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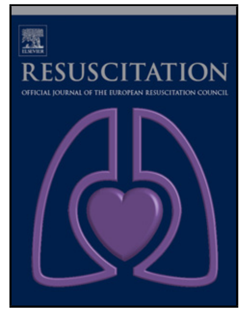

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PII: S0300-9572(20)30159-3

DOI: https://doi.org/doi:10.1016/j.resuscitation.2020.04.022

Reference: RESUS 8499

To appear in: *Resuscitation*

Received Date: 6 April 2020

Revised Date: 15 April 2020

Accepted Date: 16 April 2020

Please cite this article as: Couper K, Taylor-Phillips S, Grove A, Freeman K, Osokogu O, Court R, Mehrabian A, Morley PT, Nolan JP, Soar J, Perkins GD, COVID-19 in cardiac arrest and infection risk to rescuers: a systematic review, *Resuscitation* (2020), doi: https://doi.org/10.1016/j.resuscitation.2020.04.022

COVID-19 in cardiac arrest and infection risk to rescuers: a systematic review

Author:

Keith Couper*,[1,2] Sian Taylor-Phillips* [1] Amy Grove,[1] Karoline Freeman,[1] Osemeke Osokogu,[1] Rachel Court,[1] Amin Mehrabian,[1,3] Peter T Morley,[4,5] Jerry P Nolan,[1,6] Jasmeet Soar,[7] Gavin D Perkins[1,2].

1) Warwick Medical School, University of Warwick, Coventry, UK
2) Critical Care, University Hospital Birmingham NHS Foundation Trust, Birmingham, UK
3) Department of Pharmaceutical Nanotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
4) Intensive Care, The Royal Melbourne Hospital, Melbourne, Australia
5) Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Australia
6) Intensive Care Unit, Royal United Hospitals Bath NHS Foundation Trust, Bath, UK
7) Intensive Care Unit, Southmead Hospital, North Bristol NHS Trust, Bristol, UK

*- Joint first author

Corresponding Author:
Professor Gavin Perkins, Warwick Clinical Trials Unit, University of Warwick, Coventry, CV4 7AL
E: g.d.perkins@warwick.ac.uk

Abstract

Background: There may be a risk of COVID-19 transmission to rescuers delivering treatment for cardiac arrest. The aim of this review was to identify the potential risk of transmission associated with key interventions (chest compressions, defibrillation, cardiopulmonary resuscitation) to inform international treatment recommendations.

Methods: We undertook a systematic review comprising three questions: 1) aerosol generation associated with key interventions; 2) risk of airborne infection transmission associated with key interventions; and 3) the effect of different personal protective equipment strategies. We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and the World Health Organisation COVID-19 database on 24th March 2020. Eligibility criteria were developed individually for each question. We assessed risk of bias for individual studies, and used the GRADE process to assess evidence certainty by outcome.

Results: We included eleven studies: two cohort studies, one case control study, five case reports, and three manikin randomised controlled trials. We did not find any direct evidence that chest compressions or defibrillation either are or are not associated with aerosol generation or transmission of infection. Data from manikin studies indicates that donning of personal protective equipment delays treatment delivery. Studies provided only indirect evidence, with no study describing patients with COVID-19. Evidence certainty was low or very low for all outcomes.

Conclusion: It is uncertain whether chest compressions or defibrillation cause aerosol generation or transmission of COVID-19 to rescuers. There is very limited evidence and a rapid need for further studies.

Review registration: PROSPERO CRD42020175594

Introduction

The World Health Organization (WHO) declared a Severe Acute Respiratory Syndrome Coronavirus two (SARS-CoV-2) pandemic on 11 March 2020. As of 4th April 2020, over one million individuals are reported to have been infected with Coronavirus Disease 2019 (COVID-19), of which over 55,000 have died.[1] Data from China highlight the potential risk to healthcare workers when undertaking aerosol generating procedures (AGP) in COVID-19 patients.[2]

The WHO has categorised cardiopulmonary resuscitation (CPR) as an aerosol generating procedure, requiring the wearing of respirator masks and other personal protective equipment (PPE).[3, 4] In contrast, some national guidance describes chest compressions and defibrillation as non-aerosol generating procedures.[5] The discordance between WHO and national guidance may reflect differences in terminology, specifically WHO uses the term cardiopulmonary resuscitation to incorporate chest compressions, defibrillation and associated airway manoeuvres. Nevertheless, a 2012 review on Severe Acute Respiratory Syndrome (SARS) transmission identified uncertainty about the aerosol generating potential of chest compressions and defibrillation.[6]

Current resuscitation guidelines highlight the importance of rescuer safety.[7] Delaying the delivery of chest compressions and defibrillation for up to several minutes for healthcare workers to don personal protective equipment (PPE) will reduce the likelihood of patient survival.[8-10] In contrast, the delivery of aerosol generating procedures to a patient infected with COVID-19 may place healthcare workers at risk. Driven by concern amongst the clinical community as to the optimum approach in cardiac arrest, the International Liaison Committee on Resuscitation (ILCOR) identified the urgent need for a review of current evidence to inform international resuscitation treatment recommendations in patients with known or suspected COVID-19.

Methods

We undertook a systematic review to explore three key questions relating to the transmission of COVID-19 in relation to chest compressions, defibrillation and CPR (box one). In view of the urgent need for evidence to inform international policy, the review was completed in four-days. Our review was prospectively registered with PROSPERO (CRD42020175594) and is written in accordance with the PRISMA statement.[11]

Our first two research questions examined the association between key resuscitation interventions (chest compressions, defibrillation, CPR) and aerosol generation and airborne transmission of infection. Our third question examined the effect of different personal protective equipment systems (supplementary information).

Search strategy

The information specialist iteratively developed the search strategy in consultation with other project team members and drawing on the strategy developed for a previous review.[12] We undertook a single search to encompass all three review questions. We searched MEDLINE (OVID interface), Embase (OVID interface), Cochrane Central Register of Controlled Trials, and the Database of publications on coronavirus disease (COVID-19) developed by the World Health Organisation,[13] all from inception to 24th March 2020. We updated the search using the WHO COVID-19 database on 6th April 2020. Our full record of searches is included in the supplementary information.

In addition, we used the Science Citation Index (Web of Science) to identify additional citations from a relevant Canadian review published in 2011.[6, 12] We also assessed the reference lists of three relevant reviews.[6, 12, 14] Finally, we identified additional citations through consultation with subject experts.

Study eligibility

We assessed study inclusion using pre-defined study criteria based on the research question (see supplementary information). For all questions, we included randomised controlled trials and non-randomised studies (e.g., interrupted time series, controlled before-and-after studies, cohort studies). For questions one and two, we additionally included case reports and case-series. For questions one and three we included cadaver studies, and for question three included manikin studies.

For all studies, we required that the study be set in the context of a cardiac arrest, with delivery of chest compressions and/or defibrillation and/or CPR by any individual (healthcare worker or lay person). For infection transmission, we included all types of infection (viral/bacterial/fungal) with presumed airborne transmission. We imposed no date or language restrictions provided there was an English language abstract.

Article selection

On search completion, we used EndNote X9 software to systematically identify and remove duplicate citations. Titles/abstracts were reviewed independently by two reviewers from the team (two of STP/AG/AM), and obviously irrelevant citations excluded. We subsequently sourced full-text papers, with eligibility independently assessed by two reviewers (AG/AM) against pre-specified criteria. At each stage, disagreements were discussed and reconciled or referred to a third reviewer for adjudication (KC).

Data extraction and analysis

A single reviewer from the team (one of STP/AG/KF/OO) extracted data from eligible full-text papers using a piloted data extraction form. Accuracy was assessed by a second reviewer. We extracted key data from each study relevant to the specific research question, including details of population, exposure, intervention/ comparator, outcome and type of infection. Disagreements between reviewers were resolved by consensus, or consultation with a third reviewer (KC). Where a publication was eligible for inclusion for more than one research question, data were extracted into a single data extraction form record.

<u>Risk of bias assessment and assessment of certainty of evidence</u>

A single reviewer from the team (one of STP/AG/KF/OO) assessed risk of bias of full-text papers using quality assessment tools that were appropriate for each study design. We used the modified Cochrane Collaboration Risk of Bias tool for randomised controlled trials;[15] the Evidence Partners tool for case-control studies and cohort studies;[16, 17] and the Murad tool for case reports and case series.[18] Assessment accuracy was evaluated by a second reviewer (one of STP/AG/KF/OO). We used the GRADE system to assess certainty of evidence per outcome (outcomes for each question are listed in box one).[19]

<u>Data analysis</u>

We anticipated that identified studies would be heterogeneous. We assessed studies for clinical, methodological, and statistical heterogeneity, Where not precluded by heterogeneity, we intended to consider pooling data in a meta-analysis using a random-effects model. In the likely event that a meta-analysis was precluded, we planned a narrative synthesis.

Results

Searches of databases and other sources identified 749 citations. Following removal of duplicates and screening of titles/abstracts, we retrieved 38 full-text papers of which 11 were eligible for inclusion in the review (see Figure 1).[20-30] The electronic supplement includes characteristics of included studies, and a list of reasons for excluding studies at full text review.

Of the 11 papers, we included two studies for question one,[20, 26] eight for question two, [20-27] and three for question three.[28-30] Both papers included in question one were also included in question two. We included five case reports,[20-23, 26] three observational studies,[24, 25, 27] and three manikin randomised controlled trials.[28-30] None of the included papers described a patient with COVID-19. Study risk of bias assessments and GRADE tables are included in the electronic supplement.

<u>Question one - aerosol generation</u>

We did not find any direct evidence that chest compressions or defibrillation either did or did not generate aerosols. We included data from two case reports providing indirect evidence of aerosol generation.[20, 26] In both cases, a healthcare worker contracted an infection from patients undergoing CPR, which the report authors attribute to aerosol generation. In both cases, patients underwent prolonged resuscitation attempts that likely incorporated ventilation. Neither patient is reported as receiving defibrillation. In one case, the healthcare worker is described as wearing appropriate PPE. [26] Evidence certainty was categorised as very low.

Question two - transmission of infection

We did not find any direct evidence that chest compressions or defibrillation either are or are not associated with transmission of infection. We included indirect evidence from eight studies: two retrospective cohort studies,[25, 27] one case-control study[24] and five case reports.[20-23, 26] Studies are summarised in Table one.

In the two cohort studies, the authors compared SARS infection transmission in individuals who were exposed and not exposed to specific interventions.[25, 27] Both studies were undertaken in Canada and examined SARS transmission. In one study of 697 healthcare workers, only nine individuals were exposed to chest compressions and four were exposed to defibrillation.[27] In the other study of 43 healthcare workers, eight individuals were exposed to CPR and defibrillation. Neither study identified a statistically significant association between these exposures and infection transmission. Key study limitations were the lack of clear definition of exposures and inability to account for multiple exposures.

In the case-control study, 51 healthcare workers with probable SARS were compared with 477 healthcare workers without infection.[24] There was a correlation between giving chest compressions and tracheal intubation, indicating that often healthcare workers who were exposed to one were often exposed to the other. A multivariate analysis suggested that exposure to chest compressions was associated with an increased odds of probable SARS infection (odds ratio 4.52, 95% confidence interval 1.08 to 18.81). However, the omission of tracheal intubation in the multivariate model may mean the reported risk is primarily driven by tracheal intubation or other airway manoeuvres (e.g. bag-mask ventilation) associated with chest compressions. Questionnaires that collected details of exposure were completed one to four months after exposure, and so may be subject to recall bias.

In the five case reports, the reported transmissions were: Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), tuberculosis, novel bunyavirus, designated Severe Fever with Thrombocytopenia Syndrome (SFTS) virus, and Panton-Valentine leucocidin.[20-23, 26] The use of PPE varied across reports. In none of the cases was delivery of defibrillation described. In all cases, the patients appear to have received airway manoeuvres alongside chest compressions. In one case report,[21] a nurse wearing full PPE delivered chest compressions to a patient with SARS for 15-minutes and subsequently developed symptoms of infection. However, based on timings presented in the study it is likely the nurse was also present in the room during airway manoeuvres.

All studies and reports may be subject to recall bias, both in relation to the PPE worn and the procedures undertaken. Evidence certainty was assessed as very low.

Question three- personal protective equipment strategies

For question three, we included three manikin RCTs that recruited 104 participants.[22, 29, 30] One study was individually randomised,[30] and the other two were crossover RCTs.[22, 29] All studies simulated chest compression or CPR delivery. Two studies compared different types of respirator[22, 29] and one study compared different types of gown.[30] Characteristics of included studies and results are shown in table two.

The outcome of infection transmission was not evaluated in any study.

No studies examined infection rates with different types of PPE.

The outcome of PPE effectiveness was evaluated in one randomised crossover trial that examined the performance of different N95 (or higher-level) mask types (cup-type, fold-type, valve-type) during chest compressions (see Table 2).[29] The primary outcome was the adequate protection rate (APR) defined as the proportion of participants achieving a good fit. During chest compression delivery, the APR differed between study arms (cup-type: 44.9% (SD 42.8) v fold-type: 93.2% (SD 21.7) v valve-type 59.5% (SD 41.7), P<0.001 for difference between groups). For all mask types, APR was lower during chest compression delivery than at baseline.

The outcome of CPR quality was evaluated in three studies, two studies reported time taken to deliver key interventions,[28, 30] and one study by Shin and colleagues (2017), examined CPR quality[29] with and without PPE (see Table 2).[22, 30] In one study, delivery of pre-hospital paediatric life support (including bag mask ventilation, defibrillation, tracheal intubation, and drug administration) was quickest in individuals not wearing PPE (Control: 261 seconds (SD 12) v Conventional air-purifying respirators 275 seconds (SD 9) v air-purifying respirator-hood 286 seconds (SD 13), p<0.0001).[28] In firefighters, the type of gown used, alongside other PPE, influenced time to commence chest compressions (standard gown: 71 seconds (95% CI 66–77) v modified gown 59 seconds (95% CI 54–63) v no gown 39 seconds (95% CI 34–43), p<0.001).[30] In the trial by Shin,[29] there was no difference in CPR quality between groups.

Discussion

In this systematic review of 11-studies, we identified evidence that chest compressions may generate aerosols and are associated in some circumstances, with transmission of infection to rescuers. However, in all cases, it is likely there was simultaneous exposure to airway manoeuvres, such that the isolated effect of either chest compressions or defibrillation could not be reliably identified. Evidence from manikin studies showed that the donning of PPE delays the initiation of treatment. Furthermore, PPE may, in many cases, be less effective during chest compressions because of the risk of mask slippage, highlighting the need for careful donning and ongoing monitoring of effectiveness.

Our findings are broadly similar to those of a Canadian review completed in 2012 which found no statistically significant association between SARS transmission and chest compression delivery (odds ratio 1.4, 95% confidence interval 0.2 to 11.2) or SARS transmission and defibrillation (odds ratio 2.5, 95% confidence interval 0.1 to 43.9). This finding was based on data from three observational studies.[24, 25, 27] Whilst we included the same studies in this review, we decided that it was not methodologically appropriate to pool data between studies because of the likelihood that healthcare workers were exposed to multiple aerosol generating procedures and owing to the very low rates of disease transmission. For example, in one study, only one healthcare worker was infected in both the chest compression exposed and defibrillation exposed groups. Our confidence in any pooled estimates would be very low.

Since completing the review, we identified via ongoing literature scanning a retrospective cohort study of 72 healthcare workers (28 infected with COVID-19; 44 not infected) that met inclusion criteria for question two.[31] Healthcare workers experienced multiple potential exposures as part of their clinical duties. single non-infected individual was exposed to CPR. The risk of COVID-19 transmission in individuals exposed to CPR was not significant (relative risk 0.63, 95% confidence interval 0.06 to 7.08). Whilst this additional study does not alter the findings of our review, it highlights the rapid publication of much needed new data about COVID-19.

Our finding that there is no direct evidence that chest compressions and defibrillation either are or are not aerosol generating procedures is important. However, this absence of evidence should not be interpreted as providing evidence that these procedures are not aerosol generating.

From a physiological perspective, the generation of aerosols by chest compressions is clinically plausible, because changes in thoracic pressure during chest compressions generate airflow and small exhaled tidal volumes.[32] Evidence from the physiotherapy literature shows that manual chest physiotherapy techniques do generate aerosols.[33] In contrast, for defibrillation,[32] the mechanism for aerosol generation during defibrillation is less clear. However, tonic muscle spasms caused by defibrillation could conceivably generate a small amount of airflow.

For policy makers, there is a need to balance the known risk of treatment delays if PPE is donned before chest compressions and defibrillation are delivered, against the unknown, but potential, risk of COVID-19 transmission to rescuers. This risk may also extend beyond the rescuer, with additional risk of onward transmission to other healthcare workers, patients, and the wider community.[34] The known risk associated with treatment delay relate to the time taken to don PPE and the challenges of delivering effective treatment whilst wearing PPE.[8-10, 28] Importantly, we found evidence that delivery of chest compressions may reduce the effectiveness of face masks.[29]

This review highlights the urgent need for research to identify and quantify aerosol generation associated with chest compressions and defibrillation. This could be undertaken using observations in clinical settings, or cadaver or animal models. Such work is essential to better understand the potential risk to the rescuer when undertaking these procedures.

The aim of this review was to identify the available evidence relating to aerosol generation, infection transmission and protection afforded by personal protective equipment. Beyond this specific focus, interpretation of the evidence to guide clinical practice guidelines will need careful consideration of the prevalence of COVID-19 in specific settings, the likelihood that the resuscitation provider has already been exposed (e.g. close household contact), the availability of personal protective equipment, the time taken to train staff in its use, and the values and preferences of the wider community where any guidance will be implemented. In addition the balance of risks and benefits for specific interventions will vary; for example, early defibrillation for a witnessed cardiac arrest compared with cardiopulmonary resuscitation for cardiac arrest secondary to refractory hypoxia. As identified in this review, cardiopulmonary resuscitation is also a complex intervention comprising ventilation, chest compressions, drug therapy and defibrillation, which become difficult to separate out without reducing overall clinical effectiveness. Finally, with over one million out of hospital cardiac arrests each year around the world and the critical importance of the community's willingness to commence chest compressions and defibrillation, long term unintended consequences of restrictive policies need to be considered and necessitate clear communication strategies with local communities.

Our review has three key limitations. Firstly, in order to provide an urgent review of evidence to meet the needs of the international resuscitation community, we were unable to undertake simultaneous independent data extraction and risk of bias assessments. Instead, we performed single assessments followed by independent accuracy assessments. Secondly, for expediency, we undertook a single search to cover all three questions. If more time had been available, we might have considered an individual search strategy for each question which may have increased search sensitivity. To mitigate this, we undertook citation tracking of key papers to identify citations not identified in the search. Thirdly, the available evidence was typically at high risk of bias and indirect, which limits the inferences that can be drawn. This is reflected in our assessment that evidence certainty for all outcomes was low or very low.

In conclusion, we identified very limited evidence that does not enable us to estimate the risk of chest compressions or defibrillation in relation to aerosol generation and COVID-19 transmission from the patient to the rescuer. In developing practice recommendations, guideline writers must balance an unknown potential infection risk to rescuers against the known risk to the patient from treatment delays.

Declaration of conflicts of interest:

JN is Editor-in-Chief of Resuscitation and receives payment from the publisher Elsevier. JS and GDP are Editors of Resuscitation and receive payment from the publisher Elsevier. JS is chair of the ILCOR ALS Task Force, and GDP is co-chair of ILCOR. KC, STP, AG, KF, OO, RC, AM and PM have no conflicts of interest to declare.

Funding statement:

Not directly funded.

Dr Taylor-Phillips is supported by a National Institute for Health Research (NIHR) Career Development Fellowship (CDF-2016-09-018). Dr Grove is funded by the NIHR Advanced Fellowship Programme (NIHR300060). Karoline Freeman is funded by the NIHR Doctoral Research Fellowship Programme (DRF-2016-09-038). Prof Perkins is supported as an NIHR Senior Investigator and by the NIHR Applied Research Centre (ARC) West Midlands, UK. Rachel Court, Osemeke Osokogu and Amin Mehrabian are supported by the National Institute for Health Research Systematic Reviews Programme.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Acknowledgements

We gratefully acknowledge the support of Julia Geppert, Karoline Munro, and Emily Watkins.

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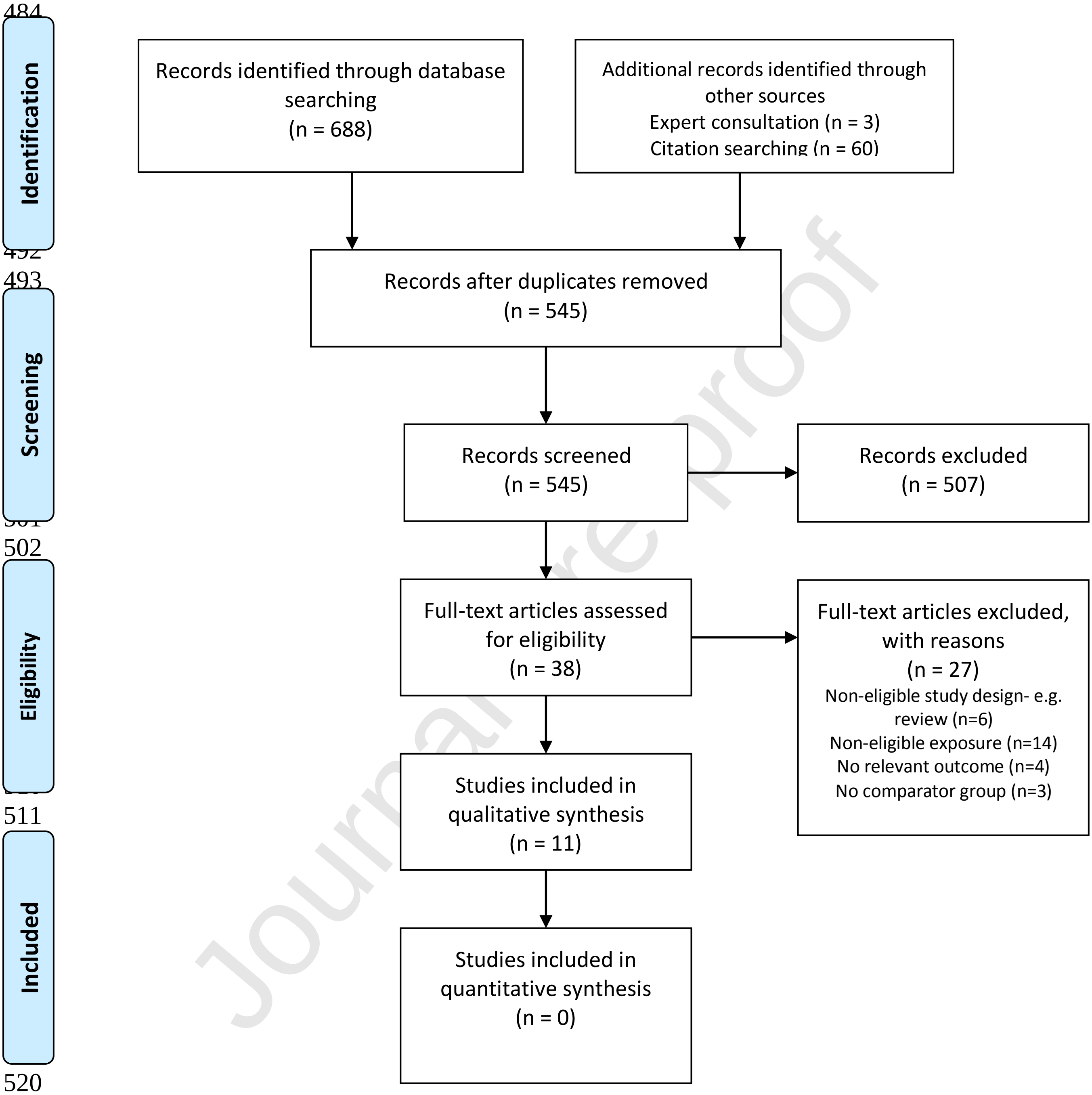
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 688)
Additional records identified through other sources
Expert consultation (n = 3)
Citation searching (n = 60)
Records after duplicates removed (n = 545)
Records screened (n = 545)
Records excluded (n = 507)
Full-text articles assessed for eligibility (n = 38)
Full-text articles excluded, with reasons (n = 27)
Non-eligible study design- e.g. review (n=6)
Non-eligible exposure (n=14)
No relevant outcome (n=4)
No comparator group (n=3)
Studies included in qualitative synthesis (n = 11)
Studies included in quantitative synthesis (n = 0)

<u>Box one: research questions</u>

> Research question one
> In individuals in any setting, is delivery of 1) chest compressions, 2) defibrillation or 3) cardiopulmonary resuscitation associated with aerosol generation?
>
> Research question two
> In individuals in any setting wearing any/no personal protective equipment, is delivery of 1) chest compressions, 2) defibrillation or 3) cardiopulmonary resuscitation associated with transmission of infection?
>
> Research question three
> In individuals delivering chest compressions and/or defibrillation and/or CPR in any setting, does wearing of personal protective equipment compared with wearing any alternative system of personal protective equipment or no personal protective equipment affect infection with the same organism as the patient, personal protective equipment effectiveness, or quality of CPR?

Table 1. Results for question two, investigating the association between chest compressions, defibrillation, and cardiopulmonary resuscitation with transmission of infection

Study,	**Design/ setting**	**Population**	**PPE worn by rescuers?**	**Exposure**	**Infection-transmitted**	**Risk of infection in u**
Observational studies						
Raboud et al 2010	Retrospective cohort 20 hospitals, Canada	624 HCWs who provided care to 45 laboratory confirmed SARS patients	Not recorded	Chest compression and defibrillation (and 32 other activities)	SARS	No chest compression No defibrillation: 25/(
Loeb et al 2004	Retrospective cohort 2 hospitals, Canada	32 nurses entering rooms with SARS patients	Variable	CPR and defibrillation (and 30 other activities)	SARS	No CPR (but other ex (28%) No defibrillation (but exposures): 8/30 (27%
Liu et al 2009	Case control 1 hospital, China	477 HCWs (51 case/ 426 control)	Variable	Chest compression (and 27 other factors)	SARS	11% (numerator and denon reported)†
Case reports						
Chalumeau et al 2005	Case report Hospital, France	15 HCWs- performed CPR on the index patient	None	CPR	Panton-Valentine leukocidin-producing S. aureus pneumonia	
Christian et al 2004	Case report Hospital, Canada	9 HCWs- performed CPR on the index patient	Full	CPR	SARS	

Kim et al 2015	Case report Hospital, Korea	7 HCWs- performed CPR on the index patient	Variable	CPR	Novel bunyavirus, designated SFTS virus	
Knapp et al 2016	Case report Pre-hospital, Germany	3 HCWs- performed CPR on index patient	Variable	CPR	TB	
Nam et al 2017	Case report Hospital, Korea	6 HCWs involved in CPR	Full	CPR	MERS	
†- Multiple other exposures. CPR- Cardiopulmonary defibrillation. SARS-Severe acute respiratory syndrome. TB- Tuberculosis. MERS- Middle East Respiratory S						

Table 1. Results of studies included in research question 3: comparison of personal protective equipment strategies effect on infection, PPE effectiveness, and quality of CPR

Study	**Design/ setting**	**Population (clinical)**	**Procedure**	**Intervention and comparator**	**Outcomes measured**
Randomised control trials					
Schumacher et al 2013	Manikin RCT (crossover) UK	16 paramedics	Paediatric cardiac arrest (airway management, defibrillation, drug administration)- paediatric manikin	Intervention group 1: Conventional air-purifying respirators (APR) Intervention group 2: Modern loose-fitting air-purifying respirator-hoods (PAPR-hood) Comparator: no PPE	Treatment duration: Control: 261 seconds (SD 12) APR: 275 seconds (SD 9) PAPR-hood: 286 seconds (SD 13) P<0.0001 for difference between groups.
Shin et al 2017	Manikin RCT (crossover) Korea	30 healthcare workers	Simulated chest compressions with real-time feedback- adult manikin	Intervention group 1: cup-type respirator mask preformed into a cup shape Intervention group 2: fold-type respirator mask that is flexible and 3-folded Intervention group 3: valve-type respirator mask similar to the fold-type respirator with valve	Adequate protection rate (%) during chest compressions:† Cup-type: 44.9% (SD 42.8) Fold-type: 93.2% (SD 21.7) Valve-type 59.5% (SD 41.7%) P<0.001 for difference between groups. Compression quality similar between groups
Watson et al 2008	Manikin RCT Canada	58 firefighters	Simulated CPR- manikin	Intervention Group 1: Standard gown plus N95 respirator, gloves and eye protection Intervention group 2: Modified gown and an N95 respirator, gloves and eye protection‡ Comparator: No gown, but PPE included an N95 respirator, gloves and eye protection.	Time to chest compressions (seconds): Standard gown: 71 (95% CI 66–77 Modified gown 59 (95% CI 54–63) No gown: 39 (95% CI 34–43) P<0.001 for difference between groups).
RCT- Randomised Controlled Trial; SD- Standard Deviation; PPE- Personal protective equipment; 95% CI- 95% confidence interval † Fit factor calculated as concentration of particles outside respirator divided by concentration inside respirator (maximum value- 200)-fit factor > 100 considered adequate protection ‡ Modified gown comprises re-tied neck ties waist ties that are tied at front.					

Conflict of interest statement

JN is Editor-in-Chief of Resuscitation and receives payment from the publisher Elsevier. JS and GDP are Editors of Resuscitation and receive payment from the publisher Elsevier. JS is chair of the ILCOR ALS Task Force, and GDP is co-chair of ILCOR. KC, STP, AG, KF, OO, RC, AM and PM have no conflicts of interest to declare.