REVIEW article

The roles of transportation and transportation hubs in the propagation of influenza and coronaviruses: a systematic review

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Running title: Influenza and coronavirus in transport systems

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ABSTRACT

Background. Respiratory viruses spread in humans across wide geographical areas in short periods of time, resulting in high levels of morbidity and mortality. We undertook a systematic review to assess the evidence that air, ground and sea mass transportation systems or hubs are associated with propagating influenza and coronaviruses.

Methods. Healthcare databases and sources of grey literature were searched using pre-defined criteria between April and June 2014. Two reviewers screened all identified records against the protocol, undertook risk of bias assessments and extracted data using a piloted form. Results were analysed using a narrative synthesis.

Results. Forty-one studies met the eligibility criteria. Risk of bias was high in the observational studies, moderate to high in the reviews and moderate to low in the modelling studies. In-flight influenza transmission was identified substantively on five flights with up to four confirmed and six suspected secondary cases per affected flight. Five studies highlighted the role of air travel in accelerating influenza spread to new areas. Influenza outbreaks aboard cruise ships affect 2% - 7% of passengers. Influenza transmission events have been observed aboard ground transport vehicles. High heterogeneity between studies and the inability to exclude other sources of infection means that the risk of influenza transmission from an index case to other passengers cannot be accurately quantified. A paucity of evidence was identified describing SARS-CoV and MERS-CoV transmission events associated with transportation systems or hubs.

Conclusion. Air transportation appears important in accelerating and amplifying influenza propagation. Transmission occurs aboard aeroplanes, at the destination and possibly at airports. Control measures to prevent influenza transmission on cruise ships are needed to reduce morbidity and mortality. There is no recent evidence of sea transport accelerating

influenza or coronavirus spread to new areas. Further investigation is required regarding the roles of ground transportation systems and transport hubs in pandemic situations.

Epidemiological evidence has demonstrated the speed and extent to which influenza A(H1N1)pdm09, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) may be disseminated globally and cause a significant burden on human health and health systems [1, 2, 3]. International passenger arrivals worldwide reached 1,087 million in 2013 and, with transport hubs expanding both in passenger volume and number of destinations, it is important to understand the role of transportation systems in respiratory virus transmission events to inform public health policy [4]. It has been hypothesised that mass transport systems are involved in amplifying and accelerating the spread of influenza and coronaviruses globally, due to high crowd densities and enclosed spaces, which provide prime conditions for person-to-person transmission via inhalation of virus in aerosols and/or droplets [5]. High passenger throughput provides enhanced opportunities for indirect transmission via fomite spread.

Transmission events of other respiratory pathogens aboard aircraft (such as *Mycobacterium tuberculosis* complex) have been widely investigated [6]. Knowledge from these incidents has contributed to guidelines for the prevention and control of disease transmission [7].

Two literature reviews published prior to the 2009 influenza A(H1N1)pdm09 pandemic investigated pathogen transmission aboard aircraft and identified SARS-CoV and influenza transmission events [6, 8]. However, these were not systematic enquiries, and no conclusions were drawn about the numbers of passengers at risk of secondary infection or whether air travel propagates influenza or SARS-CoV transmission. Adlhoch & Leitmeyer (2014) reviewed influenza transmission aboard aircraft. Suspected influenza transmission aboard long and short haul flights was identified [9] but, due to limitations within included studies, an assessment of the risk of influenza transmission aboard aircraft could not be made. Prior reviews have not considered the potential roles of sea and ground mass transport systems or hubs, synthesised evidence from mathematical modelling studies; nor attempted to ascertain the role of transport systems in accelerating the spread of viruses to new geographical areas.

We attempted to address these gaps when undertaking a systematic review to assess the evidence that air, sea and ground mass transport systems or hubs are associated with the spread of influenza, SARS-CoV and MERS-CoV between humans. We aimed to identify evidence of amplification and/or acceleration of virus transmission related to the use of such transport systems. This review was not concerned with the timing of pandemics or the effectiveness of specific interventions such as entry and exit screening.

METHODS

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10] and the protocol was registered with the National Institute for Health Research international prospective register of systematic reviews prior to execution of the search strategy [11].

The population of interest was humans using air, sea or ground mass transportation vehicles or hubs and exposed to influenza, SARS-CoV or MERS-CoV via the breathed or touched environment. Qualitative and quantitative evidence of acceleration and/or amplification of pathogen transmission related to the transport systems was gathered. This was to include laboratory confirmed and suspected cases, geographically and temporally linked to transport vehicle or hub use. No restrictions were placed on study design, language (English abstract required) or date (all studies up to the search date of 18 April 2014 were considered). Studies on military personnel and transport were excluded due to differing practices and regulations that would increase heterogeneity and limit generalisability. This review was concerned with estimating the risk of transmission related to the use of transport systems, not the timing of pandemics or the effectiveness of specific interventions.

Search strategy and study selection

Healthcare databases and sources of grey literature were searched (Appendix S1). Domain experts were contacted to request details of studies they regarded relevant to this review. Critical keyword and thesaurus heading search constructs were developed for MEDLINE (Appendix S2) and adapted for use with other sources [11]. Identified studies were imported into EndNote X6 software package (Thomson Reuters, San Francisco, United States of America). Following the removal of duplicates all records were screened against the protocol eligibility criteria (Appendix S3) by two reviewers sequentially at title, abstract and full text stages. Reference and citation tracking was performed on all eligible studies.

Data collection and risk of bias assessments

A piloted form was used to extract data in duplicate from all included studies. Data items extracted were related to study information (location, design, objectives), population details (study group, case definitions), exposure details (virus and transport type) and outcome (evidence of transmission and use of a comparator). Risk of bias assessments were performed on all included studies at study and outcome level using the Newcastle-Ottawa Scale (NOS) [12] for observational studies, the US Agency for Healthcare Research Quality tool [13] for reviews and a tool previously designed at the University of Nottingham for assessing risk of bias in mathematical modelling studies [14].

Summary measures and synthesis of results

A range of outcome measures were identified including the number of secondary cases aboard transport vehicles, attack rates on transport vehicles and the correlation between passenger arrival volumes and the number of days to the peak of virus deaths.

A qualitative approach was used to narratively synthesise results according to the framework described by the UK Economic and Social Research Council [15]. The analysis was stratified by virus and transport type. The form of data available and presence of substantial heterogeneity between studies precluded meta-analysis.

RESULTS

Study selection and characteristics

Of the 2,940 studies identified and screened, 41 met the protocol eligibility criteria (Figure 1). Twenty-seven observational studies (24 retrospective cohort, one case-control, two cross-sectional), three reviews (two systematic and one literature review), ten modelling studies and one qualitative report were included. The studies were undertaken across Europe (UK, Germany, Spain), Asia (China, Korea, Japan, Singapore), North America (USA and Canada) and Australasia (New Zealand and Australia). Computational fluid dynamics (CFD) were used in many of the included modelling studies to simulate the dispersion of pathogens in specified environments.

Study characteristics have been tabulated based on organism and transport type (Appendix S4). Twenty-nine studies were on influenza five on SARS-CoV and two on MERS-CoV. Three did not specify the virus transmitted and two were on both influenza and SARS-CoV.

The majority of studies (n=30) investigated transmission related to air transport (Appendix S5). There were six studies on sea transport (Appendix S6) and six on ground transport (Appendix S7).

Risk of bias

For observational studies there was a generally high risk of bias (median NOS score 3). Main limitations included selection bias, recall bias and an inability to exclude other sources of infection (Appendix S8). The overall risk of bias of included modelling studies was moderate to low (Appendix S9). Limitations arose from the assumptions that all journeys were homogenous and from not considering the potential effects of individuals' actions during transit (e.g. moving around an aircraft cabin).

The two literature reviews [6, 8] had moderate to high risk of bias due to non-systematic search strategies and unclear eligibility criteria. The review by Adlhoch & Leitmeyer (2014) had a low risk of bias [9] (Appendix S10).

Influenza and air transport

Laboratory confirmed in-flight transmission was limited on four flights, with only 1-2 passengers affected [16, 17, 18]. On one flight, four passengers acquired confirmed infection and a further six passengers had influenza-like-illness (ILI) fitting the CDC definition [19], giving a combined attack rate of 4.3% [20]. Symptomatic passengers aboard were essential for in-flight transmission to occur. Higher levels of in-flight transmission have been suspected, and attack rates of ILI have been reported at 2.8% [21], 5.3% -13% [22] and 20% [23]. An attack rate of laboratory confirmed influenza A(H1N1)pdm09 has been reported at 4.7% [24]. In these studies other sources of exposure could not be excluded [21-24]. An attack rate of 72% was observed on a grounded aircraft with ventilation systems switched off in 1979 [25] which the authors considered an anomaly due to the age and outdated ventilation systems of the aircraft. A Lagrangian based mathematical modelling study used an aircraft cabin mock-up with data on droplet deposition on surfaces and the frequency that people touch surfaces and their mucous membranes. The study concluded that the risk of influenza transmission from contaminated surfaces was negligible [26].

Studies using CFD show a theoretical increased risk of transmission if seated in close proximity to an index case [26, 27, 28]. Evidence from observational studies is inconclusive. Foxwell *et al* (2011) showed a 1.4% increased risk of ILI if seated within 2 rows of an index case [16] and Baker *et al* (2010) showed a higher attack rate of ILI (3.5%) within 2 rows of an index case compared to that in the rear section of the aircraft (1.9%) [18]. However, transmission has also been observed to persons seated in distant locations from an index case [17], and two studies calculated no significant association between seating location and risk of influenza transmission [20, 21]. In-flight passengers movements would potentially bring the index case into contact with non-neighbouring passengers, thus enabling transmission

The risk of in-flight transmission was shown to be theoretically higher on long haul flights [5, 27]. Long haul flights can be defined based on time, geographic location of the destination (the Civil Aviation Authority in the UK states the flights leaving the UK with destinations outside of Europe, Russia, Turkey and North Africa are classed as long haul [29]) or flight distance (medium haul flights are classed as 2000-5000 kilometres long [30]). Guputa *et al* (2012) used a probabilistic model with data on the exhalation, dispersion and inhalation of droplets carrying infectious agents [5] whilst Wagner *et al* (2009) used a Wells-Riley equation [31] and existing data on airflow patterns of cross-Atlantic airliners. Both models appear valid but assume there is one index case who remained static throughout the flight, therefore movement and possible contacts are not accounted for. Wagner *et al* (2009) also assumes that the air contamination is uniform [27]. All confirmed cases of transmission from observational studies were on long haul flights [16, 17, 18, 20]. On one short haul flight secondary transmission to up to 20 passengers was highly suspected but other sources of exposure could not be excluded [23].

Air travel accelerates the importation of community-acquired influenza to new areas. Secondary cases have been observed at previously unaffected destinations after contact with infectious air passenger arrivals [17, 32]. This has been observed both in conjunction with in-flight transmission and where no in-flight transmission events occurred. Two studies (one European, one North American) have investigated the association between the volume of air travel passenger arrivals and the timing of the seasonal peak of influenza deaths [33, 34]. Both found a strong, statistically significant negative correlation and concluded that high volumes of air travel are associated with introducing influenza to new areas. A significant association between air passenger volumes from Mexico and the likelihood of A(H1N1)pdm09 importation has also been observed [35].

Airports theoretically provide opportunities for influenza transmission [36]. Quan *et al* (2013) modelled the potential number of secondary infections caused by infectious airport terminal workers. A super-spreader working in arrivals could infect a mean average of 16.7 people per day and in departures 28.7 people per day [36]. The behaviour of people travelling in groups was shown to increase the risk of further transmission. The data sources of this model were not clearly specified and model assumptions not mentioned therefore its validity and reliability are uncertain. No observational studies were identified in this area.

Influenza and sea transport

Observed outbreaks of influenza-like illness (ILI) on cruise ships have previously affected 2% - 7% of passengers [37, 38, 39]. Higher proportions of crew (up to 13%) have reported ILI [37, 40] although this may include a case ascertainment bias due to active surveillance in this group being common. There was limited laboratory confirmation of influenza in ILI cases although when undertaken the proportion of confirmed cases were within the 2% - 7% range [39, 41]; on one ship simultaneous outbreaks were confirmed of A(H1N1)pdm09 (3% of passengers confirmed positive) and A(H3N2) (3.6% confirmed positive) [39].

Sea transport was important in accelerating the spread of influenza to new areas in the 1918 pandemic [42] although no evidence of this occurring more recently was identified. No evidence of influenza or coronavirus transmission occurring at sea ports was found.

Influenza and ground transport

Influenza transmission related to ground transport was only investigated by six quantitative studies [43, 44, 45, 46, 47, 48]. On one bus journey, transmission to one secondary case was laboratory confirmed [43] whereas on a different journey 84% of a group travelling together contracted influenza [44]. Transmission was highly suspected on a long distance train, on which a large number of secondary cases were observed with one confirmed index case aboard. The risk of transmission was associated with seating proximity to the index case and duration spent aboard [45]. However, other sources of exposure could not be excluded. Modelling studies found that the risk of transmission increases with travel duration and seating proximity to index cases [46, 47] Zhu *et al* (2012) used a CFD based model to determine that the risk of influenza transmission to bus passengers could reach 27.2% if seated in the path of the airflow and close to the index case. This assumes passengers do no move and doors do not open or close [46]. Furuya (2014) used a Wells-Riley model [31] to determine that the mean reproduction number for influenza on a commuter train was >2 and the risk of transmission increased linearly with journey duration [47].

A case-control study by Troko *et al* (2011) in the UK found that, after adjusting for confounders, persons reporting to the GP with acute respiratory infection (ARI) were almost six times as likely to have used public transport in the previous five days than controls (odds ratio 5.94, $p<0.05$) [48].

Rail transport was important in accelerating the spread of influenza to new areas in the 1918 A(H1N1) pandemic [42]. Transmission to persons in previously unaffected destinations from arriving rail passengers was observed in China during the A(H1N1)pdm09 pandemic [45].

SARS-CoV

High levels of SARS-CoV transmission have previously been suspected on flights. Three short haul flights with symptomatic passengers aboard were followed up, 16 passengers developed laboratory confirmed SARS-CoV and 6 met the WHO definition of probable infection [49, 50]**.** No significant association to seating proximity to an index case was observed and although interviews led to no other obvious sources of exposure they could not be excluded [49]. Transmission to an air stewardess was noted on one flight where other sources of exposure were deemed unlikely [51]. On six other flights carrying symptomatic SARS-CoV cases no secondary cases were identified [51]. Seven flights inbound to the USA with symptomatic and pre-symptomatic passengers on board were investigated, four passengers reported symptoms, none tested positive for SARS-CoV [52]. No studies investigated SARS-CoV transmission related to sea or ground transport systems or hubs. No studies investigated the role of these in accelerating SARS-CoV spread to new areas.

MERS-CoV

In-flight transmission was modelled to be possible and associated with flight duration and quanta per hour of virus exhaled [53]. Whilst no studies have observed this in real-life, transmission from an infectious air passenger to contacts at an unaffected destination has occurred [54]. No studies were found to investigate MERS-CoV transmission associated with sea or ground transport systems or hubs.

DISCUSSION

Summary of evidence

To our knowledge this is the first systematic review of respiratory virus transmission related to transport systems to incorporate both modelling and observational studies. Investigating the introduction of influenza and coronaviruses to geographically distinct areas via mass transport systems provides a more complete understanding of the roles of transport systems and what is required to reduce influenza and coronavirus propagation. Sea and ground transport are often overlooked in place of air transport but it is important to understand their impact on respiratory virus propagation as they are heavily used modes of transport, which may play an important role.

The results of our systematic review show that air transport accelerates the importation of community-acquired influenza to new areas [17, 32, 33, 34, 35] and that in-flight transmission of influenza has occurred on multiple occasions [16, 17, 18] with up to four laboratory confirmed secondary cases and an additional six cases of ILI identified per flight

[20]. Suspected in-flight transmission of ILI has been reported in up to 20% of passengers [23] although other sources of exposure could not be excluded. Influenza transmission in airport terminals was investigated by one modelling study, which showed the potential for transmission to occur to large numbers of passengers [36].

We found evidence of ILI outbreaks affecting 2% - 7% of passengers and 13% of crew on cruise ships [37, 38] with laboratory testing confirming cases within this range [39]. Although historically ships accelerated the spread of influenza to new areas [42] no evidence of this occurring in modern day pandemics was identified.

Influenza transmission has occurred aboard buses [43] and been highly suspected aboard trains [45]. Trains have accelerated influenza spread to new areas in historic and modern-day pandemics [42, 45].

In-flight SARS-CoV transmission was confirmed to one person from one flight [51]. Sixteen laboratory confirmed and four probable cases from three flights were identified, although other sources of exposure were deemed unlikely they could not be excluded [49]. A limited quantity of evidence on coronavirus transmission related to air, sea and ground transport was found.

Limitations

In many of the 27 observational studies included the risk of bias was high. Selection bias was common with many studies noting difficulties in obtaining flight itineraries and contacting passengers. Consequently many studies only contacted persons seated in close proximity to an index case or required passengers to self-report symptoms to be included. An underestimation of the level of transmission is therefore possible as passengers with mild or asymptomatic infections were not recorded.

Difficulties in excluding other sources of infection meant that the roles of transport systems could not be confirmed in transmission to secondary cases in many studies so our estimates may be somewhat conservative. Many studies could not distinguish whether transmission occurred during or prior to the flight. Although transmission of influenza during travel to airports and time spent in airport terminals has been suspected, the 1-4 day incubation period of influenza means that it is difficult to pinpoint the exact time and location of transmission [55].

Numerous sources of bias in the modelling studies were noted and many could not account for behaviour aboard the transport vehicle (e.g. moving around an aircraft cabin), which limits the ability to generalise model estimates to practical settings. The risk of bias tool used for modelling studies is not yet validated therefore these results must be interpreted with caution.

A paucity of evidence and high heterogeneity between studies limits the evidence base on the role of ground transport in influenza transmission and the roles of all studied modes of transport in coronavirus transmission. No analysis of the roles of transport hubs in coronavirus transmission or the introduction of coronaviruses to geographically distant areas could be undertaken.

No restrictions on the strain of influenza were applied meaning that varying levels of infectivity were possible and were not accounted for in the analysis. The majority of studies were on A(H1N1)pdm09 but all cases meeting the WHO, EDCD or CDC [19, 50, 56] definitions of ILI were considered for inclusion.

Implications for public health and policy

It is important to reduce the chance of symptomatic passengers boarding aircraft to avoid in-flight transmission. This review found evidence that pre-symptomatic passengers aboard aircraft do not pose a risk for in-flight transmission but can introduce influenza to new areas following disembarkation. It is unfeasible to detect pre-symptomatic passengers and prevent them travelling therefore increased awareness of the risk of introducing pathogens to new areas and increased information on modes of preventing onward transmission (e.g. good coughing and sneezing etiquette, self-isolation when symptomatic) could reduce the number of secondary cases at the distant loci who are epidemiologically linked to travellers. This should be considered for long-distance rail passengers in addition to air passengers.

The risk of transmission is theoretically highest in air passengers seated close to an index case [26, 27, 28] and increases with flight duration [5, 27]. As the models used do not account for the movement of passengers through the aircraft cabin there is still an unquantifiable potential risk of transmission to passengers seated further away. A CFD modelling study has shown how movement through the cabin can increase the distance a viral plume can travel [57] and when transmission has occurred there is not uniform statistically significant association between risk and seating proximity to a case. Based on these findings contact tracing may focus on, but should not be restricted to persons seated within close proximity to an index case. This is in line with recent guidance from ECDC which states that complete contact tracing of all passengers and crew is preferable but if not possible then passengers seated two seats in all directions and all crew members should be prioritised [9].

Although all confirmed cases of transmission have occurred on long haul flights, transmission has also been suspected on short haul flights but cannot be confirmed due to the inability to exclude other sources of exposures [21, 23]. Short haul flights are significantly shorter than the 1-4 day influenza incubation period [58] therefore a high number of other possible exposures can be expected. Based on this, control measures may focus on long haul flights but transmission occurring on short haul flights cannot be disregarded and might even be greater overall because of the greater number of shorter flights.

Further research

The possibility that contagious airport workers can infect large numbers of people with influenza has been identified [36]. This is an area which requires further research, if this model is valid then addressing the issues and actively screening for ILI in airport workers could potentially reduce the numbers of secondary cases travelling and spreading influenza via air transport.

Further primary research on the roles of ground transport is required. Although the small number of studies meant that conclusions could not be drawn, we did identify cases where influenza transmission has occurred on buses and is thought to have occurred on trains. Further research could determine the risk of transmission and lead to an understanding of whether control measures on ground transport systems/hubs are required to reduced influenza and coronavirus propagation.

CONCLUSION

Our systematic review concludes that transmission of influenza occurs aboard aircraft with up to four secondary cases confirmed per affected flight with no other sources of exposure. Attack rates of up to 20% have been suspected on flights but this cannot be confirmed due to difficulties in excluding other sources of exposure. Air transport plays an important role in accelerating the spread of influenza to geographical distinct areas. It is possible that airports pose a high risk of transmission and this aspect requires further investigation. Influenza outbreaks aboard ships affect significant proportions of passengers and crew but no evidence was found of sea transport accelerating influenza or coronavirus spread to new areas in the modern era.

Influenza transmission has been observed on ground transport but further primary research is required to quantify the risks. Trains have been shown to introduce influenza to new areas but additional studies are required to quantify the level of risk. In-flight SARS-CoV transmission has been observed as has transmission of MERS-CoV on arrival at uninfected destinations but further research is required to estimate the risk of coronavirus infection related to the use of air, ground and sea transport systems and hubs.

Author Contributions

Conceived and designed the study protocol: AB, CRB, JSN-V-T.

Execution of the search strategy and screening: AB, SSt-OA.

Risk of bias assessments and data extraction: AB, SSt-OA.

Data analysis or interpretation: AB, CRB, JSN-V-T.

Drafting of the manuscript: AB, CRB, JSN-V-T.

Contribution of intellectual content to the manuscript: AB, CRB, JSN-V-T.

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Potential Conflicts of Interest

AB and SS-A have no potential conflicts of interest to declare. The University of Nottingham Health Protection and Influenza Research Group (JSN-V-T) is currently in receipt of research funds from GlaxoSmithKline, unrestricted educational grants for influenza research from F. Hoffmann-La Roche, and an award as part of the Prevention and Management of High Threat Pathogen Incidents in Transport Hubs (PANDHUB) European Consortium. CRB is an external collaborator to a separate University of Nottingham Health Protection and Influenza Research Group study funded by GlaxoSmithKline. This funding and grants from F. Hoffmann-La Roche did not support any aspect of the present study. Prior to October 2010, JSNV-T received funding to attend influenza-related meetings and give lectures, and also consultancy fees from several manufacturers of antiviral drugs and influenza vaccines. JSNV-T was an employee of SmithKline Beecham, Roche Products and Aventis- Pasteur MSD prior to 2005 but now has no outstanding pecuniary interests by way of shareholdings, share options or accrued pension rights.

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Disclaimer

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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Figure legends

Figure 1: PRISMA diagram (screening and eligibility)

Supporting Information (online only)

Supporting Information may be found in the online version of this article:

Appendix S1 to Appendix S10”