Author’s response to reviews

Title: Trajectories of seasonal influenza vaccine uptake among French people with diabetes: a nationwide retrospective cohort study, 2006-2015

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Author's response to reviews:

Trajectories of seasonal influenza vaccine uptake among French people with diabetes from 2006 to 2015: a group-based modeling approach (BMC Public Health - PUBH-D-18-04224)

Response to the reviewers' comments

Daniel Nagin (Reviewer 1):

This study uses group-based trajectory modeling to identify trajectories of SIV uptake among diabetics. While I do not have substantive expertise in this domain, the study strikes me as a useful and generally well conducted application of GBTM. I do, however, have several questions/suggestions:
1) What is/are the orders of the polynomials used in the specifications of the trajectories reported in Figure 1?

Response: We used third-degree polynomials for all trajectories, except for the "Early increasingly vaccinated" trajectory, for which a second-degree polynomial was used.

We added the following note under Figure 1: “Third-degree polynomials were used for the specifications of all trajectories, except for the "Early increasingly vaccinated" trajectory, for which a second-degree polynomial was used.”

We also added the following point to the methods section (see revised version, page 7, lines 14-16): “To determine the order of the polynomials for all trajectories, we started with third-degree polynomials and used the standard operating procedure, i.e. stepwise elimination of non-significant polynomial higher orders [19].”

2) More detail on the model selection should be reported. Did the 8 group model maximize BIC or was it selected based on substantive considerations?

Response: As mentioned in the initial version of the manuscript (page 7, line 10), we started with a one-trajecotry solution and then added additional trajectories, one at a time, and tested the fit of each model with the Bayesian information criterion (BIC, i.e., the better the fit, the lower the BIC), balancing it with the objective of reporting distinguishable and interpretable trajectories. Based on the BIC values, the fit of the models improved as the number of trajectories modeled increased. From the seven-trajectory solution and after, the prevalence of some trajectories was very low and results were difficult to interpret. Accordingly, we considered that the solution that offered the best compromise between parsimony, fit, and interpretability was a six-trajectory solution, as recommended by Nagin and Odgers (Nagin and Odgers 2010). We modified the manuscript as follows:

- Methods section (see revised version, page 7, lines 11-14): “Starting with a one-trajectory solution, we added one trajectory at a time, testing each model fit and balancing it with our objective of identifying distinct trajectories. The prevalence of each trajectory and the relevance of the solutions were also considered, as recommended by Nagin and Odgers [18].”
Results section (see revised version, page 8, lines 14-17): “Based on the BIC values, the fit of the models improved as the number of trajectories modeled increased. From a seven-trajectory solution and after, the prevalence of some trajectories was very low and results were difficult to interpret. Accordingly, the solution that offered the best compromise between parsimony, fit, and interpretability was a six-trajectory solution”.

3) The risk factor analysis is not conducted in a statistically optimal fashion. The GBTM specification can be generalized to include predictors of probability of trajectory group membership. Under this generalization trajectories and predictors of the probability of trajectory group membership are estimated jointly not sequentially. The two stage procedure used by the authors does not account for uncertainty in trajectory group membership.

Response: We thank the reviewer for this helpful comment. Following his advice, we included predictors of trajectory group membership directly in the GBTM.

As two of the explanatory variables (i.e., diabetes treatment intensification and course of weighted individual chronic condition score during follow-up) can be built only for individuals with at least two full years of follow-up, we excluded individuals with shorter follow-ups: the model was computed for 15,766 patients of the 17,259 identified with diabetes in 2006, i.e. 90% of the initial study population. The 1,493 individuals excluded were older than the initial population (mean age = 73 ± 14 years versus 65 ± 14 years in the initial population). This modification slightly affected: i) the shape of the "Progressively non-vaccinated" trajectory (which we thus propose to rename "Progressively less vaccinated"), ii) its prevalence (18% versus 12% in the initial version of the article); iii) as well as the prevalence of the "Continuously vaccinated" trajectory (28% versus 34%).

Accordingly, we modified the manuscript as follows:

- Methods section (see revised version, page 7, lines 23-25): “The demographic, clinical, and healthcare utilization factors were added to the model as predictors of trajectory group membership. This joint estimation of trajectories and predictors of the probability of group membership allowed us to take into account the uncertainty in participants' trajectory group membership [15]”. 
Results section (see revised version, page 8, line 18 to page 9, line 7): “Classification quality was good for all six (mean posterior class-membership probability > 0.82). In trajectory 1 ("continuously vaccinated", 28% of the cohort), the SIV-uptake rate started at 92% at inclusion, then exceeded 97% throughout follow-up, with numbers of SIV injections over the 10-season follow-up ranging between 8 and 10. In trajectory 2 ("progressively less vaccinated", 18%), SIV uptake exceeded 95% at inclusion, finally dropping to 59% in 2015/16 (range of SIV injections: [6-9]). The uptake in trajectory 3 ("postpandemic decreasingly vaccinated", 10%) was relatively high (63-73%) and stable until the 2009/10 influenza A(H1N1) pandemic season; it dropped by 33 percentage points in 2010/11 (range of SIV injections: [2-8]). Trajectory 4 ("early increasingly vaccinated", 9%) began with a very low SIV-uptake rate at inclusion and then immediately and rapidly increased, stabilizing around 90% in 2011/12 (range of SIV injections: [4-9]). Trajectory 5 ("late increasingly vaccinated", 5%) looked like trajectory 4 with the increasing phase shifted forward several years (range of SIV injections: [2-6]). The individuals with trajectory 6 ("never vaccinated", 30%) had very low SIV-uptake rates throughout follow-up (range of SIV injections: [0-2]).”

Results section (page 9, line 9 to page 10, line 4), § “Risk factors for SIV-uptake trajectory memberships”: With the "continuously vaccinated" trajectory as the reference (Table 2), the probability of belonging to the "progressively less vaccinated" trajectory was higher for individuals aged 65 years or older at inclusion, those receiving no antidiabetic drug, with high comorbidity scores at inclusion and remaining stable during follow-up, hospitalized for influenza during follow-up, and seeing GPs frequently. It was lower among women, for those with intensified diabetes treatment, seeing endocrinologists frequently, and changing GPs during follow-up.

The remaining four trajectories ("postpandemic decreasingly vaccinated", "early"/"late increasingly vaccinated", and "never vaccinated") shared several characteristics. The probability of belonging to these four trajectories was higher in patients receiving no antidiabetic drug at inclusion and lower in those aged 65 years or older, with more comorbidities at inclusion, and with frequent visits with specialists during follow-up. These trajectories also showed some specificities. The probability of belonging to the "postpandemic decreasingly vaccinated" trajectory was higher for women and individuals hospitalized for diabetes or influenza; it was lower for those with worsening comorbidities. The probability of belonging to the "early" or "late increasingly vaccinated" trajectories was higher for those with worsening diabetes and comorbidities during follow-up, and those hospitalized for influenza (for the "early increasingly" trajectory only); it was lower for individuals with type 1 diabetes. Finally, the probability of belonging to the “never vaccinated” trajectory was higher for women and for individuals with stable comorbidities, and lower for those with type 1 diabetes, with worsening comorbidities, frequent healthcare utilization, and changing GPs during follow-up.”
Discussion section (page 10, lines 8-12): "Overall, this study shows remarkable inertia in behavioural patterns, with 28% of the subjects continuously vaccinated and 30% never vaccinated from 2006/07 to 2015/16. For two other trajectories, the SIV-uptake rate decreased during follow-up, either progressively (18%) or more sharply after the 2009/10 season (10%), while the SIV-uptake rate rose for the last two trajectories (accounting for only 14% of patients).

We also deleted from the Discussion two sentences related to the potential impact of changing GPs on SIV behaviours, as this variable was no longer associated with the “Late increasing trajectory”:

- Initial version, page 44, line 49: “Our results also suggest that changing GPs may correlate with a shift in SIV behaviour: seeing a new physician is often an opportunity to review prevention needs [32].”

- Initial version, page 12, line 31: “[...] as well as changes of GP”.

We have added the following note under Figure 1: “b Among individuals with at least two full years of follow-up (n = 15 766, 90.2%) to enable calculation of two variables included in the model (i.e., diabetes treatment intensification and course of weighted individual chronic condition score during follow-up).”

4) I do not understand how comorbidities can be used as predictors of trajectory group membership because they evolve over time along with the SIV trajectories themselves.

Response: Results from the literature suggest that regular SIV in patients with diabetes is more frequent in those with additional comorbidities, and that a worsening of the health status may foster SIV uptake. Thus, we made two hypotheses: that SIV trajectory group membership would be associated with i) the level of comorbidities at inclusion; and ii) its overall evolution over the study period. We thus calculated two covariates:
The weighted individual chronic condition score at inclusion. As expected, compared to "continuously vaccinated" people, we found that those in the other trajectories (except the “progressively less vaccinated” one) had fewer comorbidities at inclusion (see revised version, Table 2).

A second variable that summarizes the course of the comorbidity score over the 10-year follow-up period (decreasing, stable, or increasing). As explained in the manuscript (see initial version, page 6, lines 17-24), we calculated for each year of follow-up an individual chronic condition score (ICC) based on drug deliveries according to a previously published methodology and then we built a 3-category variable describing the course of the ICC score from the first to the last year of follow-up (decreasing, increasing, or stable) that was included in our analysis as a time-stable covariate (Jones et al. 2001). In this study, we found that the probability of belonging to the "early" or "late increasingly vaccinated" trajectories was higher for those with increasing comorbidities during follow-up (see revised version, Table 2).

We completed the methods section as follows (see revised version, page 6, lines 11-13): “Then we built a 3-category variable describing the course of the ICC score from the first to the last year of follow-up (decreasing, increasing, or stable) and included it in our analysis, as a time-stable variable [15].”

Lin Yang (Reviewer 2):

5) It is important to identify the characteristics of chronic patients with vaccine hesitancy. The authors conducted an interesting study to explore the clinical characteristics of DM patients with different vaccination behavior. The sample is large and the follow-up period is long. The related clinical and demographic factors identified in their model echo previous studies. However, the authors did not collect any data about the knowledge and attitude against SIV from these DM patients, which are important drivers of vaccination behaviors. The authors may add some discussions about this.

Response: We fully agree with the reviewer that knowledge and attitudes are important drivers of vaccination behaviour. As mentioned in the initial version of the manuscript (see initial version, page 10, lines 27-29), data about individuals’ knowledge, attitudes or perceptions about vaccination are not recorded in the health insurance databases (which have been set up to record health care reimbursement). In France, knowledge and attitude data are regularly collected with questionnaires among the general population through cross-sectional surveys, but for samples 1/20th the size: it would not have been possible to match them with the EGB database.
We have modified the discussion section as follows (see revised version, page 11, lines 11-13): “[…] Specifically, no data about individuals’ knowledge, attitudes or perceptions towards SIV (e.g., beliefs about SIV efficacy, side effects) were available, although they are important drivers of SIV behaviours [23,24] and thus probably differ according to trajectories.”

6) There is other information the authors may consider adding into this paper if available.

Response: We thank the reviewer for this remark and his suggestions that will help readers to better understand the French context. We have made several modifications to improve their understanding.

a. For example, was it easy and convenient for these patients to get vaccinated?

We completed the methods and discussion sections to give more information about convenience issues, regardless of whether or not patients receive a free vaccination voucher:

- Methods section (see revised version, page 6, lines 21-23): “The NHIF sends free vaccination vouchers each season to individuals aged 65 years or older and to those patients with diabetes with an LTI status […]. The voucher enables these patients to obtain the vaccine free of charge at the pharmacy, without a doctor’s prescription. They must then make an appointment with either a doctor or a nurse for its administration.”

- Discussion section (see revised version, page 12, line 3-8): “Opportunities might also have been missed: we estimated that, at inclusion, 30% of patients with diabetes did not receive free vouchers because they did not benefit from LTI status. These patients can obtain a voucher from their doctor but this makes their pathway to vaccination still more complex as it requires first a doctor’s appointment to get a free vaccine voucher, then a trip to the pharmacy to pick up the vaccine, and then a second appointment for the actual injection.”

b. Were all vaccines claimed under insurance (i.e. outcome data completeness)?

We completed the paragraph related to the study limitations as follows (see revised version, page 11, lines 1-6): “We acknowledge some limitations. Vaccinations that took place during occupational medicine visits or at vaccination centres or some nursing homes that buy vaccines for their residents (fewer than 20% of all nursing homes [24]) are not recorded in the French NHIF databases. However, these limitations are unlikely to affect our results substantially as the vast majority of vaccinations in France are administered by private healthcare workers and are thus recorded in these databases [25].”
c. “It was mentioned that free vouchers were distributed, but did all eligible people use it?”

There are patients who have received a voucher (see remark “6.a”) and do not use it because they refuse to be vaccinated (no dispensing) or who lose it and thus must pay for the vaccine (dispensing); the proportion of the latter is probably very low.

7) The authors selected the samples of working populations covered by insurance, which excluded retired elderly one of the priority groups for vaccination campaigns, in addition to self-employed people as claimed by the authors. Also the behaviors of those without insurance could be very different. The authors shall add some discussions about this point.

Response:

- Our data did include retired salaried workers. We acknowledge that the formulation was unclear and modified the manuscript as follows (see revised version, page 5, line 2): “For this study, we extracted data for salaried workers (including those who are retired) only...”.

- In France, only very few people have no insurance because all legal residents of France are covered by a health insurance fund (NHIF or another depending on their occupation). We completed the discussion section (see revised manuscript, page 10, lines 6-9): “As SIV behaviour varies by socioeconomic characteristics [26], our results cannot be extrapolated to population categories not covered by the NHIF (e.g., farmers, the self-employed) or the very few people without insurance; nonetheless, the NHIF covers 86% of the French population.”

8) I suggest the authors to separate type I and II DM in their analysis, as their age distribution and medication are very different. Stratified analysis could be considered.

Response: As SIV is recommended for both Type I and Type II DM, we decided to include both types of DM in our study. We understand that it would be interesting to explore type I and II DM separately, but the current sample size of people with Type I DM in our cohort (9% of our cohort) would not allow us to identify trajectories of SIV with acceptable accuracy.
9) A) The definitions of trajectories are quite confusing, were these based on the number of total injections or based on some distribution probabilities? Predefined by the authors or data driven? The authors list six categories, but it seems to me that these six excluded those who continuously got vaccinated for a couple of years and then stopped and got vaccinated again at the end. […] More technical details of GBT models could help readers better understand the results.

Response: With group-based trajectory modeling (GBTM), the number and the shape of trajectories are all data driven. GBTM is designed to analyze the evolution of an outcome over time and to identify, within a population with unobserved heterogeneity, distinctive clusters of individuals with similar developmental trajectories of behaviors (here, number and timing of the SIV injections during the 10-year follow-up period). It enables the selection of the model with an optimal number of distinct trajectories that most appropriately represent the heterogeneity in the population.

The trajectory mentioned by the reviewer (i.e., people who were vaccinated for a couple of years and then stopped and were then vaccinated again at the end) probably exists among patients with diabetes. However, the fact it was not identified by our six-trajectory solution means that it is rare. As mentioned in the manuscript, we chose a six-trajectory solution because it offered the best compromise between parsimony, fit, and interpretability.

We hope that the following modifications of the Statistical analysis section will help readers understand the manuscript better (see revised version, page 7, lines 2-14): “We ran group-based trajectory (GBT) modeling to identify subgroups of individuals with similar patterns of SIV dispensing over time during the 10-year follow-up period. GBT modeling is a data-driven semiparametric method designed to analyze the evolution of an outcome over time and to identify, within a population with unobserved heterogeneity, distinctive clusters of individuals following similar trajectories of behaviors related to this outcome [16,17]. It makes it possible to select the model with an optimal number of distinct trajectories that most appropriately represent the heterogeneity in the population [15]. To compare the models’ goodness of fit, we used the Bayesian information criterion (BIC) and individual posterior class-membership probabilities (i.e., the probability of belonging to a trajectory given the information collected). Starting with a one-trajectory solution, we added one trajectory at a time, testing each model fit and balancing it with our objective of identifying distinct and interpretable trajectories. The prevalence of each trajectory and the relevance of the solutions were also considered, as recommended by Nagin and Odgers [18].”
9) B) Some mean+/SD are larger than 10 or low than 0, which is not reasonable. The authors may consider showing data range instead.

Response: We agree with the reviewer and made the following modifications in the result section of the manuscript (see revised version, page 8, line 20 to page 8, line 7): “In trajectory 1 ("continuously vaccinated", 28% of the cohort), the SIV-uptake rate started at 92% at inclusion, then exceeded 97% throughout follow-up, with numbers of SIV injections over the 10-season follow-up ranging between 8 and 10. In trajectory 2 ("progressively less vaccinated", 18%), SIV uptake exceeded 95% at inclusion, finally dropping to 59% in 2015/16 (range of SIV injections: [6-9]). The uptake in trajectory 3 ("postpandemic decreasingly vaccinated", 10%) was relatively high (63-73%) and stable until the 2009/10 influenza A(H1N1) pandemic season; it dropped by 33 percentage points in 2010/11 (range of SIV injections: [2-8]). Trajectory 4 ("early increasingly vaccinated", 9%) began with a very low SIV-uptake rate at inclusion and then immediately and rapidly increased, stabilizing around 90% in 2011/12 (range of SIV injections: [4-9]). Trajectory 5 ("late increasingly vaccinated", 5%) looked like trajectory 4 with the increasing phase shifted forward several years (range of SIV injections: [2-6]). The individuals with trajectory 6 ("never vaccinated", 30%) had very low SIV-uptake rates throughout follow-up (range of SIV injections: [0-2]).”

10) In discussion, the authors made a lot of statement without support from literature or their data. For example, P11, L22, is this statement based on their own data? P12, L31, this over interprets their findings, no evidence supports that a new GP could more likely persuade a patient to get vaccinated.

Response: In the discussion, we indeed formulated a number of hypotheses to interpret our results. We regret that some of them appeared rather as statements, and made some modifications to formulate these hypotheses more carefully:

- Initial version, P11, L22: “Diabetes itself and prevention of its complications might become a lower priority among these patients, as implied, for example, by their less frequent consultations with endocrinologists and antidiabetic treatment”. We acknowledge that the initial formulation could be confusing, and modified the discussion as follows (see revised version, page 11, lines 15-18): “Our results that patients in the "progressively less vaccinated" trajectory had less frequent consultations with endocrinologists and antidiabetic treatment might also suggest that diabetes itself and prevention of its complications has become a lower priority among these patients.”
Initial version, P12, L31: “Our study also suggests that health events as well as changes of GP may represent critical periods for healthcare workers to address vaccine hesitancy.” In response to the remark n°3 of Reviewer #1 (see below), we modified the sentence as follows: “Our study also suggests that health events may represent critical periods for healthcare workers to address vaccine hesitancy.”

Revised version page 11, lines 21-25: “We may assume that subjects continuously vaccinated were aware of their vulnerability to influenza (due to age and/or comorbidities [9]) before our follow-up began. Another hypothesis is that receiving a free voucher each year at least as early as inclusion (Appendix Table 3) and regular medical consultations may foster SIV behaviours because they act as reminders [31] and the vouchers may facilitate access to the vaccine [8].”

Revised version page 13, line 6: “[…] This finding suggests that offering a voucher might foster positive behaviour change [8,31].”

Minor comments:

11) Abstracts: Which trajectories does "stable SIV behaviors" refer to? The statement " Most patients with diabetes had stable SIV behaviors, but others adopted or abandoned SIV in relation to increasing age, health events, or contextual factors (e.g., controversies about vaccine safety or efficacy)" over-interpreted their results, as they have not collected the opinions of these participants.

Response: We acknowledge that the “Conclusion” paragraph of the abstract was unclear and the formulation inappropriate. We have modified this paragraph as follows (see revised version, page 3, lines 43-46): “Most patients with diabetes had been continuously vaccinated or never vaccinated, and thus had stable SIV behaviours. Others adopted or abandoned SIV. These behaviour shifts might be due to increasing age, health events, or contextual factors (e.g., controversies about vaccine safety or efficacy)...”
12) P7 L15, it is not clear how the authors handled missing data in data analysis. More information about data completeness is also needed.

Response: Regarding covariates (Table 2), since we used a medico-administrative database, we did not have any missing data. However, as two of the explanatory variables (i.e., diabetes treatment intensification and course of weighted individual chronic condition score during follow-up) can be built only for individuals with at least two full years of follow-up, the GBTM model was computed from 15,766 patients of the 17,259 identified with diabetes in 2006. We added the following note under Figure 1 and Table 2: “Among individuals with at least two full years of follow-up (n = 15,766, 90.2%), to enable calculation of two variables included in the model (i.e., diabetes treatment intensification and course of weighted individual chronic condition score during follow-up).”

To take into account the potential biases due to nonrandom participant attrition (especially those due to mortality during follow-up – see Appendix Table 3), we used the dropout extension of the PROC TRAJ procedure. To clarify this, we completed the methods section as follows (see revised version, page 7, lines 17-22: “Early applications of GBT modelling have assumed that all attrition (including both loss to follow-up and mortality) is randomly distributed among all trajectories. A recent enhancement of the GBT approach enables the joint modelling of the outcome of interest and non-random missingness [20,21]. Using this methodology, we were able to model attrition probabilities (mortality represented the vast majority of attrition in our study) jointly with the estimation of SIV delivery trajectories.”

13) P10, L58, does "systematically" mean continuously?

Response: We have made the suggested modification (see revised version, page 12, line 1).

14) Table 1. Formats and headings need tidy up. For example, "Hospitalized for diabetes or its complications between 09.01.n-1 and 08.31.n" could change to "Annual rate of hospitalization for diabetes or its complications". Delete "n/n+1" in caption.

Response: We have followed the reviewer's advice and made the relevant changes.
15) Table 2. Reference groups for each variable should move to the note under the table. "Average annual number of consultations during follow-up ≥ Median" may change to "Frequent consultation.

Response: As suggested by the reviewer, we have added a note under the Table 2 to specify the reference group for each variable: “Reference groups. Age: "≤ 65 years"; gender: "men"; type and treatment of diabetes at inclusion: "other types -- ≥ 1 antidiabetic drug"; diabetes treatment intensification: "no"; weighted individual chronic condition score at inclusion: "< median"; course of weighted individual chronic condition score: "decreasing"; hospitalized during follow-up: "no"; consultations during follow-up: "number of consultations < median"; change of general practitioner: "no".”

16) Appendix table 4 is not referred in main text. Were those deceased cases excluded from data analysis?

Response: We thank the reviewer for this remark and have added a reference to Appendix Table 4 in the Results section (see revised version, page 8, line 10): “Over the 10-year follow-up, 31% of the initial cohort died (Appendix Table 4), …”.

As mentioned in the Methods section, paragraph “Study population” (see revised version, page 5, line 19), “Those who died […] during the follow-up period were censored at the start of the year of the event.”

Besides, as mentioned in our response to remark n°12, we used a recent enhancement of the GBT approach to model attrition probabilities (as mortality represented the vast majority of attrition in our study) jointly with the estimation of SIV trajectories.