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STUDY PROTOCOL

REVISED **Effects of the COVID-19 pandemic on prehospital emergency care for adults with stroke and transient ischaemic attack: A protocol for a systematic review and meta-analysis [version 2; peer review: 3 approved]**

Previously titled: 'Effects of the COVID-19 pandemic on prehospital emergency care for stroke and transient ischaemic attack: A protocol for a systematic review and meta-analysis'

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Abstract

Background: The COVID-19 pandemic impacted on health service provision worldwide, including care for acute time sensitive conditions. Stroke and transient ischaemic attacks (TIA) are particularly vulnerable to pressures on healthcare delivery as they require immediate diagnosis and treatment. The global impact of the COVID-19 pandemic on prehospital emergency care for stroke/TIA is still largely unknown. Thus, the aim of this study is to conduct a systematic review and meta-analysis to investigate the impact of the COVID-19 pandemic on prehospital emergency care for stroke and TIA.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines, the review is registered on PROSPERO (registration number CRD42022315260). Peer-reviewed quantitative studies comparing prehospital emergency care for adults with stroke/TIA before and during the COVID-19 pandemic will be considered for inclusion. The outcomes of interest are ambulance times and emergency call volumes for stroke/TIA. A systematic search of databases including PubMed, Embase and Scopus will be conducted. Two authors will independently screen studies for inclusion based on predetermined inclusion and exclusion

criteria. Data extraction and quality assessment will be conducted by two authors. Meta-analysis will be performed to calculate overall pooled estimates of ambulance times (primary outcome) and stroke/TIA call volumes (secondary outcome), where appropriate. Where heterogeneity is low a fixed-effects model will be used and where heterogeneity is high a random-effects model will be used. Subgroup and sensitivity analyses will include location, stroke/TIA diagnosis and COVID-19 case numbers.

Results: Data on primary and secondary outcomes will be provided. Results of subgroup/sensitivity analyses and quality assessment will also be presented.

Conclusions: This review will identify existing evidence reporting the impact of the COVID-19 pandemic on prehospital emergency care for adult patients with stroke/TIA and provide summary estimates of effects on ambulance response times.

Keywords
Ambulance times; emergency care; COVID-19 pandemic; prehospital; protocol; stroke; systematic review; transient ischaemic attack.

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Any reports and responses or comments on the article can be found at the end of the article.

Introduction

The COVID-19 pandemic was a "shock" to the health system, globally[1]. COVID-19 was declared a pandemic by the Director-General of the WHO at the media briefing on 11 March 2020[2]. Consequently, it is reported that the pandemic affected non-COVID healthcare in many countries[3,4]. Public health guidelines were introduced in an effort to manage the pandemic, including travel restrictions and stay at home orders. These interventions may have impacted on healthcare seeking behaviours. Furthermore, the healthcare workforce was directly impacted through sickness and periods of isolation/restriction of movements for cases and contacts[5].

Globally, delayed, and reduced admissions for non-COVID related care have been linked to increased mortality and morbidity[6,7]. Reports from multiple countries indicated that calls to emergency medical services vastly increased over the course of the pandemic[8]. As a result, further pressure was put on prehospital emergency services[8].

The prehospital phase of healthcare is defined in a World Health Organisation report as the period before arrival at a hospital, clinic, and other fixed healthcare setting[9]. Prehospital care generally includes the provision of care by emergency medical service providers such as emergency medical dispatchers, emergency medical responders, emergency medical technicians, and paramedics[10]. As ambulance times are internationally recognised key performance indicators for prehospital emergency care they will be used as the primary outcome of interest in this review[11]. Ambulance times are relevant to pre-hospital stroke/transient ischaemic attack (TIA) care as the role of the emergency medical services in this context involves prompt transport to secondary care specialists. As treatment strategies for stroke/TIA are time-dependent, it is important to minimise time delays in the prehospital phase of care[12].

In 2019, stroke was the second leading cause of disability-adjusted life-years (DALYs) globally, in the 50–74 years and 75+ years age groups[13]. Up to one in three strokes are preceded by a TIA, with approximately 50% of these occurring within a year after the TIA[14]. Stroke and TIA can have similar presentations and are being included in this review as it is focusing on information provided to the call taker by the caller before clinical assessment has been performed. Also, within the timeframe in which prehospital care practitioners care for the patient it may not be possible to differentiate between symptoms of a stroke/TIA. Furthermore, some dispatch systems, such as AMPDS[15], have the same code for stroke and TIA.

Stroke is a medical emergency and requires immediate evaluation, confirmation of diagnosis and treatment in order to prevent brain damage[16]. The acute ischaemic stroke chain of recovery involves recognition (of symptoms), reaction (emergency services alerted), response (medical assessment), reveal (brain imaging), and Rx (treatment initiation)[17]. Early diagnosis and treatment are also imperative for TIA, to reduce mortality and risk of stroke[18]. Stroke and TIA could be considered as particularly vulnerable to pressures on health system care delivery or changes in care seeking behaviours by patients. Due to the time-sensitive nature of stroke/TIA intervention it is imperative that stroke/TIA survivors present to hospital as soon as possible after symptoms develop[16]. An increased volume of emergency calls may mean that not as many call takers or ambulances are available. Furthermore, patients may have been hesitant to call an ambulance during COVID-19 due to fear of contracting the disease[8]. Recent preliminary evidence suggests that stroke and cardiac arrest were the emergency cases most affected by the COVID-19 pandemic[8].

There has been a global decrease in the number of patients seeking medical care for stroke and TIA during the pandemic[19–21]. Thus, COVID-19 has potentially had a disruptive effect on the stroke chain of survival[7,22]. It has been reported that stroke admissions in Southern Europe have fallen by 25% over the pandemic period[21]. Furthermore, the number of emergency medical service calls dispatched to stroke dropped, and a 30-minute delay in response times have been reported, in this region[21]. One narrative review stated that the suggested disruption in the emergency stroke care pathway due to the COVID-19 pandemic has resulted in a global surge of prehospital mortality[8].

Research in this area has previously focused on the nature and volume of emergency medical service calls, prehospital stroke triage and acute stroke hospital-based care, during the COVID-19 pandemic[8,23–25]. However, it is still largely

unknown what impacts on prehospital emergency care for stroke and TIA were seen and how they varied in different countries, with different approaches to the management of the pandemic and different underlying healthcare systems. Thus, this systematic review and meta-analysis aims to summarize the existing international evidence on the impact of the COVID-19 pandemic on prehospital emergency care for adult patients with stroke or TIA and estimate the ambulance times and emergency call volumes for stroke/TIA.

Protocol
Methods and design
This protocol was developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols Checklist (PRISMA-P)[26]. The proposed systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines[27]. This review is registered on PROSPERO (registration number CRD42022315260).

Aim
To summarize the existing international evidence on the impact of the COVID-19 pandemic on prehospital emergency care for adult patients with stroke or TIA and estimate the ambulance times and emergency call volumes for stroke/TIA.

Objectives
- To investigate if ambulance times (activation times, response times and patient care times) for adults with stroke/TIA differed before and during the COVID-19 pandemic.
- To investigate if the volume of emergency services calls for stroke/TIA differed before and during the COVID-19 pandemic.

Participants
Adult patients (≥18 years of age) with stroke or TIA.

Exposure
Prehospital emergency care for stroke/TIA during the COVID-19 pandemic.

Comparison
Prehospital emergency care for stroke/TIA prior to the COVID-19 pandemic.

Outcome
Primary outcomes: activation time, response time, patient care time.

Secondary outcome: emergency medical services call volume for stroke/TIA.

Ambulance response times
Ambulance times include three main time periods in the time from receipt of the emergency call by the call centre operator to the patient arriving at the hospital[28]. **"Activation time "**covers the period from receipt of the call to mobilisation of a fully crewed emergency ambulance[28]. **"Response time"** covers the period from receipt of call to the arrival of the ambulance at the scene of the emergency[28]. **"Patient care time"** refers to the time from arrival of an ambulance crew at the scene to arrival at hospital[28]. In this review "patient care time" 24 will include time spent on scene and the transport to hospital time[28]. The terminology used to describe these three key time periods can vary between countries and publications[8,28]. Regardless of the term used, these three distinct periods of time are a key focus of this review. Thus, the search terms of the review relating to emergency care have remained broad to encompass as many variations as possible. The time periods chosen are due to clinical significance and previous inclusion in ambulance time-related studies. Due to international variation in terminology and definitions, a standardised definition needed to be used. Members of the ambulance service are advising on this task.

Criteria for considering studies for the review
Inclusion criteria
Table 1 details full inclusion and exclusion criteria and justifications for each. This systematic review will include:

- Quantitative studies where prehospital care for adult stroke/TIA patients was compared before and during the COVID-19 pandemic.

- Stroke/TIA diagnosis does not have to be confirmed at hospital level. Due to the context of this study stroke/TIA can be suspected (based on symptoms given to call taker) or working diagnosis after review by an emergency medical services team. A study will not be excluded based on the definition of stroke/TIA diagnosis. However, if available in the study, whether the stroke/TIA was suspected or confirmed will be outlined in the review.

- Studies need to include data on ambulance times or stroke/TIA emergency call volumes in order to be considered for inclusion. A study needs to include data on at least one of: activation time, ambulance response time or patient care time to be eligible for inclusion. Regardless of the terminology used in a particular study, if data are available on any of these three time periods of interest the study is eligible for inclusion.

- Calls identified by the call taker as suspected stroke/TIA will be included and if the data are available these calls will be put in context of calls made to the wider EMS system.

- Primary, peer – reviewed studies in any language.

Exclusion criteria
- Studies where all participants are children, or where data for adults cannot be extrapolated.

- Case reports, case series, letters, commentaries, notes, editorials, and conference abstracts, dissertations, reviews, opinion pieces.

Table 1. Inclusion and exclusion criteria for study selection.

Criterion	Inclusion	Exclusion	Justification
Language	All languages	N/A	Translation of articles will ensure the largest pool of potentially eligible articles
Focus	Quantitative studies on the impact of the COVID-19 pandemic on prehospital emergency care for adult patients with stroke/TIA	Qualitative articles Opinion pieces	Pooled estimates can be calculated
Types of articles	Peer reviewed journal articles	Editorials or other opinion pieces Reviews Unpublished (grey) literature including theses, dissertations, editorials, and book chapters Newspapers and websites Conference abstracts/proceedings	Primary peer reviewed literature will provide numeric information related to primary and secondary outcomes for possible inclusion in meta-analysis
Geographic location	Any	N/A	COVID-19 is a global concern

Search strategy for identifying relevant studies
Bibliographic database searches
Initial search[29,30]: ProQuest and PubMed will be used to search for relevant articles. The librarian recommended these databases due to the context of the study, and the range of articles available on these databases. Words and phrases found in the title, abstract, and index of these papers will inform the final search strategy.

Second search: Using the identified search terms a formal search of Embase (Elsevier), ProQuest, PubMed, Scopus (Elsevier), Web of Science (Clarivate) and Wiley will be conducted. These searchers will be included in the final PRISMA flow chart[27].

Reference list search: Backward and forward citation searching will be conducted on all included studies. The Peer Review of Electronic Search Strategies (PRESS) will be used to evaluate the search strategy[31,32]. The number of studies identified in the reference list screening will be included in the PRISMA flow chart[27].

An expert university librarian was involved in the selection of initial search terms and databases for this protocol. The librarian has also advised on refining and designing the final search strategy. They have advised on the most appropriate Medical Subject Headings (MeSH) terms for the search strategy and offered input into adapting these terms for the selected databases. Table 2 details a sample initial search strategy for the PubMed database. Table 3 details the final search strategy for the PubMed database.

Selection of studies for inclusion in the review
Identified citations will be collated and uploaded into Endnote™ 20 (*Clarivate Analytics, PA, USA))* and duplicates removed. Titles and abstracts of published literature will be imported into Covidence (https://www.covidence.org/)., and

Table 2. Sample search terms for the PubMed database.

Initial Keywords
stroke OR cerebrovascular accident OR transient ischaemic attack OR TIA
emergency medical service OR EMS OR ambulance OR emergency care OR paramedic OR 999 OR 911 OR 112 OR prehospital
COVID-19 OR SARS-CoV-2 OR covid 19 OR coronavirus

screened using the software, by two independent reviewers (EB and JA) for assessment against the inclusion/exclusion criteria for the review. Potentially relevant sources will be retrieved in full, and their citation details imported into Covidence. The full text of selected citations will be assessed in detail against the inclusion criteria by EB and JA.

Reasons for exclusion of sources of evidence at full text that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion between EB and JA. If necessary, any disagreement will then be referred to a third reviewer VMc and resolved by consensus.

The results of the search and the study inclusion process will be reported in full in the final systematic review and presented in PRISMA flow diagram[27].

Data extraction and management
A standardised extraction form has been composed using Microsoft Word (version 2102), which fulfils the eligibility criteria (Table 1). This template has been compiled based

Table 3. Final search strategy for the PubMed database.

Stroke/TIA	("cerebrovascular accident*"[Title/Abstract] OR "cerebrovascular disease*"[Title/Abstract] OR "transient ischaemic attack*"[Title/Abstract] OR "transient ischemic attack*"[Title/Abstract] OR "TIA"[Title/Abstract] OR "cerebrovascular event*"[Title/Abstract]) OR (stroke*[MeSH Terms])
Pre-hospital	("pre hospital"[Title/Abstract] OR prehospital[Title/Abstract] OR "pre-hospital"[Title/Abstract] OR EMS[Title/Abstract] OR ambulance*[Title/Abstract] OR "emergency care"[Title/Abstract] OR paramedic*[Title/Abstract] OR 999[Title/Abstract] OR 112[Title/Abstract] OR 911[Title/Abstract] OR "emergency department*"[Title/Abstract] OR "out-of-hospital"[Title/Abstract] OR emergenc*[Title/Abstract] OR "hospital referral*"[Title/Abstract] OR "emergency admission*"[Title/Abstract] OR "time-to-treatment"[Title/Abstract] OR "acute stroke care"[Title/Abstract] OR "acute stroke therapy"[Title/Abstract]) OR (emergency medical services[MeSH Terms])
COVID-19	("COVID-19"[Title/Abstract] OR covid[Title/Abstract] OR coronavirus*[Title/Abstract] OR "novel coronavirus*"[Title/Abstract] OR lockdown*[Title/Abstract] OR pandemic*[Title/Abstract]) OR (SARS-CoV-2[MeSH Terms])
Combined search	(((("COVID-19"[Title/Abstract] OR covid[Title/Abstract] OR coronavirus*[Title/Abstract] OR "novel coronavirus*"[Title/Abstract] OR lockdown*[Title/Abstract] OR pandemic*[Title/Abstract]) OR (SARS-CoV-2[MeSH Terms])) **AND** (("cerebrovascular accident*"[Title/Abstract] OR "cerebrovascular disease*"[Title/Abstract] OR "transient ischaemic attack*"[Title/Abstract] OR "transient ischemic attack*"[Title/Abstract] OR "TIA"[Title/Abstract] OR "cerebrovascular event*"[Title/Abstract]) OR (stroke*[MeSH Terms]))) **AND** (("pre hospital"[Title/Abstract] OR prehospital[Title/Abstract] OR "pre-hospital"[Title/Abstract] OR EMS[Title/Abstract] OR ambulance*[Title/Abstract] OR "emergency care"[Title/Abstract] OR paramedic*[Title/Abstract] OR 999[Title/Abstract] OR 112[Title/Abstract] OR 911[Title/Abstract] OR "emergency department*"[Title/Abstract] OR "out-of-hospital"[Title/Abstract] OR emergenc*[Title/Abstract] OR "hospital referral*"[Title/Abstract] OR "emergency admission*"[Title/Abstract] OR "time-to-treatment"[Title/Abstract] OR "acute stroke care"[Title/Abstract] OR "acute stroke therapy"[Title/Abstract]) OR (emergency medical services[MeSH Terms]))

on the aim and objective of the review and what data will be required to effectively report the results of this review.

EB will extract the data from the included papers. JA will check a random sample of 20% of these studies for accuracy of data extraction. Finalising the data extraction form may be an iterative process, and modification or revision may occur after piloting. Any disagreements will be resolved upon discussion with VMc. This process ensures transparency and clarity in the process of data extraction. The categories below will be included in the first version of the form, which can be found in Table 4. Any modifications to the existing data extraction form will be reported in the systematic review.

Appraisal of the quality of included studies

The appropriate Joanna Briggs Institute (JBI) Critical Appraisal tool[33] will be used to appraise the quality of each included study. The JBI tools will be used as it is anticipated that eligible studies will be cohort studies or quasi-experimental studies. JBI offers a critical appraisal tool for both. The JBI checklist offers a series of questions to which "Yes", "No", "Unclear" and "Not applicable" are the provided answers. These checklists will be used to assess risk of bias in individual studies. The GRADE[34] tool is being used to assess the overall quality of cumulative evidence. Two reviewers (EB and JA) will independently assess study quality. If necessary, discrepancies will be resolved by VMc.

Presenting and reporting the results

A PRISMA flow diagram[27] will be included in the review to illustrate the study selection process, and also will provide a rationale for excluding studies. Tables displaying

Table 4. Categories included in the data extraction form for this systematic review and meta-analysis.

Author(s), month, year of publication, country
Aims/purpose
Study design
Country/region
Income level of country
Emergency dispatch system
Sample size in studies, sex, age
Activator response time before and during the pandemic
Ambulance response time before and during the pandemic
Patient care time before and during pandemic
Call volumes before and during the pandemic
Time period (pre and during COVID-19 pandemic)
Method of stroke/TIA diagnosis
COVID-19 cases numbers/ICU numbers/hospitalisations

study characteristics and quality assessment will be included. Forest plots will be used to present pooled estimates. If a study is eligible for inclusion in the review but does not include sufficient data for inclusion in the meta-analysis the

corresponding study authors will be contacted for access to raw data, in the first instance. If raw data cannot be obtained, the findings of the relevant studies will be included in a separate table or narratively presented.

Meta-analysis will be conducted, where the data allows, to calculate pooled estimates of the difference between ambulance times (time of call to ambulance being dispatched (activation time), time from ambulance being dispatched to arrival at the incident location (response time), and time spent on scene and from the incident location to the hospital (patient care time) and call volumes for stroke/TIA before and during the COVID-19 pandemic.

Where heterogeneity is low (I2 value of less than 50%) a fixed-effects model will be used and where heterogeneity is high (I2 value of 50% or more) a random-effects model will be used, according to the Cochrane Handbook criteria[35].

The following subgroup/sensitivity analyses will be performed using RevMan 5.4 where the data allow:

1. According to location. (Classification will be determined once papers are selected).

2. According to income level of country. (Determined by World Bank Classification[36])

3. According to study quality. (Determined by appropriate JBI critical appraisal tool[33])

4. According to COVID-19 case numbers/hospitalisations in the country/area at the time of the study. (John Hopkins Coronavirus Resource Centre and Oxford Martin School data will be used[37,38])

5. According to the number of weeks since the World Health Organisation categorized COVID-19 as a pandemic. (This was stated by the Director-General of the WHO at the media briefing on 11 March 2020[2])

6. According to stroke/TIA diagnosis (suspected stroke/ TIA, working diagnosis after review by emergency medical services, or hospital confirmed diagnosis)

A funnel plot will be used to assess publication bias if ten or more studies are included in the meta-analysis. Any asymmetry of the funnel plot arising from publication bias will be addressed using the trim and fill method[39].

If any further subgroup/sensitivity analyses need to be carried out during the meta-analysis process, these will be identified as post hoc analyses.

The quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation guidelines (GRADE)[34].

Consultation with stakeholders
A Consultant Neurologist (AM) aided in the development of the research question for this review. AM will be asked about

resources on the review topic that might not be identified through the searching of databases, and references. The consultant neurologist will help with dissemination of review results and offer suggestions on how best to disseminate the results of the review to the medical community. Members of the Irish National Ambulance Service Clinical Directorate advised on terminology and clinical significance of time periods, in this protocol. They will also be involved throughout the systematic review and will offer suggestions on how to best disseminate the results of the review to the prehospital emergency care community.

Patient and public involvement (PPI) is described in this protocol and will be described in the systematic review using the GRIPP 2 checklist (short version)[40].

A PPI panel of 5 stroke survivors (2 female, 3 male) from a stroke support group were involved in the development of this protocol and subsequent review from an early stage. The PPI panel were consulted on this protocol by means of two face-to-face meetings. PPI contributors were involved in this protocol to advise on development of the research question, which stakeholders to target for involvement in the review, possible search terms, terminology surrounding stroke survivors and their research priorities.

The PPI members emphasised that they believe that the period from onset of symptoms to arrival at hospital was the most important part of the care pathway. They were asked to advise on preferred terminology around the term "stroke survivor" or "stroke patient" and any colloquial terms used for stroke or TIA. Also, they were asked what they felt would be important to know about the impact of the COVID-19 pandemic on prehospital emergency care for those with a stroke/TIA during the COVID-19 pandemic.

As a result, the research question focuses on prehospital emergency care for those with stroke/TIA. PPI had a very positive effect on this protocol[41]. The PPI contributors used their lived experience to highlight key issues of importance and aspects of stroke care they felt could have been affected by the COVID-19 pandemic. The PPI panel prefer the term "stroke survivor" to refer to those who had a stroke. Thus, where possible this terminology will be used in outreach and dissemination of the review results, especially that targeted towards the lay population.

This group of PPI contributors will also be involved in interpreting the results of this review to identify gaps and in the dissemination of the results.

Conclusion
This systematic review and meta-analysis will summarise existing evidence investigating the impact of the COVID-19 pandemic on prehospital emergency care for those with stroke/TIA. This work may also influence policy guidelines and future research on prehospital management of non-communicable diseases during a pandemic, and prehospital care more broadly. The results may also inform our understanding of healthcare system resilience in response to crises on a broader level.

The findings of this review will be disseminated through peer and public presentations, conferences, a policy brief for relevant clinical programmes (stroke and emergency care) and a peer-reviewed journal.

Study status
The protocol was registered prospectively with Prospero (registration number CRD42022315260).

Search strategies were confirmed, stakeholders consulted, and title/abstract screening started at the time of publication of this version of the protocol.

Ethics
Ethical approval is not required for a systematic review.

Data availability
No data are associated with this article.

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Open Peer Review

Current Peer Review Status: ✔ ✔ ✔

Version 2

Reviewer Report 06 July 2022

https://doi.org/10.21956/hrbopenres.14835.r32373

✔ **Eithne Sexton** (ORCID)

Data Science Centre, School of Population Health, Royal College of Surgeons in Ireland, Dublin, Ireland

Many thanks to the author for their comprehensive response and revisions to the paper. I am happy that my comments have been addressed adequately and to approve the revised paper.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Stroke epidemiology; epidemiological modelling; health services research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 29 June 2022

https://doi.org/10.21956/hrbopenres.14835.r32375

✔ **Janet E. Bray**

Department of Epidemiology and Preventive Medicine, Department of Epidemiology and Preventive Medicine, Melbourne, Vic, Australia

The revisions are appropriate and I am happy to approve.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Prehosptial

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 June 2022

https://doi.org/10.21956/hrbopenres.14835.r32374

✔ **Graham McClelland** [iD]
¹ North East Ambulance Service NHS Foundation Trust, Newcastle upon Tyne, UK
² Newcastle University, Newcastle upon Tyne, UK

No further comments

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Prehospital care and stroke

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 22 April 2022

https://doi.org/10.21956/hrbopenres.14771.r31725

? **Janet E. Bray**
Department of Epidemiology and Preventive Medicine, Department of Epidemiology and Preventive Medicine, Melbourne, Vic, Australia

Suggestions:

1. Title -Suggest using prehospital times and volume rather than "care".

2. Objective -response times: suggest changing the overall wording from ambulance

"response" times to ambulance times -given you are also looking at time to the hospital.

3. Initial and secondary search -seems unusual. Your search strategy is not finalised? Please provide a reference supporting this method of search.

4. The inclusion criteria reads as if a study must include both volume and times, and then all times. Do you mean "or" rather than "and"?

5. Why would you exclude studies only reporting the secondary outcome?

6. Volume: Dispatcher diagnosis (most are not stroke/TIA) is quite different to paramedic diagnosis (most are stroke/TIA depending on whether a prehospital stroke screen is used). Your analysis suggests you will combine these?

7. Do you intend to include non-English language studies as stated? How will these be interpreted?

8. How will you handle studies reporting medians or means for times? How will you handle studies reporting adjusted data?

9. The English could be improved throughout (e.g. There has been some research done in the area"; "Consistency of data extraction will be achieved...").

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Prehosptial

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 May 2022
Edel Burton, University College Cork, Cork City, Ireland

Thank you for reviewing this protocol. Please find below responses to your comments:

Title-Suggest using prehospital times and volume rather than "care".

Response:

Thank you for your comment. We believe this title is appropriate as prehospital care also includes patient transport, which is one of the key outcomes of this review. Furthermore, as time is a crucial component of stroke/TIA care we believe the term "prehospital emergency care" is precise.

Objective -response times: suggest changing the overall wording from ambulance "response" times to ambulance times -given you are also looking at time to the hospital.

Response:

The word response has been "removed" leaving "ambulance times" throughout the protocol, unless we are specifically referring to response time.

Initial and secondary search -seems unusual. Your search strategy is not finalised? Please provide a reference supporting this method of search.

Response:

The approach taken is supported in the attached references:

https://libguides.uvic.ca/systematic_reviews_how_to_guide/step1
https://libguides.rcsi.ie/systematicreviews/wheretostart

The initial search was included in the protocol for the purpose of transparency and replicability. As we are using the Peer Review in Electronic Search Strategies (PRESS) criteria, the search strategy took some time to confirm, at the time of publishing this updated protocol the search strategy is now confirmed, with the help of two librarians.

*The above references are now added to the initial search section "**Initial search**[29,30]: ProQuest and PubMed will be used to search for relevant articles."*

The inclusion criteria reads as if a study must include both volume and times, and then all times. Do you mean "or" rather than "and"?

Response:

Yes, thank you. This has now been amended for clarification.

"Studies need to include data on ambulance times or stroke/TIA emergency call volumes in order to be considered for inclusion". - Inclusion and Exclusion Criteria

Why would you exclude studies only reporting the secondary outcome?

Response:

Thank you, this sentence has now been removed from "the exclusion criteria".

Volume: Dispatcher diagnosis (most are not stroke/TIA) is quite different to paramedic diagnosis (most are stroke/TIA depending on whether a prehospital stroke screen is used). Your analysis suggests you will combine these?

Response:

The secondary outcome of interest in this reviewer is dispatcher diagnosis. If a study includes paramedic diagnosis than the study will not be excluded. The two types of diagnosis will not be combined but included in a subgroup analysis.

Do you intend to include non-English language studies as stated? How will these be interpreted?

Response:

Yes, we intend to include non-English language studies if appropriate. These will be sent to colleagues in University College Cork or a relevant agency for translation.

How will you handle studies reporting medians or means for times? How will you handle studies reporting adjusted data?

Response:

Thank you, we will contact the author directly and ask for the detail.

"If a study is eligible for inclusion in the review but does not include sufficient data for inclusion in the meta-analysis the corresponding study authors will be contacted for access to raw data, in the first instance." - "Presenting and Reporting the Results"

The English could be improved throughout (e.g., There has been some research done in the area"; "Consistency of data extraction will be achieved…").

Response:

Thank you, amendments have now been made to the use of language in the protocol.

"Research in this area has previously focused on the nature of volume emergency medical services calls, prehospital stroke triage and acute stroke hospital-based care, during the COVID-19 pandemic". – introduction

"EB will extract the data from the included papers. JA will check a random sample of of 20% of

these studies for accuracy of data extraction". – "Data Extraction and Management"

Competing Interests: No competing interests were disclosed.

Reviewer Report 08 April 2022

https://doi.org/10.21956/hrbopenres.14771.r31723

?

Eithne Sexton [ID]

Data Science Centre, School of Population Health, Royal College of Surgeons in Ireland, Dublin, Ireland

Thank you for this opportunity to review this paper which makes a valuable contribution to the literature on prehospital care for stroke and the impact of Covid on healthcare delivery. In general, the protocol is clear and detailed, making good use of the PRISMA guidelines

In my view, the protocol could benefit from clarification on the following points:
  1. Selection Criteria – only studies that include all the three definitions of ambulance response time will be included in the study. The feasibility of the review is based on all studies using comparable definitions of response time (albeit with different terminology). The definitions as given are based on an Irish source. Can you provide some international evidence to

support the consistency of these definitions across locations/health systems?

2. Quality appraisal – some more detail on quality appraisal would be helpful. Please justify the choice of the JBI critical appraisal tool for this specific study. What information on quality does it generate (e.g. a score, nominal categories), and how will this be used in the sub-group analysis? The GRADE tool is also mentioned – clarify what this is being used for and how it will add to the information from the JBI tool.

3. Sub-group analysis – How will factors be categorised – e.g. location? income level? It would be useful to pre-specify how these categories are defined, as this is likely to influence the results.

4. Conclusion - Are these results only relevant to prehospital management of non-communicable diseases during a pandemic? Is there any relevance of the results for prehospital management more broadly? It would be interesting to explore how these results can inform our understanding of healthcare system resilience in response to crisis more generally.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Stroke epidemiology; epidemiological modelling; health services research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 May 2022
Edel Burton, University College Cork, Cork City, Ireland

Thank you for reviewing this protocol. Please find responses to your comments below:

Selection Criteria – only studies that include all the three definitions of ambulance response time will be included in the study. The feasibility of the review is based on all studies using comparable definitions of response time (albeit with different

terminology). The definitions as given are based on an Irish source. Can you provide some international evidence to support the consistency of these definitions across locations/health systems?

Response:

Thank you, the methods section has been amended to reflect the varying terminology and definitions used for ambulance response times internationally. The definitions of "activation time", "response time", and "patient care time" were chosen to facilitate comparison, as have been used a previous study. These are key phases in the stroke/TIA patient journey. Stakeholders from the ambulance service will now also be involved in the review to advise on terminology.

"The time periods chosen are due to clinical significance and previous inclusion in ambulance time studies. Due to international variation in terminology and definitions, a standardised definition needed to be used. Members of the ambulance service will advise on this task."

"Members of the Irish National Ambulance Service advised on terminology and clinical significance of time periods, in this review".

Quality appraisal – some more detail on quality appraisal would be helpful. Please justify the choice of the JBI critical appraisal tool for this specific study. What information on quality does it generate (e.g. a score, nominal categories), and how will this be used in the sub-group analysis? The GRADE tool is also mentioned – clarify what this is being used for and how it will add to the information from the JBI tool.

Response:

Thank you, sentences to clarify this are now added under " appraisal of the quality of included studies".

"The JBI tools will be used as it is anticipated that eligible studies will be cohort studies or quasi-experimental studies. JBI offers a critical appraisal tool for both. The JBI checklist offers a series of questions to which "Yes", "No", "Unclear" and "Not applicable" are the provided answers. These checklists will be used to assess risk of bias in individual studies. The GRADE tool is being used to assess the overall quality of cumulative evidence."

Sub-group analysis – How will factors be categorised – e.g. location? income level? It would be useful to pre-specify how these categories are defined, as this is likely to influence the results.

Response:

Thank you, some of the categories can be classified prospectively, whereas others cannot.

Location

This factor *cannot be categorised prospectively as we are unsure how this will be reported in*

different papers i.e., some may include cities, states, regions, or countries.

" Classification will be determined once papers are selected."

Income level
This will be categorized as low, lower-middle, upper-middle, and high-income countries, according to World Bank classifications.
"Determined by World Bank Classification[36]."

Study quality
"This will be determined by the appropriate JBI checklist[33] critical appraisal tool[33]criteria."

COVID-19 case numbers/hospitalisations in the country/area at the time of the study.
"John Hopkins Coronavirus Resource Centre Oxford Martin School data will be used."

According to the number of weeks since the World Health Organisation categorized COVID-19 as a pandemic. *(This was stated by the Director-General of the WHO at the media briefing on 11 March 2020[2])*

According to stroke/TIA diagnosis
This will be classified as suspected stroke/ TIA (call-taker classification), working diagnosis after review by emergency medical services, or hospital confirmed diagnosis.

Conclusion - Are these results only relevant to prehospital management of non-communicable diseases during a pandemic? Is there any relevance of the results for prehospital management more broadly? It would be interesting to explore how these results can inform our understanding of healthcare system resilience in response to crisis more generally.

Response:

Thank you for this suggestion, a sentence clarifying same has now been added to the conclusion.

"This work may also influence policy guidelines and future research on prehospital management of non-communicable diseases during a pandemic, and prehospital care more broadly. The results may also inform inform our understanding of healthcare system resilience in response to crises on a broader level".

Competing Interests: No competing interests were disclosed.

Reviewer Report 04 April 2022

?   **Graham McClelland** (iD)
[1] North East Ambulance Service NHS Foundation Trust, Newcastle upon Tyne, UK
[2] Newcastle University, Newcastle upon Tyne, UK

This is a protocol for a systematic review and meta-analysis looking at the effect of the COVID-19 pandemic on prehospital care for stroke and TIA. I think this is a worthwhile project but there are some details that need clarification or expanding upon.

- The title says prehospital emergency care whereas the paper is actually looking at times and call volumes which are not strictly the same so the title could be more precise.

- The fact that this is looking at adults only could be made clearer earlier on.

- The introduction builds a convincing argument for the impact of COVID-19 on the wider healthcare system but needs to expand on why ambulance response times are so relevant for this population, how brain damage is prevented, and why stroke/TIA are particularly vulnerable to pressures on the health system as these are stated but not explained.

- Grouping stroke and TIA together needs to be justified as some systems will have different treatment pathways for these conditions.

- The aim talks about estimating the ambulance response time, this seems somewhat vague when these times should be known and clearly reported so can be stated rather than estimated.

- Some definitions of the timeframe being examined would be useful both for how far pre-pandemic and what the authors are classing as the pandemic are needed.

- Are the authors looking at the raw number of stroke calls, how are these being identified (call taker classification, EMS clinician classification), and are these being put into the context of a number of calls to the wider EMS system at the time?

- Are any underlying trends in times and call volumes pre-pandemic being reported and how will these be accounted for in the analysis?

- I question the use of three time periods as what the authors class as 'patient care time' includes two distinct phases, the at-scene time and the transport to hospital time which are influenced by different factors.

- Why is hospital diagnosis of stroke being included and how is this relevant to the prehospital times and call volumes which are the primary aims of the study?

- Does a paper need to meet all the inclusion criteria to be included or could papers reporting one or two of the time periods be eligible?

- ○ Does the search have a defined time period, I would assume it would be literature from the last year or two years but this is not stated.

- ○ Will the authors be forward citation chaining to increase the robustness of the search strategy?

- ○ Is there a risk of missing relevant data by restricting the search to peer reviewed journals given the short time frame since the start of the pandemic and the fact that it is potentially not over?

- ○ Why are 3 articles being used to check the consistency of data collection, is there a rationale for this number?

- ○ Will the dispatch systems be reported on as these will affect the response and initial identification of stroke before face to face assessment by EMS clinicians?

- ○ How will the review account for patients assessed by EMS who then did not travel to hospital?

Is the rationale for, and objectives of, the study clearly described?
Partly

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: Publications and ongoing research in prehospital stroke care.

Reviewer Expertise: Prehospital care and stroke

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

> Author Response 30 May 2022
> **Edel Burton**, University College Cork, Cork City, Ireland
>
> Thank you for reviewing this protocol. Please see responses to your comments below:
>
> **The title says prehospital emergency care whereas the paper is actually looking at**

times and call volumes which are not strictly the same so the title could be more precise.

Response:

Thank you for your comment. We believe this title is appropriate as prehospital emergency care also includes patient transport, which is one of the key outcomes of this review. Furthermore, as a rapid response is a crucial component of stroke/TIA care, due to the time-sensitive nature of intervention and treatment, we believe the term "prehospital emergency care" is precise.

The fact that this is looking at adults only could be made clearer earlier on.

Response:

Thank you, as the population of interest is included throughout the abstract and introduction this clarification has now been added to the title of the protocol to make this fact clearer earlier on.

"*Effects of the COVID-19 pandemic on prehospital emergency care for adults with stroke and transient ischaemic attack: A protocol for* a systematic review and meta-analysis"

The introduction builds a convincing argument for the impact of COVID-19 on the wider healthcare system but needs to expand on why ambulance response times are so relevant for this population, how brain damage is prevented, and why stroke/TIA are particularly vulnerable to pressures on the health system as these are stated but not explained.

Response:

Thank you, sentences expanding on the above have been added to the introduction.

"Ambulance times are relevant to prehospital stroke/TIA care as the role of emergency medical services in this context involves rapid transport to secondary care specialists. As treatment strategies for stroke/TIA are time-dependent it is important to minimise time delays in the prehospital phase of care[12]."

"The acute ischaemic stroke chain of recovery involves recognition (of symptoms), reaction (emergency services are called), response (medical assessment), reveal (brain imaging) and Rx (treatment initiation[17]."

"Due to the time-sensitive nature of stroke/TIA intervention it is imperative that stroke/TIA survivors present to hospital as soon as possible after symptoms develop.[13] An increased volume of emergency calls may mean that not as many call takers or ambulances are available. Furthermore, patients may have been hesitant to call an ambulance during COVID-19 due to fear of contracting the disease.[7]"

Grouping stroke and TIA together needs to be justified as some systems will have different treatment pathways for these conditions.

Response:

Thank you, a justification has been added to the introduction. We wished to include both stroke/TIA as this review is focusing on the symptoms provided to the dispatcher thus no clinical assessment or working diagnosis would have yet been made. Furthermore, as some systems, like AMPDS used code 28 to identify stroke/TIA we wanted to be inclusive of these.

"Stroke and TIA can have similar presentations and are being included in this review as it is focusing on the symptoms provided to the dispatcher thus no clinical review or diagnosis would have yet been made. Also, within the timeframe in which prehospital care practitioners care for the patient it may not be possible to differentiate between symptoms of a stroke/TIA. Furthermore, some dispatch systems such as AMPDS have the same code for stroke and TIA."

The aim talks about estimating the ambulance response time, this seems somewhat vague when these times should be known and clearly reported so can be stated rather than estimated.

Response:

Thank you, we agree that these times should be known and clearly reported, but we cannot be entirely sure whether each study includes the entire population or whether the time data used is directly transcribed from digital systems or estimated by staff on scene. This is the reason that we have used the word 'estimate'.

Some definitions of the timeframe being examined would be useful both for how far pre- pandemic and what the authors are classing as the pandemic are needed.

Response:

Thank you, we had mentioned the WHO definition of the pandemic as beginning on 11th March 2020 in the "Presenting and Reporting the Results" section, however have now clarified this also in the introduction. The "pre-pandemic" period will be determined by each article, individually.

"COVID-19 was declared a pandemic by the Director-General of the WHO at the media briefing on 11 March 2020[2]."

Are the authors looking at the raw number of stroke calls, how are these being identified (call taker classification, EMS clinician classification), and are these being put into the context of a number of calls to the wider EMS system at the time?

Response:

Thank you, this has been clarified in the inclusion and exclusion criteria. We are looking at call taker classification. If the article provides information on the number of calls to the wider EMS system, then we will put this into context in the review.

"Calls identified by the call taker as suspected stroke/TIA will be included and if the data are available these calls will be put in context of calls made to the wider EMS system."

Are any underlying trends in times and call volumes pre-pandemic being reported and how will these be accounted for in the analysis?

Response:

If underlying trends are available in articles these will be reported in the results section. They will be included in a sensitivity analysis if presented.

I question the use of three time periods as what the authors class as 'patient care time' includes two distinct phases, the at-scene time and the transport to hospital time which are influenced by different factors.

Response:

Thank you. If the information is available in the articles, then the two distinct phases of "patient care time" will be included. This is now clarified in the methods and design section.

"In this review "patient care time" will include time spent on scene and transport to hospital time."

Why is hospital diagnosis of stroke being included and how is this relevant to the prehospital times and call volumes which are the primary aims of the study?

Response:

This is included to capture studies which follow the patient through from calling an ambulance to their hospital stay.

Does a paper need to meet all the inclusion criteria to be included or could papers reporting one or two of the time periods be eligible?

Response:

Thank you, we have clarified in the inclusion and exclusion criteria that papers need to include one or more of the time periods.

"A study needs to include data on at least one of: activation time, ambulance response time and patient care time to be eligible for inclusion".

Does the search have a defined time period, I would assume it would be literature from the last year or two years but this is not stated?

Response:

Thank you, there is no time period on the search so that it is as inclusive as possible. As COVID-19 was present in some countries earlier than others we wished not to exclude any potentially eligible papers by defining a search time period.

Will the authors be forward citation chaining to increase the robustness of the search strategy?

Response:

Thank you, yes both backward and forward citation chaining searching will be used. Clarification of same has been added to the "reference list search" section.

"Backward and forward citation searching will be conducted on all included studies."

Is there a risk of missing relevant data by restricting the search to peer reviewed journals given the short time frame since the start of the pandemic and the fact that it is potentially not over?

Response:

Thank you, peer reviewed literature will provide numeric information related to primary and secondary outcomes for possible inclusion in the meta-analysis. Grey literature, such as abstracts may not include information that is detailed enough to be included in this systematic review and meta-analysis.

Why are 3 articles being used to check the consistency of data collection, is there a rationale for this number?

Response:

This has now been changed to 20% in the "Data Extraction and Management" section, which is commonly seen in systematic reviews.

"JA will check a random sample of 20% of these studies for accuracy of data extraction."

Will the dispatch systems be reported on as these will affect the response and initial identification of stroke before face-to-face assessment by EMS clinicians?

Response:

*Thank you for this suggestion, we will now report the dispatch systems. This has been added to table **3.***

How will the review account for patients assessed by EMS who then did not travel to hospital?

Response:

Thank you, as the inclusion criteria have now been changed to capture at least one of the time periods of interest, patients who did not travel to hospital will be captured.

Competing Interests: No competing interests were disclosed.