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Title: Norovirus Outbreaks on Commercial Cruise Ships: A Systematic Review and New Targets for the Public Health Agenda

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Abstract

Noroviruses are recognized as the leading cause of human acute viral gastroenteritis worldwide. The rate of outbreaks on cruise ships has grown significantly in recent years. Given the potentially harmful consequences of outbreaks for passengers and crewmembers and the subsequently high costs for cruise companies, disease outbreaks on cruise ships represent a serious public health issue. The aim of our study was to systematically review published studies related to Norovirus outbreaks on commercial cruise ships. We searched the PubMed and Scopus scientific databases. We included eligible studies published from January 1990 to July 2013 that were written in English and described infectious episodes involving at least two passengers and/or crewmembers on a commercial cruise ship. As a result, 15 studies and seven reviews met the inclusion criteria, describing a total of 127 outbreaks. The majority of the cases were reported in Europe and the USA, affecting <1 to 74 % of the embarked passengers. In the majority of the studies, stool samples and/or serum specimens from ill passengers were collected and tested for laboratory confirmation. Twelve studies reported that an ad-hoc questionnaire was administered. Fifteen studies investigated the possible source of infection which was contaminated food in the majority of cases. Our findings suggest a strong need for the monitoring and implementation of preventive measures in semi-closed communities, such as cruise ships. It would be advisable to strengthen all relevant initiatives in order to improve the detection of, response to and control of Norovirus outbreaks on cruise ships.

Keywords:

Norovirus ; Cruises ; Outbreaks ; Infectious diseases

Main text

Background

Noroviruses (NoVs) are widely recognized as the leading cause of human acute viral gastroenteritis worldwide (Arias et al. 2010). Approximately, 20 million cases of acute gastroenteritis in the USA are related to NoV infections, as reported by the centers for disease control (CDC) (CDC2013). This high rate of incidence could be easily explained by considering the microbiological characteristics of the virus. First of all, the minimum infectious dose is less than approximately 100 viral particles, giving NoVs a high infection rate. NoVs may be transmitted through several routes, such as the consumption of contaminated food and/or drink, contact with contaminated surfaces, or a particular form of airborne transmission resulting from the formation of aerosols arising from vomit (Morillo and Timenetsky Mdo 2011). NoV infection confers only a short-term immunization, most likely due to the genetic variability of this type of virus (Mattei et al. 2008). Finally, this virus has a widespread distribution and causes outbreaks, especially in closed communities such as nursing homes, hospitals, dormitories, and cruise ships (Morillo and Timenetsky Mdo 2011). Cruise ships in particular have recently experienced a growth of NoV outbreaks, especially considering the increased number of passengers potentially at risk in recent years (Mouchtouri et al. 2010). With regard to this, the Cruise Line International Association (CLIA) reported that the cruise line industry has experienced record growth in the number of passengers per year since the early 2000s (CLIA2013).Moreover, on cruise ships, the ideal conditions for the emergence of new outbreaks exist: common food and drink may be a source of infection, while the semi-closed environment of the ships facilitates transmission from person to person. Finally, it should be acknowledged that one third of cruise passengers are elderly people, who may be more vulnerable to infections and complications arising from illnesses (Rooney et al. 2004a; Rooney et al. 2004b). Indeed, the health impact of NoV infection can be severe for susceptible passengers, and the economic impact of an outbreak could be evaluated in relation to a poor public image and high economic losses for cruise ship companies band public health authorities. Many initiatives have been undertaken by national and international legislators to prevent and contain outbreaks of NoV and other infectious agents on cruise ships. For instance, the U.S. CDC established the Vessel Sanitation Program (VSP) in 1975 in cooperation with the cruise ship industry to minimize the potential for disease outbreaks and to ensure a healthful environment for passengers and crewmembers (VSP 2013).

Alternatively, European legislation directly applied safety rules and standards applicable to land-based establishments to ships, although issues such as potable water management present different risks on ships and require special regulation (Mouchtouri et al. 2010). In 2007, the Health Protection Agency, the Association of Port Health Authorities and the Maritime and Coastguard Agency published UK guidelines for the management of NoV infection on cruise ships HPA (2013). Public health issues related to ships are regulated worldwide by the revised International Health Regulations of 2005 (Mouchtouri et al. 2010). Finally, the World Health Organization published the WHO Guide to Ship Sanitation to prevent and control public health threats, conduct disease surveillance, outbreak investigation, and routine inspection, and provide a framework for policy making and local decision making (WHO 2011). The improved recognition of NoV outbreaks on cruise ships and the various legislations in force in different countries require a revision of the knowledge about this public health topic. We therefore decided to systematically review the studies published in the last two decades related to NoV outbreaks occurring on

commercial cruise ships to summarize the data about the main sources of infection, the diagnostic techniques carried out to identify the virus, and the percentage of people affected.

Methods

We reviewed the scientific literature about NoV outbreaks on cruise ships using the Pubmed and Scopus scientific databases as well as the following research strings: cruise* and Norovirus and outbreak*, ‘‘Disease Outbreaks’’ (Mesh) and cruise*, (cruise* ship* or cruiseship*) and outbreak*, (cruise* ship* or cruiseship*), and Norovirus and outbreak*. An outbreak was defined as the occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season (WHO 2013). We included all of the papers written in the English language published from January 1990 to July 2013. We chose all of the studies that describing infectious episodes involving at least two passengers and/or crewmembers. Only those outbreaks that occurred on commercial cruise ships were selected. The study design was not considered a limitation for the selection of articles. All of the studies related to military ships, cargo ships, private sailing boats, and fishing vessels were excluded. Studies in which data about the location and the characteristics of the outbreak (the people involved and/or data collection tools and/or diagnostic techniques and/or source of infection) were not available were not included in our analysis.

The assessment of the eligibility of the studies was performed by three independent reviewers (GS, SP, and CV). In the first stage, the researchers analyzed the search results individually to select the reports for full text review. After reading the titles and abstracts, all of the irrelevant studies and duplicates were excluded. Using the inclusion and exclusion criteria mentioned above, three authors then independently assessed each of the selected articles for inclusion in the study. Any disagreement was resolved by consensus. Data extraction was performed independently by the same three researchers. Information about the study design (cohort study, case-control study, short report, and systematic review), the geographic location of the cruise, the year of the outbreak, the percentage of people affected, the source of infection, and the diagnostic methods carried out to identify the etiology of the outbreaks was retrieved.

Results

A total of 360 articles were returned during the initial search of the aforementioned databases. After reading the titles and abstracts, 325 studies were excluded on the basis of being irrelevant or duplicates. The remaining 35 studies were retrieved for full text review. Thirteen of these were subsequently excluded because they did not meet the inclusion criteria: five because they were reports of outbreaks on military ships, and eight because data about the location and the characteristics of the outbreak were not available. Twenty-two articles (Morillo et al. 2012; Wikswo et al. 2011; Vivancos et al. 2010; Xerry et al. 2009; Boxman et al. 2009; Xerry et al. 2008; Neri et

al. 2008; Chimonas et al. 2008; Verhoef et al. 2008a, b; Takkinen 2006; Koopmans et al. 2006; Ferson and Ressler 2005; Isakbaeva et al. 2005; Widdowson et al. 2004; Gallimore et al. 2003; CDC 2002; Minooee and Rickman 1999; McEvoy et al. 1996; Koo et al. 1996; Herwaldt et al. 1994; Khan et al. 1994) met the inclusion criteria and were thus included in our review.

Characteristics of the Studies

Of the 22 papers included, 15 were single studies and seven were reviews. The overwhelming majority (90.9 %) of the studies were published in Europe and the USA. More than 80 % of the papers' authors were affiliated with institutional organizations, such as the CDC or universities. The 15 single studies had the following study designs: – four case-control studies; – four retrospective cohort studies; – one paper describing three outbreaks on three different cruise ships with a case-control study, a retrospective cohort study and a case-control nested in a retrospective cohort study; – two descriptive studies reporting a series of outbreaks; and – four laboratory studies focusing on diagnostic methods for detecting the presence of NoV on cruise ships. All seven reviews used data that were collected from databases of institutional organizations (e.g., VSP by CDC). Six reviews were focused on epidemiological reports, while one targeted laboratory data (see Table 1).

Study Results

Overall, a total of 127 NoV outbreaks were reported. Since bsome outbreaks occurred on consecutive cruises of the same ship, the total number of vessels involved accounted for 70. The majority of them were sailing in North-Central American and European waters (37 and 30, respectively), with three exceptions: one outbreak occurred on a ship that was sailing from Europe to the USA (CDC 2002), one study described an outbreak that occurred in Brazil (Morillo et al. 2012), and one paper reported a NoV outbreak on an Australian ship (Ferson and Ressler 2005) (see Table 2). Twelve studies of NoV outbreaks on a total of 20 vessels, collected data using an ad-hoc questionnaire administered to a sample of passengers and crewmembers. Six studies (10 vessels) described the infection rate for passengers and crewmembers, separately, which ranged from 19 to 74 % and from 1.5 to 30 %, respectively. Three studies reported only the global infection rate (passengers and crewmembers together) which ranged from\1 to 41 % (Verhoef et al. 2008a; Widdowson et al. 2004; Wikswo et al. 2011). In the studies performed by Vivancos et al., Neri et al., and the CDC, data were obtained by consulting the ship's medical team and by analyzing the lists of passengers routinely collected by travel companies (see Table 2) (Vivancos et al. 2010; Neri et al. 2008; CDC 2002). Fifteen studies (of a total of 53 vessels) investigated the possible source of infection which was represented by food consumed on board only, or by a multiple sources of infection (food, water, and the environment) in the majority of cases (see Table 2). As reported in Table 2, the source of infection was occasionally ''not found.'' Stool samples and/or serum specimens from ill passengers were collected by medical personnel aboard cruise ships and tested for laboratory confirmation in all studies, with the only exception of the study by Morillo et al. in which only the food was tested (Morillo et al. 2012). Food testing was reported in five studies (Morillo et al. 2012; Verhoef et al. 2008a, b; Boxman et al. 2009; Koo et al. 1996) for a total of 11 outbreaks (data not shown). Environmental swabs were collected only in the outbreaks described by

Boxman et al. 2009; Koopmans et al. 2006; Takkinen 2006; Verhoef et al. 2008a, b (data not shown). Real time-polymerase chain reactions (RT-PCRs) were performed in 56 out of 70 vessels involved, and in 50 of them, the genotype of the NoV was detected. Moreover, an enzyme immunoassay technique was used in seven studies (Table 2).

Discussion

Our paper aimed to systematically review all of the published studies on NoV outbreaks that occurred on commercial cruise ships after January 1990. To our knowledge, this is the first systematic review that is specifically focused on published papers related to NoV outbreaks on commercial cruise ships. For instance, previous reviews focused on global outbreaks of foodborne or waterborne diseases (Rooney et al. 2004a, b), or reported the state of outbreaks that occurred on commercial cruise ships related to different microorganisms (Mouchtouri et al. 2010). As previously highlighted, a total of 22 studies met our inclusion criteria. Although some of the included papers described the same outbreak, we decided to consider these studies in our review because they provided different types of information.

The results showed how the overwhelming majority of the articles included in our review referred to cruise ships that sailed in Europe and the USA. A possible explanation for this could be represented by the inclusion criterion concerning the language limitation (English). Another reason could be the different degrees of attention paid by preventive services to this topic. The VSP of the American center for CDC and the ShipSan projects within the European Union are two relevant initiatives (VSP 2013; ShipSan Project 2013; ShipSan Trainet 2013). The common aim of these projects is to assist the cruise ship industry in preventing and controlling the introduction, transmission, and spread of gastrointestinal illnesses on cruise ships. In both cases, the final results of the initiatives were the production of an operative manual or specific guidelines providing hygiene standards, communicable disease surveillance rules, and preventive procedures (VSP 2011; ShipSan Trainet 2011). Focusing on the European continent, the results of our systematic review showed how seven out of eight European papers were published in recent years (from 2006 to 2010). Interestingly, this period coincided with the implementation of preventive programs within the European Union (ShipSan 2013). This could mean that a shared and organic preventive strategy could be useful to gain the attention of the scientific community. As reported by the present review, the most common data collection tool was a questionnaire administered to all of the people embarked on a ship to detect the infection rate among crewmembers and passengers and the possible source of infection. Questions were focused on the gastrointestinal symptoms that occurred during the cruise and on the food and beverages consumed on board. Data obtained by these questionnaires showed that the percentages of people potentially infected by NoV were often very high, reaching 74 % of the passengers in one case (McEvoy et al. 1996). These results agree with those of other studies investigating NoV outbreaks in different closed communities (Maritschnik et al. 2013; Arvelo et al. 2012; Thouillot et al. 2012; Chapman et al. 2011; Reaves et al. 2012), demonstrating the high infectivity of this virus. A difference in the infection rate between passengers and crewmembers was reported. Crewmembers experienced a lower infection rate in all of the studies considered. This could be explained by the separate sleeping and dining areas and separate areas for boarding and exiting the ships for crewmembers, leading to less direct contact

with the other people embarked (McEvoy et al. 1996). Laboratory tests to confirm the diagnosis of NoV were conducted in all of the studies included in the systematic review. A RT-PCR of the samples collected from the symptomatic passengers was the most frequently performed diagnostic method. This technique allows the detection of the virus in a solid or liquid matrix and the performance of molecular genotyping. It is therefore useful to characterize the virus responsible for the outbreak in detail in order to identify the most common strains and observe the emergence of new NoV variants. Because NoV outbreaks are usually difficult to detect, the use of PCR allowed the characterization and identification of many NoV outbreaks that would have been previously considered ‘‘unknown’’ (Stals et al. 2012).

In almost all of the outbreaks, an analysis of fecal samples was performed. Food testing, however, was carried out in few studies, while the acquisition of environmental swabs was described only in a group of outbreaks that occurred in Europe in 2006. This is understandable given that the environmental swab is considered a complementary tool to fecal and food testing (Boxman et al. 2009), and that food samples are usually difficult to obtain because of a delay in the execution of these procedures. This delay is one of the main reasons why the primary source of an outbreak often goes undetected. Indeed, the questionnaires were frequently administered in the last few days or even at the end of the cruise, and the same occurred for the collection of biological samples. This could hinder both an early and proper epidemiological mapping of the outbreak and the retrieval and consequent analysis of food samples (Morillo et al. 2012; Verhoef et al. 2011). Hence, the importance of an early investigative action and a rapid implementation of control measures once the first signs of the outbreak are discovered should be emphasized. Concerning this, it is also mandatory to achieve a high level of awareness among passengers to allow for the early identification of acute gastroenteritis symptoms and a consciousness of the need for isolation if these symptoms occur. Passengers tend to underestimate any gastrointestinal symptom or sign and do not decrease their activities as a result (Neri et al. 2008).

Our review has some limitations that should be acknowledged. For instance, the real burden of disease could suffer from underestimation or overestimation. A potential underestimation could be related to the restriction of the sample to studies published within the scientific literature. Indeed, we excluded official statistics that are not present within Pubmed or Scopus. Moreover, this could explain the lack of investigation procedures for some of the outbreaks reported in the included papers. Such procedures may have been performed but not described in the published studies. Moreover, we found very few studies published outside Europe or the USA. This could be due to a language limitation, our research excluded all of the studies not written in English. A first cause of overestimation could be related to data collection. It should be underlined that in the studies for which data were collected using questionnaires, the response rate never reached 100 %, and in one case, it was only 25 % (McEvoy et al. 1996). A low response rate may have led to a selection bias. As a matter of fact, those who showed gastrointestinal symptoms during a cruise may have been more likely to complete the questionnaire than those without symptoms, with a possible overestimation of the infection rates. This hypothesis is supported by the fact that in those studies in which the response rate is higher, the infection rate is lower. Another limit is that laboratory tests to detect NoV were usually only performed on a small sample of embarked people, not to all of the patients who showed gastrointestinal symptoms. Therefore, previously reported data on the percentage of infected people were collected only through the administration of questionnaires and

were not supported by a full laboratory confirmation. This could lead to an overestimation of the cases actually linked to NoVs.

Conclusions

The present review confirms the high infectivity of NoVs, especially, in close communities such as cruise ships, and highlights the need to strengthen preventive measures and more rigorous controls by public health professionals, cruise lines, and crewmembers. Furthermore, the large number of multiple outbreaks on the same ships demonstrated that the lack of measures to contain the outbreaks often led to the spread of the infections to the passengers embarked on the contiguous cruises (Herwaldt et al. 1994; McEvoy et al. 1996; Isakbaeva et al. 2005). In particular, given our results, we strongly recommend the establishment of common regulations for the prevention and containment of NoV outbreaks worldwide. The presence of an operating manual, such as the one proposed by the ShipSan Trainet, may therefore be useful (ShipSan Trainet 2011). Moreover, it is necessary to attract the attention of passengers and crewmembers by promoting awareness campaigns using ship tours, signage, newsletter articles, and in-room televisions (Neri et al. 2008) to explain the correct behavior to adopt in order to prevent the spread of infections. Further studies are also needed to improve the knowledge about this important and emerging topic.

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Table 1 - Charcateristics of the studies

Study	Year of the outbreak	Type of study	Subtype of study	Place of the outbreak
Morillo et al. (2012)	2010	Single study	Laboratory research	South America
Wikswo et al. (2011)	2009	Single study	Retrospective cohort study	North America
Vivancos et al. (2010)	2008	Single study	Retrospective cohort study	Europe
Xerry et al. (2008)	2007	Single study	Laboratory research	North America
Xerry et al. (2009)	2007	Single study	Laboratory research	Europe
Koopmans[a] et al. (2006)	2006	Review	–	Europe
Takkinen[a] (2006)	2006	Single study	Case series	Europe
Verhoef[a] et al. (2008b)	2006	Single study	Retrospective cohort study	Europe
Verhoef[a] et al. (2008a)	2006	Review	–	Europe
Boxman[a] et al. (2009)	2006	Single study	Laboratory research	Europe
Neri et al. (2008)	2006	Single study	Retrospective cohort study Case-control Study Case-cohort study	North America
Chimonas et al. (2008)	2004	Single study	Case-control study	North America
Ferson and Ressler (2005)	2003	Review	–	Australia
Isakbaeva[b] et al. (2005)	2002	Single study	Case-control study	North America
Widdowson[b] et al. (2004)	2002	Review	–	North America
CDC (2002)	2002	Single study	Case series	North America/Europe[c]
Gallimore et al. (2003)	1998–2002	Review	–	Europe
Minooee and Rickman (1999)	1977–1998	Review	–	North America/Europe
McEvoy et al. (1996)	1995	Single study	Case-control study	Europe
Koo et al. (1996)	1986–1993	Review	–	North America
Khan et al. (1994)	1992	Single study	Retrospective cohort study	North America
Herwaldt et al. (1994)	1990	Single study	Case-control study	North America

[a] Same outbreaks

[b] Same outbreaks

[c] Four ships were sailing in North America and one from Europe to North America

[d] Three outbreaks already described in other studies considered (McEvoy et al. 1996; Khan et al. 1994; Herwaldt et al. 1994.)

Table 2 - Studies' results

Study	Number of ships involved	Number of outbreaks	People involved (%)		Questionnaire	PCR[a]	EIA[b]	Strain by PRC[a]	Source of infection
			Passengers	Crew members					
Morillo et al. (2012)	1	1	–	–	–	yes	yes	yes	–
Wikswo et al. (2011)	1	1	15.4		yes	yes	yes	yes	PP[c]
Vivancos et al. (2010)	1	1	11.4[d]		–	yes	yes	yes	PP[c]
Xerry et al. (2008)	1	2	–	–	–	yes	–	yes	–
Xerry et al. (2009)	1	5	–	–	–	yes	–	yes	–
Koopmans[e] et al. (2006)	9	9	–	–	yes	yes	–	yes	–
Takkinen[e] (2006)	7	9	–	–	–	yes	–	yes	–
Verhoef[e] et al. (2008)	1	3	47	7	yes	yes	–	yes	WB[f], FB[g]
Verhoef[e] et al. (2008)	13	43	<1–41		yes[h]	yes	–	yes	WB[f], FB[g], PP[c]
Boxman[e] et al. (2009)	4	4	–	–	–	yes	–	yes	–
Neri et al. (2008)	3	3	A: 5.3[d] B: 7.8[d] C: 5.6[d]		yes	yes	–	–	A: FB[g] B: Not found C: Not found
Chimonas et al. (2008)	1	1	24.1	–	yes	yes	yes	yes	WB[f], PP[c], Env[i]
Ferson and Ressler (2005)	1	1	–	–	–	yes	yes	yes	PP[c]
Isakbaeva[j] et al. (2005)	1	6	–	–	yes	yes	–	yes	FB[g], PP[c], Env[i]
Widdowson[j] et al. (2004)	11	11	18[k]		yes[l]	yes	–	yes	3 PP[c] 4 PP[c], Env[i] 1 FB[g], PP[c] 1 WB[f] 2 PP[c], FB[g], Env[i]
CDC (2002)	5	5	A: 13[d] B: 41 C: 19 D: 5[d] E: 21	A: 2[d] B: – C:1.5 D: 3[d] E: –	yes	yes	–	yes	A: – B: Not found C: FB[g] D: – E: –
Gallimore et al. (2003)	14	26	–	–	–	yes	–	yes	–
Minooee[m] and Rickman (1999)	8	18	–	–	–	–	–	–	FB[g], WB[f], PP[c]
McEvoy et al. (1996)	1	4	74	–	yes	yes	–	–	Not found
Koo et al. (1996)	9	9	–	–	–	–	–	–	FB[g]
Khan et al. (1994)	1	1	30	30	yes	yes	yes	–	WB[f]
Herwaldt et al. (1994)	1	3	57	24	yes	yes	yes	–	FB[g]

a PCR: Polymerase Chain Reaction
b EIA: Enzyme Immunoassay
c PP: person to person transmission
d Data obtained consulting the ship's medical team and by the lists of passengers routinely collected by the travel company
e Same outbreaks
f B: waterborne transmission
g FB: foodborne transmission
h Three out of 13 vessels
i Env: environmental transmission
j Same outbreaks
k range 13–30
l Four out of 11 vessels
m Three outbreaks already described in other studies considered (McEvoy et al. 1996; Khan et al. 1994; Herwaldt et al. 1994.)