

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between PCV13 pneumococcal vaccination and risk of hospital admissions due to pneumonia or sepsis among patients with hematological malignancies: a single-center retrospective cohort study in Israel
AUTHORS	Draliuk, Regina; Shadmi, Efrat; Preis, Meir; Dagan, Efrat

VERSION 1 – REVIEW

REVIEWER	Payne, Thomas UW Medicine Information Technology Services, Medicine
REVIEW RETURNED	07-Dec-2021

GENERAL COMMENTS	<p>This manuscript reports result of a cohort study of patients with hematologic malignancies to determine association between PCV13 vaccination status and development of pneumonia or sepsis. It uses data from electronic health records from a single institution in Israel.</p> <p>It would be useful to provide more detail on the data sources. Which EHR was used? How complete is the recording of immunizations? In the US, many immunizations are not accurately recorded in the EHR because they may be administered in a location that does not use the same EHR as the hospital or clinic. This results in misclassification of the exposure (immunization). Can you provide information on the sensitivity and specificity of PCV13 immunization as recorded in the EHR?</p> <p>In Study Variables, it would be helpful to know more about how you assessed the presence of pneumonia and sepsis. Not all patients develop fever or leukocytosis, particularly in patients with hematologic malignancy. What findings were assessed in chest x-ray, and were chest CT findings also included? What standard did you use for assessing sepsis?</p> <p>Be consistent in reporting that this study looks for association, not causation. For example:</p> <ul style="list-style-type: none">- The first bullet of the Article summary should be change to "...demonstrate an association between PCV134..."- The second bullet of the Article Summary should be deleted. It does not demonstrate effectiveness. That requires a prospective controlled trial.
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	<p>The manuscript would be improved by careful editing to improve the prose and appropriate use of abbreviation. I have included a few examples below.</p> <p>Specific:</p> <p>Throughout: Use the phrase electronic health records, without capitalization, rather than the variations of this used in the manuscript. Note that the phrase is typically not capitalized.</p> <p>Page 3 line 9. Change to “patients with hematological malignancies”</p> <p>Page 3 line 11. Change to “...is associated with fewer hospital admissions...”</p> <p>Page 3 line 33. Change to “...patient, of which 418 (67%)...”</p> <p>Page 5 line 4. Change to “Hematological malignancies are the with most common cause of cancer..”</p> <p>Page 8 line 40. It should be Prevnar, not Prevenar.</p>
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REVIEWER	Lu, Chun-Yi National Taiwan University Hospital, Department of Pediatrics
REVIEW RETURNED	26-Dec-2021

GENERAL COMMENTS	<p>The study addresses an interesting issue: Dose PCV vaccination reduces hospital admissions due to pneumonia or sepsis in adult patients receiving immunosuppressive therapy for hematological malignancies (excluding acute leukemia). The study design is a retrospective cohort study. Comparisons in rates of hospitalizations due to pneumonia and sepsis were made between patients with and without PCV13 vaccination before initiation of immunosuppressive therapy. The results showed that 418 patients without vaccination had a hospitalization rate of 15.1% and 198 patients with vaccination 7.1%. The authors concluded that PCV13 vaccination had significantly reduced odds of hospitalization due to pneumonia or sepsis compared to non PCV13 vaccinated patients. Generally speaking, the manuscript is well written. However, some essential questions about the study methods need to be addressed before publication. First, the clinical diagnosis of pneumonia or sepsis is not specific. There were no etiologies mentioned in the current study. The diagnosis probably does not equal or close to pneumonia or sepsis caused by pneumococcus. Adding IPD (invasive pneumococcal disease) to the study outcomes is better. Background information like what proportions of pneumonia and sepsis were caused by pneumococcus may be helpful. Second, confounding factors like the functional status of patients may have significantly influenced the study results. As shown in Table 1, the ECOG (Eastern Cooperative Oncology Group) performance score is quite different in patients with and without PCV13 vaccination. Similarly, diagnosis and treatment type are also different between groups. These factors may have significantly confounded the study. It is unclear why the logistic regression analysis (Table 3) did not include more elements. These limitations should be addressed in the Discussion. In addition, several minor problems need attention. Page 7, the definition of “within 12 months” is unclear. Does it mean 12 months after initiation of immunosuppressive therapy or after PCV13</p>
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	vaccination? The current rationales for excluding patients with acute leukemia were excluded are not convincing.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Thomas Payne, UW Medicine Information Technology Services

Comments to the Author:

This manuscript reports result of a cohort study of patients with hematologic malignancies to determine association between PCV13 vaccination status and development of pneumonia or sepsis. It uses data from electronic health records from a single institution in Israel.

Comment:

It would be useful to provide more detail on the data sources. Which EHR was used? How complete is the recording of immunizations? In the US, many immunizations are not accurately recorded in the EHR because they may be administered in a location that does not use the same EHR as the hospital or clinic. This results in misclassification of the exposure (immunization). Can you provide information on the sensitivity and specificity of PCV13 immunization as recorded in the EHR?

Author's response:

The EHR of our health care system is very accurate in recording vaccination status as well as data regarding patient demographics, disease evaluations, hospital admissions, etc. We added a paragraph to clarify these points in the discussion section (page 11)

Comment:

In Study Variables, it would be helpful to know more about how you assessed the presence of pneumonia and sepsis. Not all patients develop fever or leukocytosis, particularly in patients with hematologic malignancy. What findings were assessed in chest x-ray, and were chest CT findings also included? What standard did you use for assessing sepsis?

Author's response:

The diagnosis of pneumonia or sepsis was based on the leading diagnosis made by the primary treating team. This was verified by reviewing the charts for clinical, laboratory and radiological findings (including chest CT) blinded for patients' group allocation. Some of the patients did not have blood cultures drawn prior to initiation of antibiotics therapy. Therefore we could not accurately assess the proportion of positive blood cultures. We added further clarification in the methods section under study variables, 1st paragraph.

The outcome of sepsis was based on the primary diagnosis for the hospital admission.

Comment:

Be consistent in reporting that this study looks for association, not causation.

For example:

The first bullet of the Article summary should be change to "...demonstrate an association between PCV134..."

Author's response:

We changed the first bullet according to your suggestion.

Comment:

The second bullet of the Article Summary should be deleted. It does not demonstrate effectiveness. That requires a prospective controlled trial.

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We deleted the second bullet according to your suggestion.

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The manuscript would be improved by careful editing to improve the prose and appropriate use of abbreviation. I have included a few examples below.

Specific:

Throughout: Use the phrase electronic health records, without capitalization, rather than the variations of this used in the manuscript. Note that the phrase is typically not capitalized.

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Page 3 line 13. Change to “...patient, of which 418 (67%)...”

Page 5 line . Change to “Hematological malignancies are the with most common cause of cancer..”

Page 8 line 40. It should be Prevnar, not Prevenar.

Author's response:

Thank you for these corrections. We changed the manuscript according to your suggestions.

Reviewer: 2

Dr. Chun-Yi Lu, National Taiwan University Hospital

The study addresses an interesting issue: Dose PCV vaccination reduces hospital admissions due to pneumonia or sepsis in adult patients receiving immunosuppressive therapy for hematological malignancies (excluding acute leukemia). The study design is a retrospective cohort study. Comparisons in rates of hospitalizations due to pneumonia and sepsis were made between patients with and without PCV13 vaccination before initiation of immunosuppressive therapy. The results showed that 418 patients without vaccination had a hospitalization rate of 15.1% and 198 patients with vaccination 7.1%. The authors concluded that PCV13 vaccination had significantly reduced odds of hospitalization due to pneumonia or sepsis compared to non PCV13 vaccinated patients. Generally speaking, the manuscript is well written. However, some essential questions about the study methods need to be addressed before publication.

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Second, confounding factors like the functional status of patients may have significantly influenced the study results. As shown in Table 1, the ECOG (Eastern Cooperative Oncology Group) performance

score is quite different in patients with and without PCV13 vaccination. Similarly, diagnosis and treatment type are also different between groups. These factors may have significantly confounded the study. It is unclear why the logistic regression analysis (Table 3) did not include more elements. These limitations should be addressed in the Discussion.

Author's response:

We addressed the issue in the discussion as suggested. Although the performance score was different between the study groups, the vast majority of patients were not dependent (>90%). In addition, variables were entered into the regression model if the bivariate analyses were revealed significant associations ($p < 0.05$) with the dependent variable. Nonetheless, we addressed the points you raised under the strength and limitations sections (page 11).

Comment:

In addition, several minor problems need attention. Page 7, the definition of “within 12 months” is unclear. Does it mean 12 months after initiation of immunosuppressive therapy or after PCV13 vaccination? The current rationales for excluding patients with acute leukemia were excluded are not convincing.

Author's response:

We clarified in the manuscript the time period that was counted from the initiation of therapy (page 7, paragraph 1).

Acute leukemia patients tend to have frequent hospital admission due to therapy, side effects and complications of treatment. These patients tend to have prolong neutropenic time periods and therefore may confound the study outcome. Our center does not treat significant amount of patients diagnosed with acute leukemia and therefore patients with acute leukemia were not included in this study.

VERSION 2 – REVIEW

REVIEWER	Payne, Thomas UW Medicine Information Technology Services, Medicine
REVIEW RETURNED	16-Feb-2022
GENERAL COMMENTS	This is an improved version that contributes to our understanding of the value of immunizations.