CORRESPONDENCE

Vaccination Coverage in Immunosuppressed Patients—Results of a Regional Health Services Research Study

by PD Dr. med. habil. Niels Teich, Dr. med. Tobias Klugmann, Dr. med. Astrid Tiedemann, Dr. med. Babett Holler, Prof. Dr. med. habil. Joachim Mössner, Dr. med. Anke Liebetrau, Prof. Dr. med. Ingolf Schiefke in volume 7/2011

Clarifications

The German Standing Vaccination Committee (Ständige Impfkommission, STIKO) at the Robert Koch Institute welcome the fact that the authors draw attention to gaps in vaccination and to vaccination requirements in patients with chronic inflammatory bowel disease (IBD), especially if they receive treatment with immunosuppressants. These patients quite often do not get protective vaccines although they are of particular importance for them. However, cursory reading may prompt readers to misunderstand the recommendations made by the STIKO. The STIKO therefore wish to clarify the following facts:

- Table 1 of the article might create the impression that the STIKO have issued general vaccination recommendations explicitly for patients with IBD. However, this is not the case.
- Regarding vaccination against hepatitis A and hepatitis B, the authors correctly point out that the vaccination recommendation in this context relates to patients with disorders of the liver or those that involve the liver, which may—or may not—be the case in IBD.
- According to the cited STIKO recommendations *(Epidemiologisches Bulletin of the Robert Koch-Institute 30/2010)* immunizations against influenza and pneumococci are indicated in case of congenital or acquired immunodeficiencies (for example, pharmacological immunosuppression) or in case of an increased health risk due to an underlying disease. IBD is not mentioned on the incomplete list of exemplary underlying diseases. It therefore requires individual medical assessment to establish whether an increased health risk is present.
- The statements concerning the meningococcal and Haemophilus influenzae type B (Hib) vaccinations exceed the STIKO recommendations. In the cited remarks these vaccinations are termed as "indicated" for patients with immunodeficiency in analogy to the (conjugated) pneumococcal -vaccine. However, the STIKO explicitly mentioned the unsatisfactory data situation and existing licensing restrictions. The paper of Teich et al. might lead to the incorrect impression that these remarks are formal STIKO recommendations.

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Particular Characteristics of Encapsulated Bacteria

The referenced article (1) also applies to hematological and oncological patients. The administration of dead vaccines is safe three to six months after the end of chemotherapy, although vaccine effectiveness may be reduced. Administration of attenuated live vaccines, however, has to be pondered very carefully. The Infectious Diseases Working Party of the German Society of Hematology and Oncology has published appropriate methods (www.dgho-infektionen.de).

A warning to accompany the unequivocal indication for prophylactic vaccination against encapsulated bacteria: such vaccines do not guarantee protection from infection. Meta-analyses have shown that polysaccharide vaccines in chronically ill patients do not reduce the lethality of invasive pneumococcal disease (2). Evaluating surrogate markers rather than clinical end points in studies partially explain this association. The licensed pneumococcal polysaccharide vaccine has thus far not been adequately studied in hematology/oncology patients.

Differences between vaccines also deserve attention: Pneumococcal polysaccharide vaccines—in contrast to conjugated vaccines—provoke T-cell independent, IgM dominant immune responses and lead to immunological short term memory. Because of the improved response to vaccination with conjugated vaccines in vaccine-naive immune systems, children receive conjugated vaccines. Successful studies of sequential polysaccharide vaccines and conjugated vaccines have been conducted in people who received stem cell transplants (3), accordingly, vaccination in this clientele is now being promoted. Expanding the license approval of the 13-valent conjugate vaccine from children younger than 5 years to adults older than 50 years is being investigated (www.pfizer.com). The vaccination might counterbalance the increasing antibiotic resistance of pneumococci. In reverse, increase in serotypes that are not captured by licensed vaccines might become a clinical problem.

Other vaccine-preventable encapsulated bacteria may have vaccination gaps. The incidence of *Haemophilus influenzae* type B seems to be lower in adults than the incidence of non-encapsulated *Haemophilus* strains, which moreover are associated with higher letality (4). 50% of meningococci in Germany are of serotype B, and no vaccine exists for that serotype. For this reason, anti-infective prophylaxis should be considered after exposure, even in individuals who have been vaccinated.

It seems obvious that clinical research into vaccination in at-risk adult patients needs to be intensified.

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Limitations

The question of whether immunocompromised persons, who require protection by vaccination more than most, are indeed protected—i.e., whether they may have been properly vaccinated—is undoubtedly important. Equally as important is the question of whether immunocompromised persons are able to respond to vaccination at all with an adequate or at least sufficient reaction in order to benefit from such a medical measure.

The data presented in the article (1) are not convincing. The long discussion is based only on data collections of opinion polls. Furthermore, the findings given in Tables 3, 4, and 5 are subject to at least two biases:

- The expectation and personal aura of the interviewer
- Ignorance or lack of interest on the part of the interviewee.

Indeed, the authors themselves seem uncertain and they repeatedly pointed out the limitations of their presentation.

And there are much more serious limitations: why only talk to a patient—why not measure facts? The objective proof for the questions raised could be easily brought about by providing objective, concrete results such as the antibody response to the causative pathogens. This is entirely within the realms of the possible (2). By means of laboratory medicine clear, not vague answers about the protection of immunosuppressed people can be provided. In modern medicine, collection of accurately measured data is a prerequisite for the assessment of appropriate consequences.

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In Reply:

Leidel rightly reminds us that the STIKO has not set out disease specific vaccination recommendations for patients with chronic inflammatory bowel disease—the column heading in Table 1 should have therefore said "Recommendation on the basis of STIKO" (1). The same is true for the recommendations of the Vaccination Committee for the State of Saxony (Sächsische Impfkommission, SIKO), whose chair was kind enough to help us in setting out the table. We thought that a vaccination table that could be implemented in practice would be more useful than the mere mention of the recommendations of the national and regional vaccination committees, and we mentioned the development of our disease specific vaccine recommendations as quality management module in the discussion section. The second comment by Leidel is also important: vaccination against pneumococci and influenza is indicated especially in IBD patients with pharmacological immunosuppression. Because the severity of pneumococcal infection in IBD patients is correlated with the intensity of the immunosuppressant medication (2) and pneumococcal vaccination loses its effectiveness with increasing immunosuppression (3), it may be useful to vaccinate patients with a potentially severe disease course before even starting immunosuppressant therapy. The final comment relates to footnote 14 in our Table 1 and constitutes an important further explanation.

In addition to chronic inflammatory disease, neoplastic disorders require pharmacologically induced

immunosuppression in many patients. Christopeit and coauthors discuss in this context the problems associated with the effectiveness of the pneumococcal vaccine and remind us of the lack of studies of the vaccination of patients at high risk. We hope that our article (1) gave a new impulse with regard to this dilemma.

Hof and Bartel discuss the fact that the expectations and personal aura of the person asking the questions and ignorance or lack of interest on the part of the person being asked may present limitations of our study; this is unlikely in view of our pragmatic study protocol (copies of vaccination records and completed questionnaires). Discussing possible limitations of the collected results is a part of any serious scientific study—and not a sign of insecurity. Ultimately the correspondents recommend measuring antibody titers, rather than checking the vaccination records—for example, to tetanus. This recommendation is not consistent with the recommendations of the STIKO or the guidelines of the national specialist professional societies. As long as the vaccination status of IBD patients—as we showed in our article—is notably behind the STIKO's recommendations, it is currently more useful to look at the vaccination records, rather than recommend measuring titers.

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Conflict of interest statement
The authors of all contributions declare that no conflict of interest exists.