Article details: 2012-0027	
Title	Trends of infection-related hospitalization rates in a large Canadian cohort of chronic dialysis patients accounting for dialysis-vintage
Authors	Jean-Philippe Lafrance, Elham Rahme, Sameena Iqbal, Naoual Elftouh, Louis-Philippe Laurin, Michel Vallée
Reviewer 1	**Ettore Bartoli**
Institution	Università del Piemonte orientale , Internal Medicine, Dipartimento di Scienze Mediche
General comments	Minor points Page line text correction 4 45 greatly differ than greatly differ FROM 6 17 -18 to ensure only maintenance to ensure THAT only maintenance 7 57 how instantaneous risk how THE instantaneous risk 9 26 – 27 Interaction was significant for cardiovascular WHAT ? (P=0.04). Major points This paper has a clear objective, a good design and statistics, a clear result. It demonstrates that the rate of hospital admission for infections is stable in dialysis patients, while that for cardiovascular and other causes are in steady decline. I believe that the interest is not very strong, and that its priority could be considered intermediate. The paper is too long: being clear and simple, it rests on the statistical andrecruitment techniques, which must keep the present extension, while results and discussion should be shortened considerably. Even the figures can be reduced, as it would be sufficient to state, as it is stated in the text, that adjusted rates are the same as the unadjusted ones to save figures. The discussion on the cause of the trend could be focused on the fact, briefly alluded by the authors, that it is hard to prevent infections, while cardiovascular prevention is effective, health system are keen on saving hospitali admissions, a number of cardiac procedures are carried out on an outpatient basis. Ettore Bartoli, Professor of Medicine, "Amedeo Avogadro" Medical School, Novara, Italy. I have no competition interests with the Authors.
Reviewer 2	**Vianda Stel**
Institution	ERA-EDTA Registry, Academic Medical Center, University of Amsterdam, Department of Medical Informatics
General comments	The aim of the study is interesting and is to describe the population-based incidence rate trends from 2001-2007 of infection-related hospitalization rates among incident and prevalent dialysis patients, with a focus on dialysis vintage. The study is performed in a large cohort of patients on dialysis in Canada. The paper is clearly written. I have a major comment on the combination of the incident and prevalent cohort of dialysis patients. Moreover, I kindly ask the authors to clarify the methods on other points (see below). Main comments 1. The authors combine incident and prevalent patients in their study population. In an incident cohort, one could calculate the hospital rate per person years in which the numerator is the number of hospital rates between 2001 and 2007 and the denominator the sum of person years of all incident patients until the hospital rate or end of follow-up. However, the prevalent cohort in this study contains only those patients who survived until 2001, and is per definition a “survivor” cohort (selection). This also means that this prevalent cohort represents an over-representation of patients who have been on dialysis for a longer period of time. In addition, in a prevalent cohort it is not clear to me how to calculate the hospital rate per person years. The numerator is the number of hospital rates between 2001 and 2007. But what is the denominator here? You miss the person years in the denominator of the persons who were on renal replacement therapy and are not included in the study anymore in 2001 (e.g. died, received renal transplantation before 2001). Therefore, I think the calculations on hospital rate are not correct in the prevalent cohort. In line with this, I think that one cannot perform these analyses in a combined cohort of incident and prevalent patients, as the denominator/selection is different. 2. Please clarify the methods: a. Please define in the methods what is the “end of follow-up”.

	b. In table 3 you mention that you calculated the age and sex standardized rates using the same reference population. Which reference population? c. In line with the previous comment, in the title of Table 3 you use the words standardized for age and sex (I suppose to a reference population, not clear which one, or did you adjust?). I suppose you ADJUSTED (and not standardize) for dialysis vintage. Also, can you please clarify the footnote under Table 3: what is "whole cohort distribution"? d. In the results you describe Figure 4 on the hazard function. I suppose an explanation about this method and why you are doing this is lacking. 3. The authors could elaborate on important competing risks like dying. Minor comments 1. Page 5, line 38: add the word "also" we ALSO included 2. In Figure 1 the author described: "Patients in RAMQ between Jan 1 1999". However, in the methods I do not see the year 1999, only 2001. Please clarify
Author response	We are pleased to be given the opportunity of submitting a revised manuscript and we hope you find our revision and changes to the manuscript satisfactory. Point by point answers to comments can be found below. Editors' comments to Author(s): The editors and statistician would like you to address the following major items: Major Points: 1. Were the chosen ICD codes validated? Was misclassification evaluated? We are not aware of any validation studies for ICD codes related to infections. However, our list of codes was taken from the USRDS annual report, in order to allow comparison with the United States. We added this reference to the text. 2. The calculation of hospital rates when combining the incident and prevalent cohorts must be reviewed and clarified. (see comments from Reviewer 2) Please see answer to reviewer 2. 3. Do the statistical analysis methods for the standardization of rates take the clustering of admissions by patient into consideration? Main analyses including standardization of rates do not take the clustering into consideration. However, we conducted a sensitivity analysis using a Cox model for recurrent event (therefore considering clustering). Despite not taking into account clustering, our main analyses are the primary methods used in other dialysis registry (therefore allowing comparisons). Results are easier to understand (it produces rates) and can be plotted easily, which is not the case when using more complex methods. Clustering is probably not an important issue in our case, since the results from the Cox model for recurrent event is similar. We added this issue on page 11. 4. Why were the years 20012007 selected for study? We had only access to that period of time. Because RAMQ and CORR are hold in different provinces under different laws, obtaining both linked data is a complex process that takes years. 5. Table 1: please include years on dialysis in baseline characteristics. You may wish to group patients by length of dialysis in cohorts (e.g. <1, 15, etc.) or perhaps using mean with standard deviation. We included in Table 1 incident vs. prevalent status. Since we only have a look-back period of 2 years before dialysis initiation and we do not have access to data before 1999, we can't determine exact dialysis vintage for all prevalent patients at baseline. Dialysis vintage was available for patients that initiated dialysis after 1999 and was assessed yearly (and not at baseline). For your information, we are providing an additional table with patients count per year and dialysis vintage (Table S3). However, this would add another table to the manuscript (which has already many tables as mentioned by reviewer 1) and we believe this information is not crucial. 6. Please address reviewer comments. Other minor points: 1. Dialysis vintage is a term that some readers may not be familiar with. Please explain this term in the introduction. We added a definition on page 3. 2. Under Methods, Study Cohort: how were patients identified for inclusion in the cohort? Patients were identified using RAMQ physician claims or admission discharge sheets. We added this information on page 4. 3. In the Results section, when describing the trends, please start with IRH (the main hypothesis.) We changed the Results section accordingly. 4. The Interpretation at 4 pages is too long. Please reduce length, and structure as per

	point # X below. One part to shorten could be the paragraph speculating as to why IRH is not decreasing. We shorten the Interpretation section. 5. Please include 95% confidence intervals in Table 3. Done. 6. Title should include the study type. We added “retrospective cohort” to the title. 7. Please list the highest degree(s) held by each author. CMAJ Open publishes up to one professional degree (e.g. MD) and one additional academic degree (e.g. PhD). Done. 8. Please ensure that you have provided all tables and figures in an editable format. Failure of authors to do so is one of the most common causes of delays in manuscript handling we experience. We can most easily edit files created in PowerPoint, Excel, or Word. Please note that images pasted into the above programs from elsewhere (as opposed to being created using these programs) retain the formatting of the program in which they were created and will usually NOT be editable. Most files in PDF format also will NOT be editable. We can also usually work with files in WMF or EMF format (i.e. with a .wmf or .emf file extension) – many statistical and graphics programs can output files in this format. Done. 9. Abbreviations: As per CMAJ Open style, please avoid using abbreviations and acronyms and instead spell them out in full at each occurrence in the main text and the abstract. CMAJ makes exceptions for only the most familiar and broadly recognized abbreviations (e.g., 95% CI, SD, OR, RR, HR), and even for these, please spell them out at first mention and include the abbreviation in parentheses. All abbreviations were spelled out. 10. As per CMAJ Open style, please round all p values to one significant figure (e.g., 0.8, 0.01, 0.009). Exceptionally, if rounding a p value would make the value appear nonsignificant (e.g., 0.047 rounded to 0.05), leave the value with two significant figures. P values were modified accordingly. 11. Abstract: Please write in the first person; 250 words maximum. Structure the abstract into 4 main sections: Background: Provide the context for the study. Explain the problem or issue (the reason you decided to conduct your study) in the first sentence. State the objective of your study (the question you set out to answer) in the second sentence. Methods: Include 4 elements: setting, patients, study type or design, and key measurements or outcomes. Results: Provide data for the key measurements. Describe the data in absolute and relative terms, if applicable. Give confidence intervals for differences where appropriate, or other measures of statistical significance. Interpretation: Begin with a sentence that answers your research question (What did the study show?). The second sentence should be a brief statement about implications for practice or research (What do the findings mean?). Avoid speculation and generalization. We modified the abstract accordingly. 12. Please structure the Interpretation section (discussion) into the following 4 main headings (i.e. insert the headings themselves): “Main findings” (discussing implications, not a repetition of results),”Comparison with other studies”, “Limitations”, and “Conclusions” (including implications for practice and future research). We modified the Interpretation section accordingly. 13. Please ensure your final word count is below 2500 words (excluding abstract, figures, tables and references) and the abstract is below 250 words. Please supply exact word counts with the revision. Done. 14. Please use plain numbers in parentheses for your references and do not use automatic numbering of field codes as these do not carry over well into our publishing software. Our manuscript editors will convert these into the CMAJ Open's usual reference numbering format once the manuscript is laid out for publication. Done. 15. Please include a checklist from the appropriate reporting guideline. For a retrospective cohort, this would be the STROBE checklist (available at http://www.strobestatement.org) A checklist is attached. Reviewer(s)' Comments to Author (if applicable): Reviewer: 1 Comments to the Author

	Major points This paper has a clear objective, a good design and statistics, a clear result. It demonstrates that the rate of hospital admission for infections is stable in dialysis patients, while that for cardiovascular and other causes are in steady decline. I believe that the interest is not very strong, and that its priority could be considered intermediate. 1. The paper is too long: being clear and simple, it rests on the statistical and recruitment techniques, which must keep the present length, while results and discussion should be shortened considerably. Even the figures can be reduced, as it would be sufficient to state, as it is stated in the text, that adjusted rates are the same as the unadjusted ones to save figures. We shortened the Interpretation section as suggested. We agree that some information in Figure 2 and Table 3 (crude rates by calendar years) is redundant. However, we believe that Figure 2 remains interesting because a graph is easier to understand for the reader. Because dialysis vintage-adjusted rates are the main focus of the manuscript, we believe that it should be shown in Table 3 for the reader to judge if they are really similar to crude rates. Therefore, we would suggest keeping figures as is, but would accept to remove Figure 2 if requested. 2. The discussion on the cause of the trend could be focused on the fact, briefly alluded by the authors, that it is hard to prevent infections, while cardiovascular prevention is effective, health system are keen on saving hospital admissions, a number of cardiac procedures are carried out on an outpatient basis. We agree. We restructured that section and refocus on this fact. Minor points 1. Wording: Changes were made as suggested. Reviewer: 2 Comments to the Author The aim of the study is interesting and is to describe the populationbased incidence rate trends from 20012007 of infectionrelated hospitalization rates among incident and prevalent dialysis patients, with a focus on dialysis vintage. The study is performed in a large cohort of patients on dialysis in Canada. The paper is clearly written. I have a major comment on the combination of the incident and prevalent cohort of dialysis patients. Moreover, I kindly ask the authors to clarify the methods on other points (see below). Main comments 1. The authors combine incident and prevalent patients in their study population. In an incident cohort, one could calculate the hospital rate per person years in which the numerator is the number of hospital rates between 2001 and 2007 and the denominator the sum of person years of all incident patients until the hospital rate or end of follow-up. However, the prevalent cohort in this study contains only those patients who survived until 2001, and is per definition a “survivor” cohort (selection). This also means that this prevalent cohort represents an over representation of patients who have been on dialysis for a longer period of time. In addition, in a prevalent cohort it is not clear to me how to calculate the hospital rate per person years. The numerator is the number of hospital rates between 2001 and 2007. But what is the denominator here? You miss the person years in the denominator of the persons who were on renal replacement therapy and are not included in the study anymore in 2001 (e.g. died, received renal transplantation before 2001). Therefore, I think the calculations on hospital rate are not correct in the prevalent cohort. In line with this, I think that one cannot perform these analyses in a combined cohort of incident and prevalent patients, as the denominator/selection is different. To calculate rates in a prevalent cohort, we should not measure the person-time before start of follow-up. We only count the person-time “at risk” for an event. Because a hospitalization before 2001 would not be captured, this period of time is not at risk for the event. Therefore, our method is the correct method to calculate rates in a prevalent or dynamic cohort. However, we agree that interpreting rates from a prevalent cohort is not as simple as for an incident cohort. In the introduction, we acknowledge that prevalent and incident patients greatly differ, and this is exactly why we performed this study in order to remove the effect of length of time on dialysis. We used a dynamic cohort (which combines prevalent and incident patient) since this is the population reported in other registry. Also, an incident cohort could not evaluate if adjusting for dialysis vintage makes or not a difference. As stated on page 5, including prevalent patients allowed having patients with different dialysis vintages starting in 2001, and therefore was essential to evaluate trends over the entire study period. By performing dialysis vintage standardization, we are obtaining rates for a standard cohort where the distribution of dialysis vintage strata (and therefore incident and prevalent patients) does not change with time. However, obtaining rates from an incident cohort may be

	interesting to validate that rates are decreasing with time. For this reason, we conducted a sensitivity analysis using only incident patients, which led to similar overall rates and trends through time. 2. Please clarify the methods: a. Please define in the methods what is the "end of followup". Patients were followed until death, kidney transplantation, or end of the study (December 31, 2007). See page 5. b. In table 3 you mention that you calculated the age and sex standardized rates using the same reference population. Which reference population? In line with the previous comment, in the title of Table 3 you use the words standardized for age and sex (I suppose to a reference population, not clear which one, or did you adjust?). I suppose you ADJUSTED (and not standardize) for dialysis vintage. Also, can you please clarify the footnote under Table 3: what is "whole cohort distribution"? We performed direct standardization (not model-based adjustment, except for the Poisson regression) using the whole cohort distribution as the reference. When applying direct standardization, choosing a standard dialysis vintage distribution is arbitrary. We could have chosen the distribution from 2001 or 2007. Using the whole cohort distribution is equivalent to using the mean proportions of dialysis vintage categories between 2001 and 2007. We added a reference for this common choice of standard choice technique. The same methodology applies to age and sex. c. In the results you describe Figure 4 on the hazard function. An explanation about this method and why you are doing this is lacking. The recurrent event model was used to ensure robustness of the findings when clustering of hospitalization (multiple hospitalizations for a single patient) was accounted for. An explanation is now given in the sensitivity analysis section. Since it was suggested that the manuscript had too many figures, we chose to remove Figure 4. 3. The authors could elaborate on important competing risks like dying. Since this study is not evaluating causes of infection-related hospitalizations, we do not believe that competing risks models would be useful. The aim of the study is to describe rates of IRH when adjusted for dialysis vintage. However, we acknowledge that the differential risk of dying associated with calendar time, age, sex and dialysis vintage influences rates of IRH. This fact is explained on page 10 where we hypothesized why IRH rates are declining with dialysis vintage (survival effect). The aim is not to adjust for this effect, but to describe it. Minor comments 4. Page 5, line 38: add the word "also" we ALSO included Done. 5. In Figure 1 the author described: "Patients in RAMQ between Jan 1 1999". However, in the methods I do not see the year 1999, only 2001. Please clarify. Patients that ended follow-up before 2001 were included in the diagram. We removed them and changed the dates accordingly for clarity.