PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Six-month outcomes after a GP phone call during the first French COVID-19 lockdown (COVIQuest): a cluster randomised trial using medico-administrative databases

Authors

Sauvage, Ambre; Laurent, Emeline; Giraudeau, Bruno; Tassi, Marc-Florent; Godillon, Lucile; Grammatico-Guillon, Leslie; Dibao-Dina, Clarisse

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Sarfraz, Zouina**
Affiliation	**Larkin Community Hospital**
Date	**10-Apr-2024**
COI	**None.**

General Comments

The COVIQuest trial provides valuable insights into the healthcare engagement of patients with chronic diseases during the challenging period of the first COVID-19 lockdown in France. By investigating the impact of a simple intervention, a phone call by a general practitioner (GP), on the hospitalization rates among patients with cardiovascular diseases (CVD) or mental health disorders (MHD), this study contributes to our understanding of healthcare accessibility and patient management during crises. This study is well-timed and addresses a critical gap in healthcare delivery during pandemics. However, there are several areas where minor revisions could enhance the clarity, interpretability, and applicability of the findings.

Strengths

Large, Multicenter Trial Design: The study's robust sample size and the use of a multicenter randomized controlled trial design enhance the reliability and generalizability of the findings.

Use of National Medico-Administrative Databases: Leveraging comprehensive healthcare data from the French health system (Système National des Données de Santé, SNDS)

provides a solid foundation for assessing hospitalization rates and specialized consultation rates. This approach allows for a detailed and cost-effective analysis of healthcare service consumption.

Timeliness and Relevance: The study addresses an urgent healthcare issue—the impact of the COVID-19 lockdown on patients with chronic diseases. The intervention, a GP-initiated phone call, is a practical and potentially scalable approach to mitigate the negative impacts of reduced healthcare access during lockdowns.

Areas for Minor Revision

Clarification of Intervention Timing and Overlapping National Campaigns: The study mentions potential confounding effects due to national campaigns promoting medical use during the lockdown. It would be beneficial to discuss these overlaps in more detail, including the timing of such campaigns relative to the study intervention, to better understand the study's context and potential confounding factors.

Discussion on the Selection of Control and Intervention Groups: While the study briefly mentions the selection process, further clarification on how patients were assigned to control and intervention groups, ensuring the comparability of these groups, would improve the reader's understanding of the study design.

Broader Contextualization of Findings Within Existing Literature: The discussion could benefit from a more detailed comparison with similar studies conducted in other countries or healthcare settings. This could help to position the study's findings within the broader global response to healthcare challenges posed by the COVID-19 pandemic.

Implications for Future Pandemic Preparedness: The conclusion section could be expanded to offer more specific recommendations for healthcare policy and practice, based on the study's findings. Suggestions for how similar interventions could be implemented or adapted in future crises would be particularly valuable.

Addressing Limitations Related to Self-Reported Outcomes: The paper mentions the use of self-reported outcomes as a limitation. Including strategies for validating these outcomes or future research directions to overcome this limitation would strengthen the study.

Specific Recommendations

Methodological Details: Provide more details on the logistic regression model and the generalised estimating equation framework used for analysis. Clarifying these statistical methods will help readers assess the analytical rigor of the study.

Subgroup Analyses: If data permits, conducting subgroup analyses (e.g., age, severity of chronic conditions) might reveal nuanced insights into the intervention's effectiveness across different patient demographics or disease severities.

Consideration of Telehealth: Given the rise of telehealth during the pandemic, discussing how the intervention aligns or contrasts with telehealth initiatives could provide a richer context for interpreting the findings.

Final Comments

The COVIQuest trial offers important insights into the role of GP-initiated phone calls in managing hospitalization rates among patients with chronic diseases during the COVID-19 lockdown. With minor revisions, particularly in clarifying the study's context, methods, and the broader implications of its findings, this paper could significantly contribute to the literature on healthcare delivery during pandemics. The authors are commended for their timely and relevant work.

Reviewer	**2**
Name	**Kulkarni , Prashanth**
Affiliation	**Heart Care center , Cardiology**
Date	**13-Apr-2024**
COI	**None**

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(1) The objectives of the study are clearly articulated, focusing on evaluating the impact of GP phone calls on hospitalization and specialized consultation rates among chronic patients during the COVID-19 lockdown.

(2) The authors could share more details on how potential confounders (such as national campaigns promoting medical use during lockdown) were addressed in the analysis that would strengthen the methodological clarity.

(3) The authors could consider refining the conclusion to emphasize the complexity of interpreting the findings in light of the potential confounders and external influences during the COVID-19 lockdown. Clearly articulate the study's limitations, including the impact of external campaigns and potential biases introduced by the study design.

Reviewer	**3**
Name	**Zhang, Dr Jufen**
Affiliation	**Anglia Ruskin University**
Date	**08-Jul-2024**
COI	**None.**

Abstract: it stated that "… concluded that the intervention had no effect on the rate of self-reported hospitalisations for CVD patients, whereas the intervention group might have a higher rate for MHD patients." The study period time needs to be specified. In addition, please explain "OR" reported in the results section.

In the methods section, suggest providing briefly the study design regarding to the sample size determination and randomization procedure.

In the main outcomes section, "The main outcome of the 6-month analysis of COVIQuest was the occurrence of at least one hospitalization during the study period". What's the type of hospital admission (any type?)

"ICD-10 main diagnosis in Ix.x" reported in other outcomes, what's the meaning of "Ix.x"?

In the other outcomes section, noted that time to first hospitalization was collected. However, the information was not used. It looks that incidence rate based on person-years data needs to be reported and compared between two groups.

Missing data are common in this type of study, how were the missing values handled in the analysis?

In the results section (6-month specialized practitioner consultations): Suggest changing "77[IQ47-137]" to (IQR): 77 (IQR 47-137).

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1
Dr. Zouina Sarfraz, Larkin Community Hospital

Comments to the Author:

General Comments
The COVIQuest trial provides valuable insights into the healthcare engagement of patients with chronic diseases during the challenging period of the first COVID-19 lockdown in France. By investigating the impact of a simple intervention, a phone call by a general practitioner (GP), on the hospitalization rates among patients with cardiovascular diseases (CVD) or mental health disorders (MHD), this study contributes to our understanding of healthcare accessibility and patient management during crises. This study is well-timed and addresses a critical gap in healthcare delivery during pandemics. However, there are several areas where minor revisions could enhance the clarity, interpretability, and applicability of the findings.

Strengths
Large, Multicenter Trial Design: The study's robust sample size and the use of a multicenter randomized controlled trial design enhance the reliability and generalizability of the findings.

Use of National Medico-Administrative Databases: Leveraging comprehensive healthcare data from the French health system (Système National des Données de Santé, SNDS) provides a solid foundation

for assessing hospitalization rates and specialized consultation rates. This approach allows for a detailed and cost-effective analysis of healthcare service consumption.

Timeliness and Relevance: The study addresses an urgent healthcare issue—the impact of the COVID-19 lockdown on patients with chronic diseases. The intervention, a GP-initiated phone call, is a practical and potentially scalable approach to mitigate the negative impacts of reduced healthcare access during lockdowns.

Thank you for all these encouraging comments.

Areas for Minor Revision

Clarification of Intervention Timing and Overlapping National Campaigns: The study mentions potential confounding effects due to national campaigns promoting medical use during the lockdown. It would be beneficial to discuss these overlaps in more detail, including the timing of such campaigns relative to the study intervention, to better understand the study's context and potential confounding factors.

Thank you for this request. The idea for COVIQuest appeared following the lockdown which was established in France on March 17, 2020 limitating patients' access to their GP the following days. The protocol was barely finalized (letter of intent submitted on April 6, 2020) when the Government recommended the intervention implemented in our protocol on April 8, 2020, i.e. 20 days before our study received the necessary regulatory approvals to start the study. This very tight timing may have led to an underestimation of the effect of our intervention.

This was expressed in the discussion section, but in order to clarify it, we modified it as such:

"Due to research regulatory issues, the study started six weeks after the lockdown was established, and the Ministry of Health outlined the intervention implemented in our protocol on April 8, 2020. This was 20 days before our study received the necessary regulatory approvals to start, leading to contamination in the control groups."

Discussion on the Selection of Control and Intervention Groups: While the study briefly mentions the selection process, further clarification on how patients were assigned to control and intervention groups, ensuring the comparability of these groups, would improve the reader's understanding of the study design.

Thank you for this comment. Because the two sub-trials were cluster randomised trials, it is the GPs who were assigned to the control and intervention groups rather than patients themselves. Each GP recruited his/her eligible patients. We added some clarification in the "study design" paragraph of the methods section:

"The COVIQuest trial was a randomised 1:1 controlled trial, open-labelled, comparing two parallel groups: […]"

"The patients ≥70 years old with CVD and ≥18 years old with MHD were included by voluntary GPs from eight French regions. The GPs selected patients according to their inscription on the long-term illness list (*Affection Longue Durée* ALD number 1, 3, 5, 12 and 13) (7)."

"Each sub-trial was a cluster randomised trial with GPs being clusters (i.e., randomisation units). The randomisation process was extensively described elsewhere (7)."

All these details were included in the reference number 7 (first article about the COVIQuest study), but we agree that it was probably preferable to re-include details in this second article, as well as more reminders to this reference.

Broader Contextualization of Findings Within Existing Literature: The discussion could benefit from a more detailed comparison with similar studies conducted in other countries or healthcare settings. This could help to position the study's findings within the broader global response to healthcare challenges posed by the COVID-19 pandemic.

Thank you for this remark. To our knowledge, no such study evaluating long-term outcomes was conducted in other countries. We added this precision in the discussion.
The objective of contact with the general practitioner was to be able to reduce the morbidity and mortality of vulnerable populations that the absence of contact with their general practitioner could impact. This impact on morbidity and mortality could not be demonstrated; however, hospitalisations increased in the intervention group. The lack of contact with their general practitioner for these fragile populations may therefore have led to a loss of opportunity with an absence of hospitalizations which would have been necessary. It was thus shown that hospitalisations of patients at cardiovascular risk were more complex during the first lockdown (*Cho K, Femia G, Lee R, Nageswararajah D, Doulatram H, Kadappu K, Juergens C. Exploration of Cardiology Patient Hospital Presentations, Health Care Utilisation and Cardiovascular Risk Factors During the COVID-19 Pandemic. Heart Lung Circ. 2023 Mar;32(3):348-352*). For patients with a mental health disease, these hospitalisations may have avoided more complicated or critical issues such as suicides, psychiatric decompensations, or substance/drug abuse (*Robillard R, Daros AR, Phillips JL, et al. Emerging New Psychiatric Symptoms and the Worsening of Pre-existing Mental Disorders during the COVID-19 Pandemic: A Canadian Multisite Study: Nouveaux symptômes psychiatriques émergents et détérioration des troubles mentaux préexistants durant la pandémie de la COVID-19: une étude canadienne multisite. Can J Psychiatry. 2021:706743720986786*).
We therefore implemented the discussion as follow:
"The 6-month results were the opposite of what was expected since the intervention (in line with public campaigns) was supposed to manage chronic diseases' complications earlier to avoid later hospitalisation. However, the lack of contact with their GP for these vulnerable populations may have resulted in missed opportunity, including necessary hospitalisations. It has been shown that hospitalizations for patients at cardiovascular risk were more complex during the first lockdown (15). For patients with a mental health condition, such hospitalisations might have prevented more complicated or critical issues such as suicides, psychiatric crises, or substance/drug abuse (16).
The increase shown in hospitalisation rates for intervention groups can therefore supports that the intervention allowed a higher level of care management, allowing a return to pre-pandemic levels."

Implications for Future Pandemic Preparedness: The conclusion section could be expanded to offer more specific recommendations for healthcare policy and practice, based on the study's findings. Suggestions for how similar interventions could be implemented or adapted in future crises would be particularly valuable.
Thank you, we ended the discussion with these sentences:
"Maintaining possible contact with primary care for people with chronic cardiovascular disease or mental health conditions should be encouraged during epidemic periods. Our study demonstrated that a simple phone call with one's GP can be enough to detect complications requiring hospitalisation during lockdown, a finding that has also been supported by other studies (*Murphy M, Scott LJ, Salisbury C, Turner A, Scott A, Denholm R, Lewis R, Iyer G, Macleod J, Horwood J. Implementation of remote consulting in UK primary care following the COVID-19 pandemic: a mixed-methods longitudinal study. Br J Gen Pract. 2021 Feb 25;71(704):e166-e177*) – (*Bouchez T, Gautier S, Le Breton J, Bourgueil Y, Ramond-Roquin A. The challenge for general practitioners to keep in touch with vulnerable patients during the COVID-19 lockdown: an observational study in France. BMC Prim Care. 2022 Apr 18;23(1):82*) – (*Johnsen TM, Norberg BL, Kristiansen E, Zanaboni P, Austad B, Krogh FH, Getz L. Suitability of Video Consultations During the COVID-19 Pandemic Lockdown: Cross-sectional Survey Among Norwegian General Practitioners. J Med Internet Res. 2021 Feb 8;23(2):e26433*)."

Addressing Limitations Related to Self-Reported Outcomes: The paper mentions the use of self-reported outcomes as a limitation. Including strategies for validating these outcomes or future research directions to overcome this limitation would strengthen the study.

Indeed, self-reported hospitalisations was the outcome chosen at 1 month and led to errors and missing data. The use of SNDS data makes it possible to avoid these hazards and could be favoured in the future.
We therefore implemented the discussion as such:
"Thus, the clinical database could be considered as gold standard regarding the chronic conditions of patients included by the GPs, whereas the SNDS database was gold standard for healthcare services consumption: hospitalisations, consultations, drug deliveries; as all reimbursed care consumption is comprehensively included in the SNDS database. Therefore, using SNDS data helps prevent missing data and classification bias associated to self-reported outcomes and could be preferable in the future. The SNDS database allowed an automated and cost-effective follow-up of over 4,000 patients and addressed the questions of the GP phone call impact at 6-months."

Specific Recommendations

Methodological Details: Provide more details on the logistic regression model and the generalised estimating equation framework used for analysis. Clarifying these statistical methods will help readers assess the analytical rigor of the study.
The method used to analyze data was a very classical one. We specified that this allows considering clustering at the cluster level. We also specified the fixed effects considered in the models. So we consider that there is no need to add anything else, provided that this statistical method is classically used.

Subgroup Analyses: If data permits, conducting subgroup analyses (e.g., age, severity of chronic conditions) might reveal nuanced insights into the intervention's effectiveness across different patient demographics or disease severities.
Thank you for this important remark. The number of overall events was probably too low, resulting in insufficient power particularly in the MHD sub-trial, to consider subgroup analyses. Indeed, the overall 95% confidence intervals were wide, with statistical significance at the limit for the occurrence of at least one hospitalisation at 6 months, and not significant for the occurrence of at least one dedicated specialist consultation at 6 months.
Regarding age, all patients from the CVD sub-trial (which included more patients, thus with subgroup analyses potentially doable) were ≥70 years old, a precision that we added in the methods section as it was missing.
Regarding the severity of chronic condition, this cannot be easily approached by the SNDS database and would require a more refined algorithm, taking into account a larger period before the inclusion date, in order to quantify all clinically significant events related to the chronic condition in the two previous years for example. However, data from this time interval were not requested from the CNAM, and were not included in the study protocol.
In order to mention this, we added this sentence in the discussion section:
"Eventually, nuanced insights could potentially have emerged from subgroup analyses, such as those based on the severity of the chronic conditions. However, the number of events, and consequently the study's statistical power, was insufficient for such analyses, and assessing the severity of chronic conditions would have required more temporal distance than the SNDS data allowed."

Consideration of Telehealth: Given the rise of telehealth during the pandemic, discussing how the intervention aligns or contrasts with telehealth initiatives could provide a richer context for interpreting the findings.
This is indeed an important point which we added, please see above the answer to the comment "Implications for Future Pandemic Preparedness".

Final Comments

The COVIQuest trial offers important insights into the role of GP-initiated phone calls in managing hospitalization rates among patients with chronic diseases during the COVID-19 lockdown. With minor revisions, particularly in clarifying the study's context, methods, and the broader implications of its findings, this paper could significantly contribute to the literature on healthcare delivery during pandemics. The authors are commended for their timely and relevant work.
We thank you for the relevance of your comments and we hope that the changes we have made meet your expectations.

Reviewer: 2
Dr. Prashanth Kulkarni, Heart Care center

Comments to the Author:

(1) The objectives of the study are clearly articulated, focusing on evaluating the impact of GP phone calls on hospitalization and specialized consultation rates among chronic patients during the COVID-19 lockdown.
Thank you for this positive comment.

(2) The authors could share more details on how potential confounders (such as national campaigns promoting medical use during lockdown) were addressed in the analysis that would strengthen the methodological clarity.
Thank you for this remark, which was also underlined by the first reviewer. This limitation could unfortunately not be addressed.
We paste here the answer made to reviewer 1:
The idea for COVIQuest appeared following the lockdown which was put in place on March 17, 2020 and which limited patients' access to their general practitioner in the days that followed. The protocol was barely finalized (letter of intent submitted on April 6, 2020) when the government recommended the intervention implemented in our protocol on April 8, 2020, i.e. 20 days before our study received the necessary regulatory authorizations to begin. This very tight timing may have led to an underestimate of the effect of our intervention.
This was expressed in the discussion section, but in order to clarify it, we modified it as such:
"Due to research regulatory issues, the study started six weeks after the lockdown was established, and the Ministry of Health outlined the intervention implemented in our protocol on April 8, 2020. This was 20 days before our study received the necessary regulatory approvals to start, leading to contamination in the control groups."

(3) The authors could consider refining the conclusion to emphasize the complexity of interpreting the findings in light of the potential confounders and external influences during the COVID-19 lockdown. Clearly articulate the study's limitations, including the impact of external campaigns and potential biases introduced by the study design.
Please see the previous answer. We hope that this implementation will adequately address this comment. We thank you for your reviewing.

Reviewer: 3
Dr. Dr Jufen Zhang, Anglia Ruskin University

Comments to the Author:

Abstract: it stated that "… concluded that the intervention had no effect on the rate of self-reported hospitalisations for CVD patients, whereas the intervention group might have a higher rate for MHD

patients." The study period time needs to be specified. In addition, please explain "OR" reported in the results section.
Thank you for this well-spotted remark. We added "at one month", which was indeed forgotten. We also added the description of the OR acronym.

In the methods section, suggest providing briefly the study design regarding to the sample size determination and randomization procedure.
Thank you for this comment. Indeed, we report here the answer to the reviewer 1, who made the same comment:
We added some clarification in the "study design" paragraph of the methods section:
"The COVIQuest trial was a randomised 1:1 controlled trial, open-labelled, comparing two parallel groups: […]"
"The patients ≥70 years old with CVD and ≥18 years old with MHD were included by volunteer GPs from eight French regions. The GPs selected patients according to their inscription on the long-term illness list (*Affection Longue Durée* ALD number 1, 3, 5, 12 and 13) (7)."
"Each sub-trial was a cluster randomised trial with GPs being clusters (i.e., randomisation units). The randomisation process was extensively described elsewhere (7)."

We also added some clarification about the sample size in the "study design" paragraph of the methods section:
"As there was no data available to formulate hypothesis regarding sample size, the sample size was based on the minimum number of GPs expected to be recruited and the mean numbers of eligible patients per GP, as previously described (7)."

All these details were included in the reference number 7 (first article about the COVIQuest study), but we agree that it was probably preferable to re-include details in this second article, as well as more reminders to this reference.

In the main outcomes section, "The main outcome of the 6-month analysis of COVIQuest was the occurrence of at least one hospitalization during the study period". What's the type of hospital admission (any type?)
We tried to precise this in the next sentence of the same paragraph:
"For the CVD patients, only the hospitalisations of more than one night (except for patients dying the first day), for any reason, in an acute care unit were considered, given the various motives of one-day hospitalisation irrelevant for the study aims (e.g. dialysis sessions for patients with chronic renal failure). For the MHD patients, in addition, the hospitalisations in the psychiatric ward were also considered."

"ICD-10 main diagnosis in Ix.x" reported in other outcomes, what's the meaning of "Ix.x"?
We considered all diagnosis codes starting with "I", since they all refer to cardiovascular diseases included in chapter IX from the ICD-10 classification. In order to clarify this, since it is indeed confusing, we modified the sentence as followed: "(main diagnosis from chapter IX of the ICD-10 classification)".

In the other outcomes section, noted that time to first hospitalization was collected. However, the information was not used. It looks that incidence rate based on person-years data needs to be reported and compared between two groups.
Thank you for this remark.
The median time from randomisation to first hospitalisation, as well as the first and third quartiles, did not seem to differ between intervention and control groups:
"For CVD patients, the median time from randomisation to first hospitalisation was 91 [IQ 51-146] days in the intervention group, versus 101 [47-143] in the control group. […] For MHD patients, the

median time to first hospitalisation was 75 [35-124] days in the intervention group, versus 109 [62-144] in the control group […].”
Therefore, we propose maintaining a simple percentage for the hospitalization rate, so as not to weigh down the text, which already contains numerous figures.

Missing data are common in this type of study, how were the missing values handled in the analysis?
All data used in this part of the COVIQuest study were extracted from the SNDS database. As all reimbursed care consumption is exhaustively included in the SNDS database, this implies that there were no missing values. This is one of the greatest strengths of this kind of study using medico-administrative databases. In order to support this statement, we completed the sentence in the discussion section:
“Thus, the clinical database could be considered as gold standard regarding the chronic conditions of patients included by the GPs, whereas the SNDS database was gold standard for healthcare services consumption: hospitalisations, consultations, drug deliveries; as all reimbursed care consumption is comprehensively included in the SNDS database. Therefore, using SNDS data helps prevent missing data and classification bias associated to self-reported outcomes and could be preferable in the future. The SNDS database allowed an automated and cost-effective follow-up of over 4,000 patients and addressed the questions of the GP phone call impact at 6-months.”

In the results section (6-month specialized practitioner consultations): Suggest changing “77[IQ47-137]” to (IQR): 77 (IQR 47-137).
Thank you for this remark, we made the changes as requested.

We wanted to thank the reviewer 3 for their valuable comments, which allowed to improve the manuscript.

VERSION 2 - REVIEW

Reviewer	**3**
Name	**Zhang, Dr Jufen**
Affiliation	**Anglia Ruskin University**
Date	**23-Oct-2024**
COI	

The authors have addressed my concerns. I have no further comments.