these cases, many commercially available assays can measure the antibodies targeting a given pathogen. Antibody values above a set threshold indicate immunity, while values below the threshold suggest revaccination may be required. This sounds straightforward, but there's a small problem. Antibody titers decrease with age, but the thresholds used to determine immunity were derived from adults. Does application of an adult threshold to a child's titer accurately define their immune status? Or, are we generating falsely reassuring immune results in kids who probably should be revaccinated?

A new research article, appearing in the May 2025 issue of *Clinical Chemistry*, addresses this problem by defining age-appropriate reference intervals for vaccine serologic tests, an important first step in accurately defining immune status in children. In this podcast, we welcome the article's lead and senior authors. Dr. Megan Culler Freeman is a physician scientist and virologist and Assistant Professor in the Department of Pediatrics, Division of Infectious Diseases, at the UPMC Children's Hospital of Pittsburgh.

Dr. Sarah Wheeler is an Associate Professor in the Department of Pathology at the University of Pittsburgh and medical director for Clinical Immunopathology at UPMC.

And Dr. Freeman, let's start with you. Vaccines like MMR, varicella, and hepatitis B are highly effective, and guidelines from groups like the Advisory Committee on Immunization Practices generally state that routine verification of immune response is not necessary in healthy individuals, but in clinical practice, vaccine-induced antibody levels are sometimes assessed. Can you walk us through why this testing is done and when it might be warranted, despite the broad recommendations against?

Megan Freeman: That is such an important point, especially in pediatrics, where we're often balancing broad public health guidance with individual patient considerations. It's true that vaccines like MMR, varicella, and hepatitis B are highly effective, and routine antibody testing isn't needed for healthy kids. The ACIP, like you mentioned, emphasizes that a documented vaccine series is enough to assume that kids have immunity, and this makes sense for the majority of children that have normal immune function.

That being said, pediatric practice isn't always straightforward, and there are several important reasons why we still check antibody levels in certain kids. Children with underlying immunodeficiencies or those who are about to begin immunosuppressive medicines, like if they're getting a transplant or if they have a newly diagnosed autoimmune condition, they might not mount the same immune response as their peers, and live attenuated vaccines are then contraindicated for them once they start those immunosuppressive therapies. In those cases, serologic testing helps us confirm whether the child is protected or if they might need re-vaccination.

Another reason is uncertainty in vaccine history. Pediatricians often care for children who are in foster care or recently adopted, or children who were born abroad. And sometimes these are groups for whom vaccine documentation might be missing or unobtainable. And in those cases, checking titers can help us make smart decisions about vaccination status. And it's hard to talk about this without acknowledging the recent resurgence of measles in parts of the U.S. With measles being so contagious, we're reminded just how crucial it is to identify gaps in immunity early. If there's a local outbreak, testing might be warranted in at-risk children, particularly those with unclear records.

So, while the default is not to routinely test, there are definitely clinical scenarios, and now even within public health contexts where it becomes a valuable tool, while also recognizing that serology is not the only correlative immunity, although it is the most widely available clinical test.

Bob Barrett: Okay, thanks for that. Now, Dr. Wheeler, your study emphasizes the importance of defining age-appropriate thresholds for vaccine-induced antibodies, especially with vaccines like MMR, hep B, and varicella. Can you tell us about the significance of these age-based thresholds and how they could influence clinical practice, especially in immunosuppressed populations?

Sarah Wheeler: A big takeaway from our work is that timing really matters. It's not just when vaccines are given, but also in how we interpret the immune response to them. Pediatric vaccine schedules like those for measles, mumps, rubella, varicella, hepatitis B are designed so that kids receive their doses early in life. Typically, most of these series are done by ages four to six, so we expect that healthy children will have a relatively high antibody titer immediately following vaccination.

What's concerning is that not all children reach those expected titers, particularly those with autoimmune diseases or those later found to require immunosuppressive treatment. If these children start out with a kind of lower than expected antibody level for their age. They may lose their protective immunity earlier as their titers wane over time. That means we're seeing a missed opportunity to catch them in that critical pre-treatment window when vaccination or revaccination is still possible.

Right now, most of the commercially available serologic assays that we have use fixed thresholds and these are often derived from adult reference data. These can tell us the patient is protected or not, but they don't account for what's expected in a healthy 3-year-old versus a healthy 30-year-old.

In fact, a titer that seems acceptable by adult standards may actually be low for a child who was recently vaccinated and that may lead to misinformed decisions. Our study really aims to establish age-specific reference intervals for vaccine-induced antibodies in healthy children, and then use those to assess immune responses in children with autoimmune disease. The goal isn't to raise alarms, but to really fine tune how we're interpreting these serologic results so that we can help clinicians recognize when kids may not have mounted an adequate initial response and who could benefit from revaccination before becoming immune suppressed.

Ultimately, this age-specific lens might improve how we manage vaccine-preventable disease risk in these vulnerable pediatric populations and hopefully, help prevent downstream failures of immunity that we could have addressed earlier.

Bob Barrett: At your institution, you found that vaccination responses in children with autoimmune diseases were similar to those in

healthy controls. Dr. Freeman, can you explain why this might be the case and how this impacts vaccination strategies for children with autoimmune conditions?

Megan Freeman: That's right. At our institution, we observed the vaccine-induced antibody responses in children with autoimmune disease, particularly those with inflammatory bowel disease, were largely comparable to those in healthy age-matched peers. IBD, or inflammatory bowel disease, made up the largest proportion of our immune dysregulated cohort, which allowed for meaningful comparisons of subgroups. While we didn't see significant differences in measles, mumps, or varicella titers, those patients did have lower rubella titers and interestingly, higher titers to hepatitis B. And as we thought about it, we believe that this pattern actually might be influenced by clinical practices at our center, specifically the common use of this serologic testing and subsequent revaccination prior to when immunosuppressive drugs are started in IBD patients.

So when we looked specifically at patients that had prior IBD diagnoses versus new diagnoses, those with established disease had higher median titers, suggesting that they probably received boosters prior to when we sampled their blood. This highlights an important strategy. Early evaluation of seroprotection and revaccination before the beginning of an immunosuppressive therapy can effectively raise antibody levels in at-risk children. It also suggests that with proactive care, children with autoimmune conditions can mount immune responses similar to healthy children, at least true for our IBD cohort, supporting current guidelines that recommend vaccinating prior to starting immunomodulatory therapy.

Bob Barrett: You discussed the variability in antibody responses among different components of the MMR vaccine. Dr. Wheeler, could you explain how this variability affects clinical decision-making and why relying on a single component as a surrogate for vaccine-induced immunity might not be enough?

Sarah Wheeler: One of the more surprising findings in our study was just how discordant the antibody responses were between different measles, mumps, rubella, or MMR as we often refer to it, components. Even though they're delivered in a single vaccine, while measles titers are often used as a surrogate for MMR immunity. Overall, we found that when measles and another vaccine induced antibody like mumps or rubella were tested together, they were only concordantly below the immunity threshold about 60% of the time. That means in about 40% of cases, using measles alone would miss suboptimal immunity to other components in the vaccine. This has real implications for clinical care if we are trying to determine whether a child is protected before starting

immunosuppression or after exposure to a vaccine-preventable disease. If we're relying only on measles IgG, that may lead us to overestimate immunity. Each vaccine component, whether it's measles, mumps, or rubella, has to be assessed individually to ensure we're not overlooking gaps in protection, particularly in these vulnerable populations.

Bob Barrett: Well, finally doctors, we'll open this question up to both: given the limitations of current serologic thresholds and the variability between assays. What steps can the field take to improve the assessment of vaccine induced immunity?

Sarah Wheeler: One of the major takeaways from our work is that current adult-derived serologic thresholds may not be appropriate for children. Vaccine-induced antibodies are naturally going to wane over time, and what we define as "protective" (in air quotes) in adults may not actually reflect normal healthy responses in younger populations. So, we're proposing establishing age-appropriate thresholds as a more accurate benchmark.

Megan Freeman: In terms of next steps, we see a few important directions. First, reanalyzing existing pediatric vaccine trial data could help define better age-based reference ranges, ideally across multiple assay platforms given the variability between them.

Second, longitudinal studies linking serology with infection outcomes would be invaluable for validating new thresholds and improving our understanding of what truly correlates with protection, at least as far as these antibody assays is concerned.

Finally, for some vaccines like hepatitis B and varicella, where antibody levels wane significantly and might not correlate well with protection, we should just consider shifting away from serologic testing altogether in certain settings. Instead defaulting to revaccination if there's uncertainty, especially before a period of immunosuppression, might be more practical and clinically meaningful.

Bob Barrett: That was Dr. Megan Culler Freeman and Dr. Sarah Wheeler from UPMC in Pittsburgh, Pennsylvania. They authored a research article in the May 2025 issue of *Clinical Chemistry*, revisiting antibody thresholds used to determine vaccine-induced immunity, and they've been our guests in this podcast on that topic. I'm Bob Barrett. Thanks for listening.