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)	HIGHER INCIDENCE OF ADVERSE EVENTS IN ISOLATED PATIENTS COMPARED TO NON-ISOLATED PATIENTS: A COHORT STUDY
AUTHORS	Jiménez Pericás, Fátima; Gea Velázquez de Castro, María Teresa; Pastor-Valero, María; AIBAR REMÓN, CARLOS; Miralles, Juan José; Meyer García, María del Carmen; ARANAZ ANDRÉS, JESÚS MARIA

VERSION 1 – REVIEW

REVIEWER	Hideo Okuno Osaka University Hospital
REVIEW RETURNED	25-May-2020

GENERAL COMMENTS	In this paper, the author addresses the frequency of adverse events associated with isolation precautions. While I think the topic is good, I have serious concerns on several issues to be improved in this paper, as delineated below. 1. The authors should revise the statistical data analysis. The authors matched sex and ages (+- 5years) to collect the data between isolated and non-isolated patients. I think the authors should not include these matched factors into the independent variables of multiple logistic regression shown in Table 4. 2. The authors mentioned intrinsic risk factors could be protective for adverse events due to greater monitoring for patients with comorbidity. However, patients with extrinsic risk factors also would be monitored carefully. If the authors found the differences of comorbidity between patients with intrinsic and extrinsic risk factors, it would be reader-friendly to indicate it. In this study, most of patients have intrinsic and extrinsic risk factors and the number of patients without these risk factors is small. I am afraid the result in Table 4 could be influenced by overfitting of multiple logistic regression. I think the authors should discuss more precisely based on the present data or previous studies to clarify why intrinsic factors could be protective. 3. Although the authors describe that including 3 types of isolation precautions (contact, droplets, and airborne) is a strength of this study, I do not think this interpretation is convincing since most of cases in this study were isolated by contact precaution and only 2 cases were isolated due to airborne precaution. I think the authors should focus only on contact precaution in this data setting.

REVIEWER	Edward Purssell City, University of London, London UK
REVIEW RETURNED	02-Jun-2020

GENERAL COMMENTS	Thank you for allowing me to review your paper. It is interesting, and a welcome addition to the literature in this area. I like the fact that you have reported raw numbers as well as the logistic regression. There have been a couple of updates to the Abad paper, I suspect published while this paper was in preparation: Purssell E, et al. BMJ Open. 2020 Feb 18;10(2):e030371. doi: 10.1136/bmjopen-2019-030371. Brooks SK, et al. The Lancet. 2020;395(10227):912-20. Sharma A, et al. J Hosp Infect. 2020. Doi: 10.1016/j.jhin.2020.02.004 I think as this paper will need a little more work I would reflect the current situation a little more – I think the Brooks paper will be particularly useful for this. This: “Selection error could also have occurred as a result of the participants not having been randomly selected” is a limitation in terms of generalising from this sample to another, but I would not worry too much about it as long as you don’t over-interpret the results. The fact that this is a cohort is a strength as well as a weakness; you could use the GRADE criteria for observational studies to strengthen this (see section 5 here for example https://gdt.gradepro.org/app/handbook/handbook.html) I am not clear how you selected your sample. You say “We prospectively collected data from consecutive isolated and non-isolated patients ≥ 18 years old admitted between April 2014 and October 2018.” In this period you must have had >400 patients admitted, so how were these patients selected? If they are from across the hospital, were there differences between different areas? In the power calculation you were using a RR of 2.2 - depending upon the negative effect you were looking for this seems quite high. I would hope if I were a patient that any mechanism for identifying adverse events would be a bit more (a lot more!) sensitive than this. The main issue with the sample size is that you end up with quite small numbers of patients with an AE – 37 and 22 in each group. While this may be satisfactory statistically, I am not sure it makes a lot of sense to make judgements based on such small numbers. A little more consideration could be given to these two scales: To determine whether the AE is due to healthcare, the reviewers scored them on a 6- point scale; The preventability of each AE was determined by the reviewer by means of a 6-point scale – was there any assessment of the validity and reliability of this assessment? I was surprised at the high numbers of infections generally, and particularly among those who were isolated, can you explain this? This comment is true I am sure, but needs a bit more consideration I think: "This may be explained by greater monitoring of these patients". Are there any quality improvement mechanisms in place, locally or nationally to improve monitoring of patients? For example, in the UK we have the concept of ‘Intentional rounding’ (see

	https://bmjopen.bmj.com/content/7/1/e014776) – might this help? Also with regards to COVID-19, might an infection make people less likely to be observed or interacted with? It does not look as if you collected any data on psychological outcomes? This is a limitation of the study and needs some discussion. Also are there any positive sides to isolation, for example privacy? With regards to the AE you did look for, can these be included as a supplementary file along with the scales you used to assess causality and preventability? Latin names for organisms should be italicised. I could not see a reporting check-list.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name
Hideo Okuno

Institution and Country
Osaka University Hospital

Please state any competing interests or state 'None declared':
None

Please leave your comments for the authors below
In this paper, the author addresses the frequency of adverse events associated with isolation precautions. While I think the topic is good, I have serious concerns on several issues to be improved in this paper, as delineated below.

1. The authors should revise the statistical data analysis. The authors matched sex and ages (+-5years) to collect the data between isolated and non-isolated patients. I think the authors should not include these matched factors into the independent variables of multiple logistic regression shown in Table 4.
It was decided to include the sex and age variables in the logistic regression in order to minimize any confusion that these variables, especially age, might generate in the analysis, as was done in other studies of adverse events in which some of the authors of the current study took part, such as the National Study of Adverse Events (ENEAS).
Aranaz JM, Aibar C, Vitaller J, Ruiz P. Estudio Nacional de Efectos Adversos ligados a la Hospitalización. ENEAS 2005. Madrid: Ministerio de Sanidad y Consumo. 2006 Feb. Available at: https://www.seguridaddelpaciente.es/resources/contenidos/castellano/2006/ENEAS.pdf

Aranaz-Andrés JM, Aibar-Remón C, Vitaller-Burillo J, et al. Impact and preventability of adverse events in Spanish public hospitals: results of the Spanish National Study of Adverse Events (ENEAS). Int J Qual Health C. 2009 Dec 1;21(6):408-14. https://doi.org/10.1093/intqhc/mzp047

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We use a standard unconditional analysis rather than perfect matching, that is to say the matching was not exact for the same value, age (+ - 5 años). “That matching does not control for confounding by the matching factors. Provided that there are no problems of sparse data, control for the matching factors can be obtained, with no loss of validity and a possible increase in precision, using a “standard” (unconditional) analysis, and a “matched” (conditional) analysis may not be required or appropriate”. BMJ 2016;352:i969:

2. The authors mentioned intrinsic risk factors could be protective for adverse events due to greater monitoring for patients with comorbidity. However, patients with extrinsic risk factors also would be monitored carefully. If the authors found the differences of comorbidity between patients with intrinsic and extrinsic risk factors, it would be reader-friendly to indicate it. In this study, most of patients have intrinsic and extrinsic risk factors and the number of patients without these risk factors is small. I am afraid the result in Table 4 could be influenced by overfitting of multiple logistic regression. I think the authors should discuss more precisely based on the present data or previous studies to clarify why intrinsic factors could be protective.
It is true that previous studies13,14,23 indicate greater AE risk in patients exhibiting higher risk factor levels, both intrinsic and extrinsic, which is why, given the fact that in our study we have arrived at this result, we understand that this is an interpretation on our part and further studies will be necessary with higher sample sizes in order to demonstrate whether such a link exists. In the discussion, the following comment was added (line 334):
However, previous studies 13,14,23. indicate greater AE risk in patients exhibiting higher risk factor levels, both intrinsic and extrinsic. We believe that, for our population, the fact that they had intrinsic factors entailed a higher level of monitoring of these patients. These results were unexpected and further studies will be necessary with higher sample sizes in order to demonstrate whether such a link exists.

Aranaz-Andrés JM, Limón R, Mira JJ, Aibar C, Gea MT, Agra Y, ENEAS Working Group. What makes hospitalized patients more vulnerable and increases their risk of experiencing an adverse event?. Int J Qual Health C. 2011 Dec 1;23(6):705-12. https://doi.org/10.1093/intqhc/mzr059
Aranaz-Andrés JM, Aibar-Remón C, Vitaller-Burillo J, et al. Impact and preventability of adverse events in Spanish public hospitals: results of the Spanish National Study of Adverse Events (ENEAS). Int J Qual Health C. 2009 Dec 1;21(6):408-14. https://doi.org/10.1093/intqhc/mzp047
Aranaz-Andrés JM, Aibar-Remón C, Vitaller-Burillo J, et al. Incidence of adverse events related to health care in Spain: results of the Spanish National Study of Adverse Events. J Epidemiol Commun H. 2008 Dec 1;62(12):1022-9. https://doi.org/10.1136/jech.2007.065227

3. Although the authors describe that including 3 types of isolation precautions (contact, droplets, and airborne) is a strength of this study, I do not think this interpretation is convincing since most of cases in this study were isolated by contact precaution and only 2 cases were isolated due to airborne precaution. I think the authors should focus only on contact precaution in this data setting.

We thank the reviewer for this comment. Indeed, in our study most cases deal with patients undergoing contact and droplet isolation precaution as these are the transmission precautions most often deployed in our hospital, with airborne isolation precautions being rare in our context. As the reviewer rightly states, there were not enough patients of each of the types of isolation precaution to carry out statistical inferences, and as such this should not be considered a strength. Nevertheless, it seemed important to us to provide this information as in other previous studies these are not described nor contact precautions referred to.

Reviewer: 2
Reviewer Name
Edward Purssell

Institution and Country
City, University of London, London UK.

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
Thank you for allowing me to review your paper. It is interesting, and a welcome addition to the literature in this area. I like the fact that you have reported raw numbers as well as the logistic regression.

There have been a couple of updates to the Abad paper, I suspect published while this paper was in preparation:
Purssell E, et al. BMJ Open. 2020 Feb 18;10(2):e030371. doi: 10.1136/bmjopen-2019-030371.
Brooks SK, et al. The Lancet. 2020;395(10227):912-20.
Sharma A, et al. J Hosp Infect. 2020. Doi: 10.1016/j.jhin.2020.02.004

I think as this paper will need a little more work I would reflect the current situation a little more – I think the Brooks paper will be particularly useful for this.

We thank the reviewer for this comment and updates.
We have included the reference Purssell E, et al. BMJ Open. 2020 Feb 18;10(2):e030371. doi: 10.1136/bmjopen-2019-030371 in the introduction with the following paragraph (line 113):
In fact, a recent systematic review and metanalyses has shown that there was a number of apparently negative aspects to contact precautions, in particular with regard to psychological effects and a reduction in the quality of some aspects of care.10

10Purssell E, et al. Impact of isolation on hospitalized patients who are infectious: systematic review with meta-analysis. BMJ Open 2020;10:e030371. doi:10.1136/bmjopen-2019-030371
This: "Selection error could also have occurred as a result of the participants not having been randomly selected" is a limitation in terms of generalizing from this sample to another, but I would not worry too much about it as long as you don't over-interpret the results. The fact that this is a cohort is a strength as well as a weakness; you could use the GRADE criteria for observational studies to strengthen this (see section 5 here for example https://gdt.gradepro.org/app/handbook/handbook.html)
The principal advantages of this design are that it includes potent studies for the evaluation of incidence and that the evaluation of the levels of risk factor before illness occurs before the time sequence, and hence causality, are established. Among the limitations is the fact that this is an observational study (experimental studies provide a greater degree of evidence), but they are expensive and are not useful for unusual illnesses or events.
We have now included at the end of discussion comments on the limitations and strengths of the present study (line 342):

STRENGTHS AND LIMITATIONS OF THIS STUDY: In the present study several limitations might have arisen. Those inherent to medical records, such as missing data and limited predetermined information included in the AE Monitoring and Control (SIVCEA) System database.
Potential misclassification error might also have occurred based on wrong clinical judgements made by the reviewer of clinical records; however, we tried to minimise this risk by including trained professionals in the screening guidelines (MRF1) and the MRF2 modular form to collect the data of

the present study. A previous pilot study was carried out to train reviewers on medical data collection using these guidelines

Selection error could also have occurred as a result of the participants not having been randomly selected, i.e., exposed patients were included through consecutive sampling; however, we selected non-exposed patients to match with isolated patients as closely as possible, according to the date of admission and reference department, sex, age (+/- 5 years), and disease severity measured using the McCabe scale. However, the participants were incorporated over a long period of time (a year and a half) and consecutively, hence if their hospitalisation and isolation had been linked to particular times of the year, this effect would have been minimised by the fact that this incorporation took place at all times of year. Additionally, generalising our results to other populations is beyond the scope of our study.
The present study has several strengths. It has a prospective design with trained reviewers and high-quality measurements performed to collect EA from medical records
Moreover, this is the first prospective cohort study to examine the relationship between the incidence of AEs in isolated and non-isolated patients in our clinical setting. Furthermore, our study also included patients in isolation because of colonisation with multidrug-resistant microorganisms, and was not limited to patients with infections.
Eventually, the sample size included 400 patients, a larger sample size than previous studies, which permitted the identification of significant statistical differences between isolated and non-isolated patients.

I am not clear how you selected your sample. You say “We prospectively collected data from consecutive isolated and non- isolated patient ≥ 18 years old admitted between April 2014 and October 2018.” In this period you must have had >400 patients admitted, so how were these patients selected? If they are from across the hospital, were there differences between different areas?
We apologize for the mistake in the patient data collection which started in April 2017. Previously, during 2014 and 2015, we adapted the different measurements scales and tested them in our clinical setting. Later on, due to different logistic reasons in our daily hospital work, we could not start the field work until 2017.
We have modified this in the methods section as follows (line 130):
Participants: We prospectively collected data from consecutive isolated and non-isolated patient ≥ 18 years old admitted between April 2017 and October 2018

In relation to your question: The participants in our study were selected consecutively from April 2017 from among patients admitted with isolation precautions as a result of being infected or colonised by multi-resistant microorganisms and/or were transmissible from any hospitalisation department (medical or surgical). Non-isolated patients also came from the hospital’s medical or surgical departments. The differences with regard to AE incidence in different hospitalisation areas were not analysed as, though interesting, it was not among the objectives of our study.
In the power calculation you were using a RR of 2.2 - depending upon the negative effect you were looking for this seems quite high. I would hope if I were a patient that any mechanism for identifying adverse events would be a bit more (a lot more!) sensitive than this. The main issue with the sample size is that you end up with quite small numbers of patients with an AE – 37 and 22 in each group. While this may be satisfactory statistically, I am not sure it makes a lot of sense to make judgements based on such small numbers.
We agree with the reviewer that a RR of 2.2 seems quite high for power calculation. We based our calculation on the RR value previously published by Stelfox1. In fact, this is the basis on which our sample size of 176 exposed patients and 176 non-exposed patients looked to find statistically significant differences. However, we increased the sample to 400 to improve the potency of the study.

Stelfox HT, Bates DW, Redelmeier DA. Safety of patients isolated for infection control. JAMA. 2003 Oct 8;290(14):1899-905. https://doi.org/10.1001/jama.290.14.1899

A little more consideration could be given to these two scales:
To determine whether the AE is due to healthcare, the reviewers scored them on a 6- point scale; The preventability of each AE was determined by the reviewer by means of a 6-point scale – was there any assessment of the validity and reliability of this assessment?

In order to identify possible adverse events, the validated Screening Guidelines (MRF1) from the IDEA Project, a survey derived from a previous research study, based on a list of conditions similar to the studies carried out in New York (1,2), Utah and Colorado (3), using consensus techniques (4).
The references are set out below as they are not included in the article.
(1). Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. N Engl J Med 1991;324:370-6.

(2). Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients: Results of the Harvard Medical Practice Study II. N Engl J Med, 1991; 324:377-84.

(3). Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. Med Care 2000;38:261-71.

(4). Aranaz JM, Limón R, Requena J, Gea MT, Núñez V, Bermúdez MI, Vitaller J, Aibar C, Ruiz P, Grupo de trabajo del proyecto IDEA. Incidencia e impacto de los Efectos Adversos en dos hospitales. Rev Calidad Asistencial, 2005; 20(2): 53-60.

The MRF2 (Modular Review Form) was handed out15,16, in the course of hospitalisation, or upon discharge, which enabled an exhaustive analysis of the adverse event and associated circumstances.
15Aranaz JM, Limón R, Requena J, et al. Incidencia e impacto de los efectos adversos en dos hospitales. Rev Calidad Asistencial. 2005 Mar 1;20(2):53-60. https://doi.org/10.1016/s1134-282x(08)74723-7
16Woloshynowych M, Neale G, Vincent C. Case record review of adverse events: a new approach. Qual Saf Health Care 2003;12:411-15.
The six-point scale belongs to the Spanish version of the MRF2 survey. It is a modular survey that has been validated and used in Spain for the ENEAS 10,12 and EPIDEA studies (www.proyectoidea.com).
As the ENEAS study indicates, the depiction of the AEs as being produced by the treatment, rather than the nosological process itself, is a value judgement on the part of the individual carrying out the survey, and as such these are asked to rate on a scale of 1 to 6 the likelihood of the treatment being the cause, with a value of 4 or higher being required for it to be considered as such. The same criterion was used to assess whether the adverse effect was avoidable, with a view to improving the objectivity of the value judgement.12

2 Aranaz JM, Aibar C, Vitaller J, Ruiz P. Estudio Nacional de Efectos Adversos ligados a la Hospitalización. ENEAS 2005. Madrid: Ministerio de Sanidad y Consumo. 2006 Feb. Available at: https://www.seguridaddelpaciente.es/resources/contenidos/castellano/2006/ENEAS.pdf

It should be noted that before the study was carried out, training was undergone by the 3 health professionals who were to carry out the field work and a pilot study was carried out to assess the concordance index of the reviewers. In this study the concordance with regard to screening was good

(the percentage of simple concordance was above 76%). Concordance in terms of precise identification of the AE relating to treatment was lower (concordance percentage between 50% and 93.3%). In the light of these results the training of the reviewers was enhanced to improve concordance in the present study.
We include a sentence in limitations at the end of discussion:
Potential misclassification error might also have occurred based on wrong clinical judgements made by the reviewer of clinical records; however, we tried to minimise this risk by including trained professionals in the screening guidelines (MRF1) and the MRF2 modular form to collect the data of the present study. A previous pilot study was carried out to train reviewers on medical data collection and using these guidelines

I was surprised at the high numbers of infections generally, and particularly among those who were isolated, can you explain this?
It is a significant number, but it is in line with Spain's national study of adverse events (ENEAS)12 for the general hospital population, where the second most frequent AEs were from infections relating to medical treatment. Thus, it is not surprising that our study should have produced these results, as, although it is focused on patients subjected to transmission precautions, these are also part of the hospital population.

This comment is true I am sure, but needs a bit more consideration I think: "This may be explained by greater monitoring of these patients". Are there any quality improvement mechanisms in place, locally or nationally to improve monitoring of patients? For example, in the UK we have the concept of 'Intentional rounding' (see https://bmjopen.bmj.com/content/7/1/e014776) – might this help?
Thank you for this insight and for sharing this highly interesting reference. In our location there are measures in place to improve treatment quality for surgery patients, by means of bundles like those included in the Zero Surgery Infection Project
https://www.seguridaddelpaciente.es/resources/documentos/2016/seguridad-bloque-quirurgico/Protocolo-Proyecto-IQZ.pdf and the surgical checklist.
https://www.who.int/patientsafety/safesurgery/es/
There are also measures in place to improve treatment quality for ICU patients, such as the Zero Pneumonia Project https://www.seguridaddelpaciente.es/es/practicas-seguras/seguridad-pacientes-criticos/proyecto-neumonia-zero/ and Zero Bacteriemia Project
https://www.seguridaddelpaciente.es/es/practicas-seguras/seguridad-pacientes-criticos/proyecto-bacteriemia-zero/
There are also security rounds for critical ICU patients. These are all implemented at a local level within our Service and at national level in other hospitals in Spain.
The reference suggested is of great interest. It would indeed be of assistance and this type of tool should be implemented to improve the care and treatment of patients.

Also with regards to COVID-19, might an infection make people less likely to be observed or interacted with?
Our opinion, both from clinical experience and in the light of the results of the study, is that the lack of adequate training of our health professionals can lead to fear and anxiety when it comes to treating patients of this type, which could in turn lead to lower quality medical care, along with a higher incidence of AEs in these patients. This is an opinion that requires further scientific studies for it to be corroborated or not.

It does not look as if you collected any data on psychological outcomes? This is a limitation of the study and needs some discussion.
These results were collected by means of telephone interviews with a sample of the study population once these patients had been discharged from hospital. In this opinion and perception of patient

safety survey, satisfaction levels with healthcare along with issues pertaining to perception of safety while in hospital were collected. Due to the length of the manuscript submitted, the decision was taken to present the survey results in a subsequent study.
Also are there any positive sides to isolation, for example privacy?

Unfortunately, we have not collected patient satisfaction levels with regard to isolation, such as the privacy provided. This should certainly be borne in mind for future studies.

With regards to the AE you did look for, can these be included as a supplementary file along with the scales you used to assess causality and preventability?
Many thanks, we include the MRF2 modular survey as supplementary material.

Latin names for organisms should be italicised.

I could not see a reporting check-list.
The STROBE check-list was included in the submission page to BMJ.
Apologies for the omission, it will be included again.

VERSION 2 – REVIEW

REVIEWER	Hideo Okuno Osaka university hospital
REVIEW RETURNED	09-Aug-2020

GENERAL COMMENTS	The manuscript has been revised well. I think this manuscript will be acceptable for publication.

REVIEWER	Edward Purssell City, University of London
REVIEW RETURNED	17-Aug-2020

GENERAL COMMENTS	Thank-you for resubmitting your manuscript. I have a few suggestions, but none are substantial. Line 264 - Isolation increased the risk of experiencing an AE by 73% (OR 1.74; 95% CI: 0.92-3.25), although this result was not statistically significant (p 0.09). There must be different rounding to make one 73% and the other 1.74; also this sentence risks confusing odds and risk, I would suggest “Isolation increased the odds of experiencing..” Line 307 - The decision to indicate or not to use special precautionary measures in a patient requires evaluating the potential excess risk linked to the isolation of the patient compared to the decrease of the risk of transmission of the multiresistant bacteria to the rest of the patients – this is quite a confusing sentence; can it be simplified at all? Line 327 - In our study, the incidence of AEs was associated with longer stays in hospital and a greater number of extrinsic risk factors – Is this because patients with AE stayed longer, or because those who stayed longer had more AEs do you think?

	Line 331 - However, the presence of intrinsic factors (such us coma, hepatic cirrhosis, coronary heart disease, renal insufficiency, hypertension, diabetes, obesity, hypercholesterolaemia, neoplasia ...) showed a protective effect against the occurrence of AEs. - minor typo ‘us’ instead of ‘as’. Not sure about using … at the end. This is a very interesting finding, are you aware of any other study that has found this? Line 371 - Eventually, the sample size included 400 patients, a larger sample size than previous studies, which permitted the identification of significant statistical differences between isolated and non-isolated patients. - I would take care about emphasising the importance of statistical significance, maybe just say that it was adequately powered? 400

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name

Hideo Okuno

Institution and Country

Osaka university hospital

Please state any competing interests or state ‘None declared’:

None declared

Please leave your comments for the authors below

The manuscript has been revised well. I think this manuscript will be acceptable for publication.

Reviewer: 2

Reviewer Name

Edward Purssell

Institution and Country

City, University of London

Please state any competing interests or state ‘None declared’:

None declared

Please leave your comments for the authors below

Thank-you for resubmitting your manuscript. I have a few suggestions, but none are substantial.

Line 264 - Isolation increased the risk of experiencing an AE by 73% (OR 1.74; 95% CI: 0.92-3.25), although this result was not statistically significant (p 0.09).

There must be different rounding to make one 73% and the other 1.74; also this sentence risks confusing odds and risk, I would suggest “Isolation increased the odds of experiencing.”

Thank you. We have modify this sentence accordingly

"Isolation increased the odds of experiencing an AE by 74%"

Line 307 - The decision to indicate or not to use special precautionary measures

in a patient requires evaluating the potential excess risk linked to the isolation of the patient compared to the decrease of the risk of transmission of the multiresistant bacteria to the rest of the patients – this is quite a confusing sentence; can it be simplified at all?

We agree and have simplified the paragraph.

"The decision to indicate special isolation precautionary measures

requires evaluating the potential excess risk linked to the isolation."

Line 327 - In our study, the incidence of AEs was associated with longer stays in hospital and a greater number of extrinsic risk factors – Is this because patients with AE stayed longer, or because those who stayed longer had more AEs do you think?

Our study was a longitudinal design and therefore what we observed was that those with incidence of AEs had longer stays in hospital.

Line 331 - However, the presence of intrinsic factors (such us coma, hepatic cirrhosis,

coronary heart disease, renal insufficiency, hypertension, diabetes, obesity, hypercholesterolaemia, neoplasia ...) showed a protective effect against the occurrence of AEs. - minor typo ‘us’ instead of ‘as’. Not sure about using … at the end. This is a very interesting finding, are you aware of any other study that has found this?

Thank you we have modify the minor typo. As far as we know this is the first study showing this finding. We also think it is a very interesting result.

Line 371 - Eventually, the sample size included 400 patients, a larger sample size than previous studies, which permitted the identification of significant statistical differences between isolated and non-isolated patients. - I would take care about emphasising the importance of statistical significance, maybe just say that it was adequately powered? 400

Thank you we agree and have changed it.

"Eventually, the sample size included 400 patients, a larger sample size than previous studies, adequately powered to identify differences between isolated and non-isolated patients."

VERSION 3 – REVIEW

REVIEWER	Edward Purssell City, University of London, UK
REVIEW RETURNED	02-Oct-2020

GENERAL COMMENTS	Thank you, you have dealt with all of my concerns. I hope that you think that this has been a positive experience. I have not been through the paper line-by-line, as my comments were quite specific.

Correction: *Higher incidence of adverse events in isolated patients compared with non-isolated patients: a cohort study*

Jiménez-Pericás F, Gea Velázquez de Castro MT, Pastor-Valero M, *et al*. Higher incidence of adverse events in isolated patients compared with non-isolated patients: a cohort study. *BMJ Open*. 2020;10:e035238. doi: 10.1136/bmjopen-2019-035238

This article was previously published with error in affiliation. The below affiliation has been updated and added for both authors, Maria Pastor-Valero and Jesús Maria Aranaz Andrés.

Centro de Investigación Biomédica en Red en Epidemiología y Salud Pública (CIBERESP), Madrid, Spain.

BMJ Open 2020;**10**:e035238corr1. doi:10.1136/bmjopen-2019-035238corr1