In healthcare settings, what is the current epidemiology and latest evidence on transmission pathways and infection prevention and control measures for Norovirus Gastroenteritis?

Literature Review

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Background

The National Health and Medical Research Council (NHMRC) commissioned this independent literature review to provide assurance that the revision of the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* is grounded in the most up-to-date and relevant scientific evidence.

Norovirus is the most frequently occurring cause of community-acquired acute gastroenteritis in people of all ages. It is also one of the most frequent causes of outbreaks in healthcare settings, affecting both long-term care facilities and acute care hospitals (Kambhampati, Koopmans & Lopman 2015; Lindsay et al. 2015) These outbreaks lead to patient morbidity resulting in extended length of stay and occasionally mortality (Sadique et al. 2016). Norovirus outbreaks also cause additional costs associated with treatment provision and bed-days lost due to temporary closure of wards, as well as productivity losses associated with infected hospital staff (Harris 2016; NHMRC 2010; Sadique et al. 2016; Zheng et al. 2015). It is evident that prevalence of norovirus infection in the community is high and it is difficult to prevent the infection because persons may shed the virus without being ill, and transmission occurs not only through direct and indirect person-to-person contact, but also through food, water, surfaces and aerosols (NHMRC 2010; Petrignani et al. 2015; Rahamat-Langendoen et al. 2013). Therefore, it is important to explore the current epidemiology and latest evidence on transmission pathways and infection prevention and control measures for Norovirus Gastroenteritis.

The purpose of this literature review was to identify the current epidemiology of norovirus infection and transmission of disease within healthcare setting including acute care, aged care, paediatric, neonatal and rehabilitation settings. In addition, this literature review examined the available evidence on transmission based precautions methods and infection control measures. The literature review will contribute to a discussion paper that will identify key areas that need updating, or

further consideration within the Australian Guidelines for the Prevention and Control of Infection in Healthcare (2010).

Objectives

The purpose of this literature review was to examine the current epidemiology and latest evidence on transmission pathways and infection prevention and control measures for Norovirus Gastroenteritis.

Specifically, the three review questions of this literature review were:

- Q 1: What is the current epidemiology (clinical features, occurrence diagnostics/Screening strategies) for Norovirus Gastroenteritis in acute care, aged care, paediatric, neonatal and rehabilitation settings?
- Q 2: What is the latest evidence on transmission pathways for Norovirus Gastroenteritis in acute care, aged care, paediatric, neonatal and rehabilitation settings?
- Q 3: What are the infection prevention and control strategies (eg disinfection bleach vs other, frequency of cleaning, hand hygiene alcohol vs soap/water,) for Norovirus Gastroenteritis in acute care, aged care, paediatric, neonatal and rehabilitation settings?

Methods

This literature review was conducted using a documented search strategy, inclusion and exclusion criteria, critical appraisal methodology and evidence synthesis and practice recommendations. The review method utilised Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green 2011) in particular; the Cochrane Public Health Group: Guide for developing a Cochrane protocol (2011); "How to review the evidence: systematic identification and review of the scientific literature"(NHMRC 1999). "NHMRC additional levels of evidence and grades for recommendations for developers of guidelines (NHMRC 2000) and The Joanna Briggs Institute Reviewers' Manual 2014 -The Systematic Review of Prevalence and Incidence Data (JBI 2014).

Please refer the Technical Report for detailed review process.

Inclusion and exclusion criteria for considering studies for this review

This review considered all relevant studies regardless of publication status (published, unpublished, in press, and ongoing) within the last 10 years, from 2006 to 2016. There was no search time limit for randomized controlled trials (RCTs). The search was limited to human and English language publications.

Review question	Condition	Context	Population	Outcomes	Study Designs
Q 1	Norovirus Gastroenteritis	epidemiology (clinical features, occurrence diagnostics/Screening strategies)	all type of patients/participants including children and adults in healthcare settings	incidence, prevalence, frequency of outbreaks	all types of observational studies -prospective and retrospective cohort studies, case-control studies, cross-sectional studies, and case series
Q 2	Norovirus Gastroenteritis	transmission pathways	all type of patients/participants including children and adults in healthcare settings	surfaces, droplet, and oral faecal route	all types of observational studies -prospective and retrospective cohort studies, case-control studies, cross-sectional studies, and case series
Review question	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study Designs**
Q 3	all type of patients/participants including children and adults in healthcare settings	Disinfection /Bleach hand washing/ soap/water Personal Protective Equipment etc	Other alcohol based	Severity of infection, number of people infected, duration of outbreak	RCTs, cluster RCTs, non-randomised controlled trials (Non-RCTs), controlled before and after studies and interrupted time series studies (ITS), cohort studies, case-control studies, cross-sectional studies

Results

Review questions 1 and 2

The literature search identified 1172 abstracts and a further 11 papers were identified through other sources including reference lists and grey literature searching. After removing 493 duplicates, 690 abstracts were screened for inclusion of the review and 643 abstracts were found not relevant to the study purpose. Application of the inclusion/exclusion criteria resulted in the further exclusion of 14 full text papers leaving 33 studies for the review question 1 and 2. Figure 1 illustrates the study selection process.

PRISMA Flow Diagram

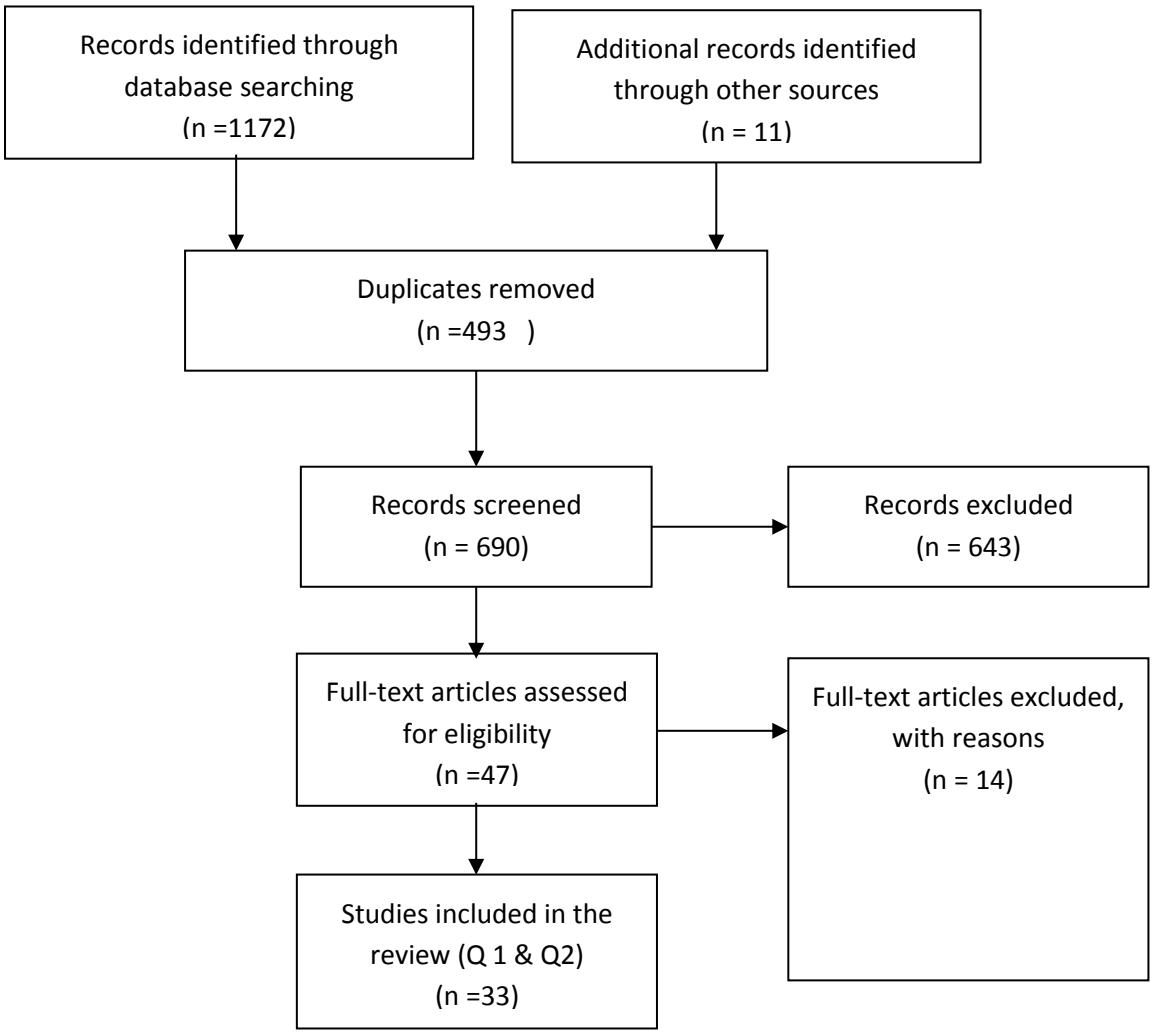

Figure 1. The study selection process

Characteristics of included studies

In this literature review, review questions 1 and 2 considered all types of observational studies including prospective and retrospective cohort studies, case-control studies, cross-sectional studies, and case series that address one or more of the areas of interest; current epidemiology and transmission pathways. The review questions 1 and 2 included 33 observational studies which were Level III and IV with moderate quality. This review included 14 cohort studies, 1 Observational comparative study, 2 case control studies, 5 case series 11 cross sectional studies. Observational studies are considered as appropriate study designs to address issues regarding prevalence and incidence (JBI 2014). A detailed description of included studies and the methodological quality are presented in the Table 1.

Table 1 Included studies and the methodological quality

Reference	Study design	Level of Evidence[1]	Methodological quality[2] Yes/Overall
(Beersma et al. 2009)	Retrospective analysis	Level IV	7/9
(Cheng, FWT et al. 2006)	Case series	Level IV	4/9
(Cheng, VCC et al. 2011)	Observational comparative study	Level III-2	8/9
(Costantini et al. 2016)	Prospective cohort study	Level III-2	8/9
(Cummins & Ready 2016)	Prospective cohort study	Level III-2	4/9
(Danial et al. 2011)	Prospective cohort study	Level III-2	7/9
(Franck et al. 2014)	Retrospective cohort study	Level III-2	8/9
(Franck et al. 2015)	Retrospective cohort study	Level III-2	9/9
(Godoy et al. 2015)	Descriptive Epidemiological study	Level IV	8/9
(Harris et al. 2014)	Retrospective Record Analysis	Level IV	6/9
(Harris et al. 2013)	Prospective cohort study	Level III-2	8/9
(Heijne et al. 2012)	Cross sectional study	Level IV	6/9
(Hoffmann et al. 2013)	Cross sectional study	Level IV	8/9
(Johnston et al. 2007)	Case series	Level IV	8/9
(Kanerva et al. 2009)	Cross sectional study	Level IV	8/9
(Lopman et al. 2006)	Prospective cohort study	Level III-2	6/9
(Mattner, Guyot & Henke-Gendo 2015)	Retrospective analysis	Level IV	8/9
(Munir et al. 2014)	Prospective cohort study	Level III-2	8/9
(Nenonen et al. 2014)	Case control study	Level III-2	7/9
(Nguyen & Middaugh 2012)	Descriptive epidemiological study	Level IV	8/9
(Ohwaki et al. 2009)	Retrospective cohort study	Level III-2	9/9
(Partridge et al. 2012)	Retrospective cohort study	Level III-2	8/9
(Rao et al. 2009)	Cross sectionals study	Level IV	8/9
(Rosenthal et al. 2011)	Retrospective chart review	Level IV	8/9
(Schmid et al. 2011)	Retrospective cohort	Level III-2	8/9
(Sheahan et al. 2015)	Case series	Level III-3	5/9
(Simon et al. 2006)	Case series	Level III-3	8/9
(Sukhrie et al. 2011)	Case control study	Level III-2	6/9
(Sukhrie et al. 2012)	Retrospective cohort study	Level III-2	9/9
(Tsang et al. 2008)	Retrospective cohort study	Level III-2	9/9
(Tseng et al. 2011)	Retrospective cohort study	Level III-2	8/9
(Tu et al. 2008)	Cross sectionals study	Level IV	6/9
(Zheng et al. 2015)	Case series	Level III-3	6/9

[1] NHMRC Level of Evidence (NHMRC 2000) [2] The Joanna Briggs Institute Reviewers' Manual 2014 -The Systematic Review of Prevalence and Incidence Data (JBI 2014)

Healthcare settings

This review considered all type of patients/participants including children and adults in healthcare settings. The health care settings of interest for this review include acute care, aged care, paediatric, neonatal and rehabilitation. The majority of studies were conducted in USA (7) followed by UK (6), Netherlands (4), Hong Kong (3), Germany (3), Denmark (2) and individual studies from 8 countries including Australia. This review involved 28 hospitals and 5 aged care facilities. Included studies ranged from 1992 to 2015. Table 2 provides details of healthcare settings, participants and study duration.

Table 2. Details of healthcare settings, participants and study duration

Reference	Healthcare setting /Country	Participants	Study duration
(Beersma et al. 2009)	A tertiary care hospital Netherlands	Hospitalised children and adults	03/2002 to 07/2006
(Cheng, FWT et al. 2006)	Public Hospital Hong Kong	Children, visitors medical students	19 and 28 August (Year Not available)
(Cheng, VCC et al. 2011)	Public Hospital Hong Kong	Hospitalised children	11/ 2009 to 2/2010
(Costantini et al. 2016)	Long-term care facilities (LTCFs) USA	Adults and older adults	11/ 2009 to 01/2013
(Cummins & Ready 2016)	Hospitals (coded A–E). London, UK	Hospitalised patients and staff	02 -04 / 2015
(Danial et al. 2011)	Hospitals in NHS Lothian, UK	Hospitalised patients	09/ 2007 to 06/ 2009
(Franck et al. 2014)	Hospitals Denmark	Hospitalised patients	2006–2010
(Franck et al. 2015)	Hospitals Denmark	Hospitalised patients	2002-2010
(Godoy et al. 2015)	Hospitals and nursing homes Spain	Hospitalised patients	01/ 2010 -12/2011
(Harris et al. 2014)	NHS Hospitals UK	Hospitalised patients	1992–2011
(Harris et al. 2013)	NHS Hospitals UK	Hospitalised patients	11/ 2009 -11/2011
(Heijne et al. 2012)	Psychiatric wards Netherlands	Patients with mental health conditions	2008
(Hoffmann et al. 2013)	University hospital, Munich, Germany	Patients and staff	06/2011
(Johnston et al. 2007)	Hospital (JHH) Baltimore, USA	Patients and staff	01-05/2004
(Kanerva et al. 2009)	Tertiary care hospital Finland	Patients and staff	12/2006 -05/ 2007
(Lopman et al. 2006)	Hospitals UK	Hospitalised patients	04/ 2002- 03/2003
(Mattner, Guyot & Henke-Gendo 2015)	University and teaching hospitals Germany	Hospitalised patients	2002-2012
(Munir et al. 2014)	Paediatric hospitals in Atlanta USA	Hospitalised children	2009-2010
(Nenonen et al. 2014)	University Hospital Sweden	Hospitalised patients	01-05/ 2012
(Nguyen & Middaugh 2012)	Long-term care facilities USA	Older residents	02-03/ 2010
(Ohwaki et al. 2009)	Hospital and attached LTCF Japan	Adults and older residents	02-03/ 2007
(Partridge et al. 2012)	A teaching hospital UK	Hospitalised Adults and older adults	2009-2010
(Rao et al. 2009)	Tertiary care facility & LTCF	Hospitalised Adults and	2007

	USA	older adults	
Reference	**Healthcare setting /Country**	**Participants**	**Study duration**
(Rosenthal et al. 2011)	Long-term care facilities (LTCFs), USA	Older residents	2003-2006
(Schmid et al. 2011)	600-bed Hospital, Austria	Hospitalised Adults and older adults	03/ 2009
(Sheahan et al. 2015)	Inpatient paediatric unit of tertiary care hospital USA	Hospitalised children	01-02/2014
(Simon et al. 2006)	Paediatric oncology unit, Germany	Hospitalised children with cancer	01-02/2004
(Sukhrie et al. 2011)	Tertiary care Hospital Netherlands	Hospitalised patients	2002-2007
(Sukhrie et al. 2012)	Tertiary care hospital and nursing homes Netherlands	Hospitalised Adults and older adults	01/ 2009 -03/ 2010
(Tsang et al. 2008)	Public hospitals Hong Kong	Hospitalised older adults	05-07/2006
(Tseng et al. 2011)	Psychiatric Unit Taiwan.		01/ 2005 -04/2007
(Tu et al. 2008)	Aged-care facility Australia	Older residents	06/ 2003
(Zheng et al. 2015)	Aged care facility China	Older residents	12/ 2012.

Q 1: Epidemiology for Norovirus Gastroenteritis in healthcare settings

Norovirus detection methods

Noroviruses (NoV) belong to the family *Caliciviridae* and NoV are a single-stranded RNA, non-enveloped viruses that cause acute gastroenteritis in humans (Costantini et al. 2016; Siqueira et al. 2016). Noroviruses are divided into at least 6 genogroups (GI-GVI) and further subdivided into more than 38 genotypes based on phylogenetic analysis of the major capsid protein (Costantini et al. 2016; Franck et al. 2015). Currently, human noroviruses belong to one of three norovirus genogroups (GI, GII, or GIV), which are further divided into more than 25 genetic clusters (de Graaf, van Beek & Koopmans 2016).

Human noroviruses cannot be grown in cell culture (Vinje 2015), therefore, diagnostic methods focus on detecting viral RNA or antigen. Since the cloning of Norwalk virus in 1990, reverse transcription-polymerase chain reaction (RT-PCR) assays have been developed for detection of NoVs in clinical and environmental specimens, such as water and food, however RT-PCR was rapidly replaced by second-generation assays that proved to be more broadly reactive and able to detect the majority of the circulating norovirus strains (Pang & Lee 2015). Except one study, all other 32 observational studies used real-time RT-PCR to detect the NoV and some studies used ELISA in addition to real-time RT-PCR._Until norovirus diagnostic tests become widely available, the Kaplan criteria (Kaplan et al. 1982) was widely used in healthcare setting as a diagnostic tool to identify noroviruses outbreaks, and subsequent studies also showed that this set of criteria is highly specific (99%) with moderate sensitivity (68%) (Turcios et al. 2006). In this review, two studies used Kaplan

criteria for the identification of norovirus-associated outbreaks (Nguyen & Middaugh 2012; Tsang et al. 2008), however only one study reported details of the NoV detection using the Kaplan criteria and the study reported that many cases did not comply with these criteria (Tsang et al. 2008). Table 3 provides details of Norovirus detection methods, prevalence of NoV outbreaks and other screening method utilised for NoV detection.

Table 3. Details of Norovirus detection methods, prevalence of NoV outbreaks and other screening method

Reference	Norovirus detection methods	Outbreaks/NoV detection/ Participants	Screening methods
(Beersma et al. 2009)	Real-time RT- PCR	221 (9.0%) of 2458 hospital patients with diarrhoea tested positive for NoV	Not reported
(Cheng, FWT et al. 2006)	Real-time RT-PCR	9 children , 1 visitor, and 1 medical student affected	Not reported
(Cheng, VCC et al. 2011)	Real-time RT-PCR	242 (25%) were positive for norovirus; 114 (47%) of those 242 patients had norovirus detected by added test.	Not reported
(Costantini et al. 2016)	Real-time RT-qPCR	10 Outbreaks /39 (62 patients)	Not reported
(Cummins & Ready 2016)	Real-time RT-PCR	57 Patients/7 Staff from 4 Hospitals	Not reported
(Danial et al. 2011)	Real-time RT-PCR	192 unit outbreaks /Norovirus was confirmed as the aetiological agent by PCR in 142 (82%) outbreaks	Not reported
(Franck et al. 2014)	Real-time RT-PCR	46 suspected foodborne outbreaks/ an association between infection with GII.4 and increasing age	Not reported
(Franck et al. 2015)	Real-time RT-PCR	3656 NoV-infected patients	Not reported
(Godoy et al. 2015)	Real-time RT-PCR	358 patients and the results were positive for norovirus in 45%.	Not reported
(Harris et al. 2014)	Polymerase chain reaction (PCR)	Norovirus was laboratory confirmed in 69% (2737) of the reported outbreaks	Not reported
(Harris et al. 2013)	Polymerase chain reaction (PCR)	65 outbreaks	Not reported
(Heijne et al. 2012)	No data for diagnostic	46 patients	Not reported
(Hoffmann et al. 2013)	Real-time RT-PCR	116 patients; 28 staff	Not reported
(Johnston et al. 2007)	Real-time RT-PCR	265 staff; 90 inpatients	Not reported
(Kanerva et al. 2009)	Real-time RT-PCR	502stools specimens were tested for norovirus RNA, 181 (36%) - positive	Not reported
(Lopman et al. 2006)	RT-PCR and/or ELISA	76 outbreaks/ one or more specimen was positive for norovirus by RT-PCR [26] and/or ELISA [27] in 76 (63%) outbreaks	Not reported
(Mattner, Guyot & Henke-Gendo 2015)	RT-PCR and/or ELISA	Majority of outbreaks occurring on medical wards [medicine 42 (59%), surgery 12 (17%), neurology 4 (6%), urology 2 (3%), obstetrics 1 (1%), psychiatry 3 (4%), combined medicine/surgery 3 (4%), paediatrics	Not reported

		1 (1%) and dermatology 1 (1%)].	
Reference	**Norovirus detection methods**	**Outbreaks/NoV detection/ Participants**	**Screening methods**
(Munir et al. 2014)	Real-Time RT-PCR	NoV was identified in 16.3% (15/92) of all stool specimens; 23.4% (11/47 immunocompromised children	Not reported
(Nenonen et al. 2014)	RT-PCR (rRT-PCR)	NoV GII was detected in 48 of 101 (47%) environmental swabs and 63 of 108 patients (58%);	Not reported
(Nguyen & Middaugh 2012)	RT-PCR (rRT-PCR)	Older residents /32 stool specimens were positive for norovirus	Patients who did not meet the Kaplan criteria were also tested using RT-PCR- No further details provided
(Ohwaki et al. 2009)	Real-Time RT-PCR	older residents/ 23 out of 32 stool samples were positive for NoV	Not reported
(Partridge et al. 2012)	Real-Time RT-PCR	623 hospitalised Adults and older adults positive for NoV	Not reported
(Rao et al. 2009)	NA	Survey of hospitalised Adults and older adults	Not reported
(Rosenthal et al. 2011)	Real-Time RT-PCR	Older residents-163/234 (70%) Outbreaks	Not reported
(Schmid et al. 2011)	Real-Time RT-PCR	17/204 positive for NoV	Not reported
(Sheahan et al. 2015)	Real-Time RT-PCR	14 Hospitalised children	Automated hourly NV diagnostic testing report Screening (using xTAG GPP) on stool samples
(Simon et al. 2006)	RT-PCR and/or ELISA	21/ 246Hospitalised children with cancer positive for NoV	Not reported
(Sukhrie et al. 2011)	Real-Time RT-PCR	264 patients (of 2,458 tested) were diagnosed with NoV infection during the 5-year period	Not reported
(Sukhrie et al. 2012)	polymerase chain reaction (PCR)	Five outbreaks were investigated, involving 28 patients with recognized symptomatic NoV infection	Not reported
(Tsang et al. 2008)	Real-Time RT-PCR	151 (72.6%) samples were NoV positive. The median age of our patients was 74.5 years	Kaplan's criteria used for the identification of norovirus-associated out-breaks. Many cases did not comply with these criteria. Only 46.3% of patients had vomiting and the median duration of diarrhoea in the cohort was 3 days with a range of 1-24 days instead of 12-60 hrs. The duration of symptoms may indeed last longer than previously recognised
(Tseng et al. 2011)	ELISA method and RT–PCR	4 norovirus outbreaks occurred within this psychiatric unit (172)	Not reported
(Tu et al. 2008)	Real-Time RT-PCR	14 Older residents positive for NoV	Not reported
(Zheng et al. 2015)	Real-Time RT-PCR	RT-PCR revealed that 39 samples were norovirus-positive	Not reported

Prevalence of Norovirus Geno-groups

In this review, 21 observational studies reported the prevalence of NoV genogroups and 17 studies (81%) identified that NoV genotype GII.4 have caused the majority of clinical outbreaks in healthcare settings during the past decade. Nine observational studies involving 4 long-term aged care facilities (Costantini et al. 2016; Nguyen & Middaugh 2012; Rosenthal et al. 2011; Zheng et al. 2015), 2 aged care facilities attached to the major hospitals (Godoy et al. 2015; Ohwaki et al. 2009) and 3 public hospitals (Franck et al. 2014; Franck et al. 2015; Tsang et al. 2008), revealed NoV GII.4 predominated in older adults. Franck et al. (2014) conducted a Cohort study involving 3,846 patients who were positive for NoV by routine diagnostic procedures for gastroenteritis in Denmark during 2006–2010, the study detected an association between an age ≥60 years and infection with NoV GII.4 in patients from community and health care settings. Table 4 provides details of NoV Genogroups prevalence in healthcare settings.

Table 4. Details of Norovirus Genogroups prevalence in healthcare settings

Reference	Healthcare setting/Participants	Outbreaks/NoV detection/ Participants	Norovirus genogroups
(Costantini et al. 2016)	Long-term care facilities (LTCFs) Adults and older adults	10 Outbreaks /39 (62 patients)	GII.4 Sydney outbreaks was significantly higher than in outbreaks caused by other genotypes
(Nguyen & Middaugh 2012)	Long-term care facilities Older adults	Older residents /32 stool specimens were positive for norovirus	Sequenced specimens were closely related to GII.4 New Orleans
(Rosenthal et al. 2011)	Long-term care facilities (LTCFs), Older Adults	Older residents-163/234 (70%) Outbreaks	Overall, strains belonging to eight NoV genotypes (GI.1, GI.4, GI.6, GII.3, GII.4, GII.5, GII.6, GII.10) were detected in LTCFs during the study period. GII.4 strains accounted for 108 (84%)
(Zheng et al. 2015)	Long-term care facilities Older Adults	RT-PCR revealed that 39 samples were norovirus-positive	Epidemiological Investigation of a Norovirus GII.4 Sydney Outbreak
(Godoy et al. 2015)	Hospitals and attached nursing homes Hospitalised adults and older adults patients	358 patients and the results were positive for norovirus in 45%.	GII.4 was detected in 66·7% (10/15) of outbreaks.
(Ohwaki et al. 2009)	Hospital and attached LTCF Adults and older residents	older residents/ 23 out of 32 stool samples were positive for NoV	NoV GII/4 detected in23/32 samples
(Franck et al. 2014)	Hospitals Hospitalised patients	46 suspected foodborne outbreaks/ 3,846 NoV Positive	/strong association between infection with NoV GII.4 and patient age ≥60 years in community and health care settings
(Franck et al. 2015)	Hospitals Hospitalised adults and older patients	3656 NoV-infected patients	Nosocomial infection was mainly associated with older age but also with the specific genotype GII.4.
(Tsang et al. 2008)	Public hospitals Hospitalised older adults	151 (72.6%) samples were NoV positive. The median age of our patients was 74.5	New strains of genotype II.4 emerged

		years	
Section 2			
(Beersma et al. 2009)	A tertiary care hospital Hospitalised children and adults	221 (9.0%) of 2458 hospital patients with diarrhoea tested positive for NoV	GIIb strains occurred mainly in children below the age of two-and-a-half years [odds ratio (OR): 14.7; P<0.0001] GII.4 strains affected all age groups
(Cheng, VCC et al. 2011)	Public Hospital Hospitalised children	242 (25%) were positive for norovirus; 114 (47%) of those 242 patients had norovirus detected by added test.	Forty-three (93%) of 46 norovirus isolates sequenced belonged to the G II.4 variant
(Cummins & Ready 2016)	Hospitals (coded A–E Hospitalised patients and staff	57 Patients/7 Staff from 4 Hospitals	GII was the dominant genogroup detected and comprised 94.6% of all the norovirus-positive samples
(Hoffmann et al. 2013)	University hospital, Munich Patients and staff	116 patients 28 staff	Novel strain classified as GII.g/GII.1 - causative agent for an extended outbreak.
(Johnston et al. 2007)	Hospital Patients and staff	265 staff 90 inpatients	Detected noroviruses had 98%–99% sequence identity with representatives of a new genogroup II.4 variant
(Kanerva et al. 2009)	Tertiary care hospital Patients and staff	502stools specimens were tested for norovirus RNA, 181 (36%) - positive	Three main GII.4-2006b subvariants entered the hospital with gastroenteritis patients
(Lopman et al. 2006)	Hospitals Hospitalised patients	76 outbreaks/ one or more specimen was positive for norovirus by RT-PCR [26] and/or ELISA [27] in 76 (63%) outbreaks	95% closely clustered with genogroup II4
(Munir et al. 2014)	Paediatric hospitals Hospitalised children	NoV was identified in 16.3% (15/92) of all stool specimens; 23.4% (11/47 immunocompromised children	All NoV positive cases were genogroup II (GII), and GII.4 was the predominant strain followed by GII.3, GII.12, and GII.13
(Nenonen et al. 2014)	University Hospital Hospitalised patients	NoV GII was detected in 48 of 101 (47%) environmental swabs and 63 of 108 patients (58%);	NoV genotype II.4 was sequenced from 18 environmental samples, dust (n=8), virus traps (n=4), surfaces (n=6), and 56 patients. In contrast, NoV GII was detected in 2 (GII.4) of 28 (7%) environmental samples and in 2 (GII.6 and GII.4) of 17 patients in the outbreak-free ward. Sequence analyses revealed a high degree of similarity (>99.5%, 1,040 nt) between NoV GII.4environmental and patient strains from a given ward at a given time.
(Sukhrie et al. 2011)	Tertiary care Hospital Hospitalised patients	264 patients (of 2,458 tested) were diagnosed with NoV infection during the 5-year period	51% (n= 82) belonged to GII.4, 34% (n= 54) belonged to GII.3, and 15% (n=24) belonged to other genotypes (GI.6B, GII.17, GII.7, and GII.2). In children's wards, GII.3 strains were associated with nosocomial spread
(Sukhrie et al. 2012)	Tertiary care hospital and nursing homes	Five outbreaks were investigated, involving 28	NoV genotypes (ie, GII.4, GII.2, and GII.7).

	Hospitalised Adults and older adults	patients with recognized symptomatic NoV infection	
(Tu et al. 2008)	Aged-care facility Older residents	14 Older residents positive for NoV	Norovirus genogroup II excretion during an outbreak of gastroenteritis was investigated in an aged-care facility.

Clinical features of norovirus gastroenteritis in outbreaks

Norovirus infections generally have a shorter incubation period and are characterized by acute onset of nausea, vomiting, abdominal pain and diarrhoea (Cheng, VCC et al. 2011; Cummins & Ready 2016). This review identified 10 observational studies that provided clinical features of patients with norovirus gastroenteritis in outbreaks. The review found that the prevalence of diarrhoea (range: 61%-97%) and vomiting (range: 46%-98%) was higher in adults and older adults, whereas the prevalence of vomiting (82%) was higher in children. The mean duration of symptoms is 2-3 days. Table 5 provides details of clinical features, symptom duration and populations of included 11 observational studies.

Table 5. Details of clinical features, symptom duration and populations

Reference	Clinical features	Duration	Population
(Cheng, FWT et al. 2006)	Vomiting (82%) Diarrhoea (63%) Fever (18%)	The median duration of Gastroenteritis was three days (range: 2-6 days).	Mostly children
(Costantini et al. 2016)	Diarrhoea (84%), fatigue (81%), vomiting (76%), nausea (74%). Presence of both vomiting and diarrhoea (62%)	Illness duration was longer in cases aged ≥70 years (n = 29; median, 4; interquartile range [IQR], 3–4) than aged <70 years(P = .041), with 19 (60%) lasting >3 days and 4 (13%) lasting >5 days	Mostly older adults
(Godoy et al. 2015)	Diarrhoea (61·5%) Vomiting (55·0%) Abdominal pain (34·9%), nausea (33·8%) and fever (20·2%)	The mean duration of symptoms was 2·24 (S.D.=1·5) days and was greater in hospital patients (2·56, S.D.=1·7) than in nursing home residents (2·05, S.D.=1·4) (P<0·001).	Mostly older adults
(Johnston et al. 2007)	Nearly 50% of HCWs reported fever (42.2%), chills (59.2%), or myalgia (55.7%). Thirteen (4.9%) of the 265 HCWs required emergency department visits (n=9) or hospitalization (n=4) for intravenous hydration	Symptoms lasted for a mean duration (±SD) of 3.2±1.4 days and 3.7±3.2 days for HCWs and patients, respectively	On average, HCWs were younger than patients, with mean ages (±SD) of 36.2±10.4 years and 45.5±23.4 years, respectively
(Nguyen & Middaugh 2012)	Of 207 cases, 176 (85%, range 68–100%) experienced diarrhoea and 98 (47%, range 19–64%) vomiting	No details	Mostly older adults
(Ohwaki et al. 2009)	Staff members (285) Diarrhoea (72%),	No details	Mostly adults (staff) older adults (patients)

	Vomiting (57%) and fever (57%)		
Reference	**Clinical features**	**Duration**	**Population**
(Rao et al. 2009)	93 (91%) experienced at least 2 episodes of vomiting, and 71 (70%) had at least 3 episodes of diarrhoea).	The median number of days ill was 3 (range, 0.25–14 days; mean, 3.5 days	Adult staff members
(Tsang et al. 2008)	Diarrhoea 97.2% Vomiting - 46.3%	The median duration for diarrhoea was 3 days and the longest 24 days. The median duration of vomiting was one day and the longest 15 days. Fever occurred in one-third of all cases	Mostly older adults
(Tseng et al. 2011)	Diarrhoea (87.5%), Vomiting (25.5%), Abdominal pain (4.9%) and fever (2.2%)	The mean duration of all 184 affected patients was 2.1±1.5 days. Most patients (159/184, 86.4%) experienced illness for 1–3 days	Mostly adults
(Tu et al. 2008)	Vomiting (78.6% Diarrhoea (71.4%), Nausea (50.0%) Abdominal cramps (35.7%)	symptoms lasted on average 2.6 days (range, 1 to 4 days; median, 3 days)	Mostly older adults
(Zheng et al. 2015)	Abd pain (86.5%), Diarrhoea (67.6%), Vomiting (45.9%).	The disease remitted within 2-3 days	Mostly older adults

Q 2: Transmission pathways for Norovirus Gastroenteritis in healthcare settings

Transmission pathways

Faecal-oral pathway is generally the most prominent mode of transmission for norovirus infections. This review found that transmission for NoV infections in healthcare setting mainly occurs by the faecal–oral route, either through person to person contact or through exposure to contaminated food. Table 6 shows the details of NoV transmission pathways based on available data from 9 observational studies. Two studies assumed that NoV infection was hospital-acquired if there was an interval of at least five days between hospital admission and initial diagnostic sampling (Beersma et al. 2009; Franck et al. 2015). Determination of transmission pathways are varied and details are provided in Table 6.

In addition five observational studies suggested that there is a possibility of viral transmission via aerosols that were likely to be generated during severe vomiting. Table 7 shows summary of viral transmission via aerosols, although there is no data or determination criteria provided to support this assumption except one study which detected airborne dispersal of NoV in dust particles (Nenonen et al. 2014)

It appears that genotype GII.4 is more often associated with transmission mediated by person-to-person contact than with other types of transmission.

Table 6. Details of NoV major transmission pathways

Reference /Healthcare setting /Country	Transmission pathways	Transmission determined criteria	Norovirus genogroups
(Beersma et al. 2009) A tertiary care hospital Netherlands	Among 197 patients who were in hospital at the time of diagnosis, NoV was acquired nosocomially in 113 (57.4%). The proportion of NoV infection that was nosocomially acquired was highest in the youngest patients (58%) and in the elderly (78%)	It was assumed that NoV infection was hospital-acquired if there was an interval of at least five days between hospital admission and initial diagnostic sampling. This assumption was confirmed by analysing the clinical symptoms at admission	GIIb strains occurred mainly in children below the age of two-and-a-half years [odds ratio (OR): 14.7; P<0.0001] GII.4 strains affected all age groups
(Franck et al. 2014) Hospitals Denmark	157 (2109) admitted to hospital - foodborne outbreaks (community)/ Nosocomially infected patients (n = 539)	A genotype based on sequence information from the polymerase and the capsid genes was obtained for NoVs in 349 (17%) samples. No further details available	Healthcare setting GII.4 (91%), children <3 years of age infected with NoV GII.3 or GII.P21 ranged from 11% to 25%
(Franck et al. 2015) Hospitals Denmark	64% of the patients (range, 37%– 87%) had nosocomial NoV infections. Nosocomial Infections among inpatients (≥60 years) (67%), children and adolescents (age, <18 years). (28%)	NoV infections were classified as community acquired if stools were sampled on the day of admission (day 0) or the following day (day 1) and nosocomial if sampling was performed on day 5 or later.	GII.4 infections were also associated with nosocomial NoV infections
(Godoy et al. 2015) Hospitals and nursing homes Spain	Person-to-person transmission 81·5% (22/27) of NoV confirmed outbreaks. Foodborne and person-to-person transmission -11·1% (3/27) and Foodborne 7·4% (2/27).	The mechanism of transmission was determined through microbiological and statistical analysis for all outbreaks by epidemiologists.	GII.4 was detected in 66·7% (10/15) of outbreaks.
(Heijne et al. 2012) Psychiatric wards Netherlands	Patient to patient (64%), Patient to healthcare worker (29%)	The construction of transmission trees- (1) constructed a transmission matrix by calculating serial intervals (the duration in days between the dates of symptom onset) for any pair of cases. (2) this transmission matrix is translated into a transmission tree.	No details
(Kanerva et al. 2009) Tertiary care hospital Finland	NoV confirmed cases, 121 (67%) were nosocomial	A detailed sequence comparison of viruses in a random sample of microbiologically verified norovirus patients in the most heavily affected	Three main GII.4-2006b subvariants entered the hospital with gastroenteritis patients,

		wards enabled an estimation of local virus transmission.	
Reference /Healthcare setting /Country	**Transmission pathways**	**Transmission determined criteria**	**Norovirus genogroups**
(Mattner, Guyot & Henke-Gendo 2015) University and teaching hospitals Germany	NoV nosocomial acquisition confirmed in 30 (68%) outbreaks	Patients who became symptomatic more than 48 h after admission were defined as having nosocomially acquired disease.	No details
(Ohwaki et al. 2009) Hospital and attached LTCF Japan	Main mode of transmission: foodborne	Observations suggested that lunch on 20 Feb- was the potential source of the outbreak. Standard diet may have been contaminated while being prepared in the central kitchen	NoV GII/4 detected in23/32 samples
(Rosenthal et al. 2011) Long-term care facilities (LTCFs), USA	All confirmed NoV outbreaks, primary transmission mode was - person-to-person (94%), foodborne (2.5%) and undetermined for 3.5%.	If a point source of infection is suggested by the epidemic curve and other epidemiological evidence, an investigation of the source of exposure was conducted. No further details available	GII.4 strains accounted for 108 (84%)

Table 7. Summary of viral transmission via aerosols

Reference /Healthcare setting /Country	Summary of possible aerosol transmission
(Cheng, FWT et al. 2006) Public Hospital, Hong Kong	The study recommended surgical masks for staff in the ward areas in order to minimize the possibility of viral transmission via aerosols that were likely to be generated during severe vomiting.
(Harris et al. 2013) NHS Hospital, UK	Vomiting and the resultant aerosols are important in transmitting the Infection. People exposed to vomiting events, either by being close to the person who initially vomited, or by occupying the same area sometime after the initial event, have a higher infection risk
(Lopman et al. 2006) NHS Hospital, UK	During vomiting virus is aerosolised. It can then be transmitted directly through the air or can settle and contaminate the surrounding environment or foodstuffs, later to be inadvertently swallowed.
(Nguyen & Middaugh 2012) Long Term Care Facilities, USA	NoV-containing faecal matter or aerosolized vomitus, or by indirect contact with these via environmental surfaces may have spread the virus to other residents and staff in the course of their work
(Nenonen et al. 2014) University Hospital Sweden	NoV genotype II.4 was sequenced from 18 environmental samples, dust (n=8), virus traps (n=4), surfaces (n=6), and 56 patients. Airborne dispersal of NoV detected in dust particles and in Virus tap samples from patient rooms, may be a source of contamination in nosocomial outbreaks.

NoV Shedding in healthcare settings

Based on four observational studies individuals may shed NoVs more than 21 days after the resolution of symptoms, possibly acting as a possible source for nosocomial transmission. However no data has been reported on ongoing transmission or secondary cases. The age group of included 4

studies consisted of children and older adults and prolonged viral shedding has been reported in paediatric oncology patients infected with NoV (median 23 days; range 3-140 days). Table 8 shows the details of NoV shedding and NoV genogroups associated with virus transmission.

Table 8. Details of NoV shedding and NoV genogroups associated with virus transmission.

Reference /Healthcare setting /Country	Population	Virus shedding	Norovirus genogroups/ Ongoing Transmissions/ Secondary cases
(Beersma et al. 2009) A tertiary care hospital Netherlands	Among 197 patients (Children and adults), NoV was acquired nosocomially in 113 (57.4%).	Follow-up samples were obtained from 53 of 197 admitted patients (26.9%). Long-term shedding (more than one month) was demonstrated for 12 patients (22.6% of those with adequate follow-up, 6.1% of all admitted NoV patients). Twenty patients were co-infected with rotavirus (n=5 patients) or parechoviruses (n =15); most of these occurred in patients aged <10 years. Virus shedding may be detected after discharge	GIIb strains occurred mainly in children below the age of two-and-a-half years [odds ratio (OR): 14.7; P<0.0001] GII.4 strains affected all age groups No data available ongoing transmissions or secondary cases
(Costantini et al. 2016) Long-term care facilities (LTCFs) USA	Sixty-two cases (65% aged ≥70 years), 34 exposed controls (9% aged ≥70 years), and 18 nonexposed controls (5% aged≥70 years) were enrolled	Prolonged shedding (≥21 days) was detected in 16 (47%) of the 35 cases with positive acute stool. Spearman correlation was used to compare illness and shedding duration with severity score. Shedding duration was analyzed as Kaplan–Meier survival probability. No associations between severity of disease, illness duration, and virus shedding was found. Virus shedding may be detected during the stay -LTCF	GII.4 Sydney No data available ongoing transmissions or secondary cases
(Simon et al. 2006) Paediatric oncology unit, Germany	Stool and vomitus samples from 11 Paediatric oncology patients were tested for NoV	Follow-up investigation demonstrated viral shedding for a maximum of 140 days (median 23 days; range 3-140 days) in 12 hospitalised children with cancer. Virus shedding may be detected after discharge	No details No data available ongoing transmissions or secondary cases
(Tu et al. 2008) Aged-care facility Australia	14 volunteers (six males and eight females) (median, 85 years), 13 were patients (aged 63 to 93 years) and one	The duration of viral shedding: average 28.7 days (median, 28.5 days), with a range of 13.5 to 44.5 days Virus shedding may be detected	Norovirus GII No data available ongoing transmissions or secondary cases

	was a staff member (58 years old)	during the stay -LTCF	

Results

Q 3: Infection prevention and control strategies

The literature search identified 614 abstracts and a further five papers were identified through other sources including reference lists and grey literature searching. After removing 155 duplicates, 464 abstracts were screened for inclusion of the review and 449 abstracts were not relevant to the study purpose. Application of the inclusion/exclusion criteria resulted in the further exclusion of six full text papers leaving nine (n=9) studies for the review question 3. Figure 1 illustrates the study selection process.

PRISMA Flow Diagram

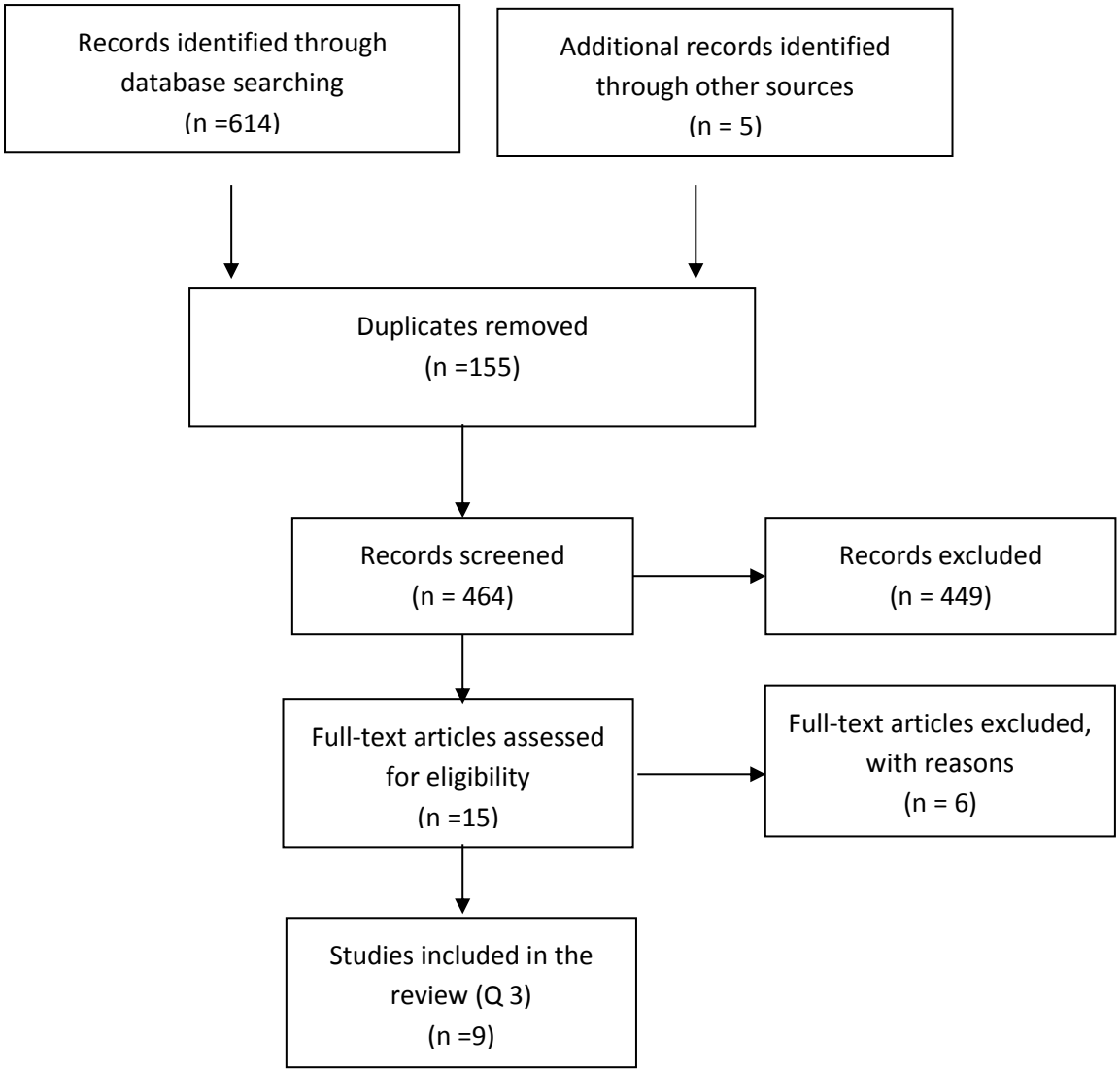

Figure 2. The study selection process

Characteristics of included studies

To evaluate the effectiveness of transmission based precautions and control strategies, the gold standard study design is a randomised controlled trial (RCT). However, this literature review failed to find a RCT or other research designs including cluster RCTs, non-randomised controlled trials (Non-RCTs), controlled before and after studies and interrupted time series studies (ITS). In the absence of above research studies, other quantitative research designs were considered. The included nine studies were observational studies and experimental controlled laboratory designs. Table 6 presents included studies and the methodological quality.

Table 9. Included studies and the methodological quality

Reference	Study design	Level of Evidence[1]	Methodological quality[2] Yes/Overall
(Blaney et al. 2011)	A cross-sectional survey	Level IV	8/9
(Cheng, VCC et al. 2011)	Observational comparative study	Level III-2	8/9
(Haill et al. 2012)	Prospective Intervention study	Level III-2	8/9
(Harris, Adak & O'Brien 2014)	Retrospective Record Analysis	Level IV	8/9
(Illingworth et al. 2011)	Pre and Post Test Design	Level III-3	8/9
(Liu et al. 2010)	Experimental Controlled Laboratory Design	+	5/9
(Morter et al. 2011)	Pre and Post Test Design	Level III-3	8/9
(Park et al. 2010)	Experimental Controlled Laboratory Design	+	5/9
(Tung et al. 2013)	Experimental Controlled Laboratory Design	+	5/9

[1] NHMRC Level of Evidence (NHMRC 2000) [2] The Joanna Briggs Institute Reviewers' Manual 2014 - The Systematic Review of Prevalence and Incidence Data (JBI 2014) [+] NHMRC Level of Evidence not determined

Healthcare settings

This review considered all type of patients/participants including children and adults in healthcare settings. The health care settings of interest for this review include acute care, aged care, paediatric, neonatal and rehabilitation. Table 7 provides details of healthcare settings, participants and study duration.

Table 10. Details of healthcare settings, participants and study duration

Reference	Healthcare setting /Country	Participants/ NoV outbreaks	Study duration
(Blaney et al. 2011)	State health departments in Maine, New Hampshire, and Vermont, USA	Patients and staff of LTCFs (survey responses) Confirmed norovirus outbreaks 29/73	2006-2007
(Cheng, VCC et al. 2011)	6 hospital networks in Hong Kong	Hospital staff Confirmed norovirus cases 242/988	2009-2010
(Haill et al. 2012)	A 1200-bed teaching hospital in southwest England	11 and 44 outbreaks per year	2005-2011
(Harris, Adak & O'Brien 2014)	NHS Hospitals, UK	3650 laboratory-confirmed norovirus outbreaks	2009-2012
(Illingworth et al. 2011)	Lancashire Teaching Hospitals, UK	67 NoV Outbarks	2007-2010
(Liu et al. 2010)	Laboratory setting, USA	10 volunteers human finger pads	No details

Reference	Healthcare setting /Country	Participants/ NoV outbreaks	Study duration
(Morter et al. 2011)	963-bedded teaching hospital, UK	NoV was detected in 75 (31.4%) of 239 environmental swabs	2009-2010 (4 months)
(Park et al. 2010)	Laboratory setting, USA	NA	2009
(Tung et al. 2013)	Laboratory setting, USA	NA	No details

NoV Infection prevention and control strategies in healthcare settings

The effectiveness of hand sanitizers

The World Health Organization recommends the use of alcohol-based hand sanitizer (ABHS) for hand hygiene in health care settings when hands are not visibly soiled. Based on the findings of 5 included studies, no reliable conclusion can be made on the effectiveness of alcohol-based hand sanitizer for the prevention and control of NoV infection in healthcare settings. According to Park et al. (2010) 90% Ethanol or 90% Isopropanol may be effective against NoV, however it is not clear whether lower concentrations (50 to 70%) of alcohols, which are widely used in commercial sanitizers, are effective against human NoV. Table 8 provides study summaries on the effectiveness of hand sanitizers. In combination with other infection control strategies, alcohol based hand rub may be useful in controlling nosocomial transmission of norovirus (Cheng, VCC et al. 2011)

Table 11. Effectiveness of hand sanitizers

Reference	Intervention/ Comparison	Results/Outcomes	Conclusion
(Blaney et al. 2011) A cross-sectional survey Level IV	Alcohol-based hand sanitizer (ABHS) versus soap and water 91 LTCFs (60%) provided survey responses 61 facilities reporting 73 outbreaks; 29 were confirmed norovirus	In LTCFs with laboratory-confirmed norovirus outbreak, Staff were equally or more likely to use ABHS than soap and water for routine hand hygiene had higher odds of an outbreak than facilities with staff less likely to use ABHS (adjusted odds ratio, 6.06; 95% confidence interval:1.44-33.99 p = .02).	Preferential use of ABHS over soap and water for routine hand hygiene might be associated with increased risk of norovirus outbreaks in LTCFs.
(Cheng, VCC et al. 2011) Observational comparative study Level III-2	Staff education (N=3594 - 18 months) and promotion of directly observed hand hygiene using alcohol based hand rub (ethanol (80% vol/vol), 242/988 patients were positive for norovirus	Overall rate of hand hygiene compliance of hospital staff - between 60% and 70% after 3 year follow up During12 months period, the incidence of hospital-acquired norovirus infection decreased from 131 to 16 cases per 1,000 potentially infectious patient-days (P< .001)	Strategic infection control measures including staff education and observed hand hygiene using alcohol based hand rub with an added test to detect the Norovirus may be useful in controlling nosocomial transmission of norovirus
(Liu et al. 2010) Experimental controlled laboratory design	Efficacy of (1) sodium hypochlorite Vs ethanol (2) antibacterial liquid soap (Fisher Scientific International-Hampton, NH) and alcohol-based hand sanitizer (2% ethyl alcohol) for the inactivation of Norwalk virus (NV) on	Reduction in genomic copies of NV cDNA with the antibacterial liquid soap treatment (0.67 to 1.20 log10 reduction) and water rinse only (0.58 to 1.58 log10 reduction). The alcohol-based hand sanitizer was relatively ineffective, reducing the genomic copies of NV cDNA by only 0.14 to 0.34 log10 compared to	Ethanol-based hand sanitizers are less effective controlling the transmission of HuNoV group

	human finger pads	baseline	
Reference	**Intervention/ Comparison**	**Results/Outcomes**	**Conclusion**
(Park et al. 2010) Experimental controlled laboratory design	Virucidal efficacy of seven hand sanitizers containing various active ingredients ethanol, triclosan, and chlorhexidine GII.4 norovirus, feline calicivirus (FCV), murine norovirus (MNV), fecal extract	For GII.4 NoV, 50 and 70% ethanol and isopropanol resulted in 0.0- to 0.6-log reductions of viral RNA, whereas both 90% ethanol and 90% isopropanol significantly reduced GII.4 RNA (P , 0.001) by 1.2 and 1.8 log PCR units per ml, respectively, after 5 min of exposure	Significant reduction in RNAtiters of GII.4 NoV after exposure to 90% ethanol or 90% isopropanol indicates that both alcohols could be effective against HuNoV.
(Tung et al. 2013) Experimental controlled laboratory design	Ethanol (50, 70, and 90%), sodium/hypochlorite (5, 75, 250, 500, and 1,000 ppm)/a quaternary ammonium compound blend (at 0.1x, 1.0x, and 10x concentrations Two norovirus (NoV) genogroup II strains (GII.2 and GII.4) and two surrogates (feline calicivirus [FCV] and murine norovirus [MNV-1]).	Both HuNoV strains were more resistant to hypochlorite than were either of the animal surrogates, with the human strains requiring >_500 ppm of hypochlorite to achieve statistically significant reduction (>_3.0 log) in virus concentration. All four viruses were resistant to inactivation (,0.5-log reduction) using the quaternary ammonium compound formulation at all concentrations tested.	Overall, all 3 products are not effective against HuNoV

The effectiveness of ward or bay closures

In the past, ward closure was considered as a central control measure for managing hospital outbreaks of norovirus. However, this review found that entire ward closure may not always be necessary, and that more efficient control may be achieved by the closure of bays. If implemented, this approach needs to occur promptly and early (within three days of the first case becoming ill) in an outbreak before extensive transmission has occurred within a clinical area. Table 9 provides the effectiveness of the ward or bay closures.

Table 12. The effectiveness of ward or bay closures

Reference	**Intervention/ Comparison**	**Results/Outcomes**	**Conclusion**
(Haill et al. 2012) A 1200-bed teaching hospital in southwest England Prospective Intervention study Level III-2	11 - 44 outbreaks per year. First, soon after an outbreak had been identified, symptomatic patients were cohorted in single rooms or bays in an attempt to contain the outbreak without closing the entire ward. **Wards:** 14 - 34 Beds per wards **Bays**: beds configured in 5- or 6-bedded bays, at least two of which are fitted with doors.	Prior to June 2007, 90% of outbreaks were managed by closure of an entire ward, compared with only 54% from June 2007 onwards. The duration of closure was significantly shorter for bays compared with entire wards, both before (3.5 vs 6, P = 0.0327) and after (3 vs 5, P < 0.0001) June 2007. When considering all outbreaks, there was a significant reduction in duration of closure after the change in strategy (6 vs 5, P = 0.007).	Many norovirus outbreaks can be controlled by containment in bays rather than by entire ward closures, particularly when this is combined with adequate infection control support
Reference	**Intervention/**	**Results/Outcomes**	**Conclusion**

	Comparison		
(Harris, Adak & O'Brien 2014) NHS Hospitals, UK Retrospective Record Analysis Level IV	3650 laboratory-confirmed norovirus outbreaks. Ward or bay closures, specifically, whether prompt closure of an affected ward Vs not to close **Wards:** 16-28 Beds per wards **Bays**: No details	Closing a bay or ward promptly (within 3 days of the first case occurring) in an outbreak of norovirus, the duration of the outbreak is shorter compared with the outbreaks where closure is not prompt.	There is no compelling evidence that closing the ward is an effective way of curtailing an outbreak of norovirus.
(Illingworth et al. 2011) Lancashire Teaching Hospitals, UK Pre and Post Test Design Level III-3	67 NoV Outbreaks Closure of affected ward bays (rather than wards), installation of bay doors, enhanced cleaning, a rapid in-house molecular test and an enlarged infection control team **Wards:** No detail of number of bays per wards **Bays**: four-bedded bays (most open plan without doors)	Significant decrease in the ratio of confirmed hospital outbreaks to community outbreaks(r = 0.317, P =0.025), the number of days of restricted admissions on hospital wards per outbreak (r = 0.742, P= 0.041), and the number of hospital bed-days lost per outbreak (r = 0.344, P< 0.001). However, there was no significant change in the number of patients affected per hospital outbreak (r =1.080, P= 0.517), or the number of hospital staff affected per outbreak (r = 0.651, P =0.105).	Closure of entire wards during norovirus outbreaks is not always necessary. The changes implemented at the study hospital resulted in a significant reduction in the number of bed-days lost per outbreak, and this, together with a reduction in outbreak frequency, resulted in considerable cost savings

Environmental cleaning

This review found a Pre and Post-test study which was conducted to assess the efficiency of cleaning and identify any NoV contamination in the environment (Morter et al. 2011). In this study, NoV was detected in 75 (31.4%) of 239 environmental swabs collected from sites on five wards and one day room. The ward environments and clinical equipment were washed using Actichlor solution (Ecolab Ltd, Leeds, UK). If soiled with blood or body fluids, equipment was cleaned first with water and detergent, followed by 10 000 ppm Actichlor plus. However the study does not provide ingredient/composition of Actichlor solution. It is difficult to determine the effectiveness of cleaning agents. Ward environment and equipment can be considered as NoV reservoirs (Morter et al. 2011). Table 10 provide the details of the study.

Table 13. Effectiveness of Environmental cleaning

Reference	Intervention/ Comparison	Results/Outcomes	Conclusion
(Morter et al. 2011) 963-bed teaching hospital., UK Pre and Post test design Level III-3	Time 1: Wards environment and clinical equipment were washed using Actichlor.. If soiled with blood or body fluids, equipment was cleaned first with water and detergent, followed by 10 000 ppm Actichlor plus Environmental monitoring	NoV contamination was reduced on surfaces sampled from 42.1%to 13.2% and from 48.7% to 19.4% on K2 and H3 wards 45% swabs from soap and alcohol dispensers, 45.9% from equipment, 29.4% within the nurses' station, 42.9% at the bedside and 23.6% from furniture, fixtures and fittings were positive for NoV	It is difficult to determine the effectiveness of cleaning agents however ward environment and equipment can be considered as NoV reservoirs

	was performed after cleaning using Cotton-tipped swabs Time 2: Re-cleaned and re-tested four-month period during 2009-2010		

Other infection control strategies

Considering the limited number of comparative observational studies, this review examined 33 observational studies relevant to Question 1 and 2 to identify NoV infection prevention and control strategies in healthcare settings. Although there is no evaluation data relevant to the effectiveness of interventions, 24 (73%) studies provide infection control strategies used during the outbreaks and are summarised in Table 11. In addition, Table 12 provides details of infection control strategies used during NoV outbreaks.

Table 14. Reported infection prevention and control strategies

Infection control strategies	Number of times action undertaken	%
Early detection		
Early detection/ rapid diagnostic testing	4	4.5
Efficient contact tracing of exposed patients	2	2.2
Restriction of movements		
Isolation of patients	9	10.1
Cohorting of symptomatic patients	6	6.7
Restricting of staff & patients	5	5.6
Restricting of visitors	4	4.5
Environmental cleaning		
concentrated disinfectant (hypochlorite solution 1000 ppm or above),	7	7.9
Meticulous handling of waste products	5	5.6
Environmental cleaning (not specified)	9	10.1
Intensive environmental cleaning with bleach or chlorine	5	5.6
Enhanced hand hygiene		
Hand hygiene (not specified)	6	6.7
Washing with soap and water	4	4.5
Alcohol hand rubs	2	2.2
Directly observed hand hygiene	1	1.1
Other actions		
Standard precautions / personal protective equipment	5	5.6
Staff education	4	4.5
Exclusion of ill staff (2–5 days after symptoms pass)	7	7.9
Ward or Bay close	4	4.5
Total	**89**	**99.8**

Table 15. Details of infection control strategies used during NoV outbreaks

Reference	Healthcare setting /Country	Infection control strategies
(Cheng, FWT et al. 2006)	Children, visitors medical students/ Public Hospital Hong Kong	Strict contact precautions, prompt isolation and cohorting of symptomatic patients, vigorous environmental cleansing with concentrated disinfectant (hypochlorite solution 1000 ppm), meticulous handling of waste products, and efficient contact tracing of exposed patients, family members, and medical students.
(Cheng, VCC et al. 2011)	Hospitalised children Public Hospital Hong Kong	Staff education and promotion of directly observed hand hygiene, reverse-transcription polymerase chain reaction for norovirus was performed as an added test by the microbiology laboratory for all faecal specimens irrespective of the request for testing. Laboratory-confirmed cases were followed up by the infection control team for timely intervention.
(Cummins & Ready 2016)	Hospitalised patients and staff Hospitals (coded A–E). London, UK	Control measures included isolation, hand hygiene, environmental cleaning, and rapid diagnostic testing.
(Danial et al. 2011)	Hospitalised patients Hospitals in NHS Lothian, UK	The decision to re-open award is made by the infection control team when there have been no new cases for 72 h and there has been no vomiting or diarrhoea for 72 h from the last uncontained episode, or if the symptomatic patients are isolated. A terminal deep clean (remove and change all curtains, remove all bed linen from all beds, decontaminate all care equipment in line with manufacturers' instructions, and thoroughly clean and then decontaminate all surfaces with a combined detergent/hypochlorite product) is performed before the ward is re-opened. Healthcare workers with gastrointestinal symptoms are taken off duty and advised not to return to work until they have been symptom-free for 48 h. For the duration of the outbreak, staff are allocated to care exclusively for either affected cases or unaffected cases to help prevent spread of the outbreak.
(Franck et al. 2015)	Hospitalised patients Hospitals Denmark	Increased focus on cleaning procedures along with immediate isolation of patients with suspected infectious gastroenteritis may help diminish the number of nosocomial NoV infections.
(Godoy et al. 2015)	Hospitalised patients Hospitals and nursing homes Spain	Environmental decontamination with solutions of hypochlorite at 1000–5000 ppm, the prevention of food contamination, the exclusion of sick workers, the cohorting of infectious patients and ensuring hand washing or the use of alcoholic solutions among healthcare workers
(Harris et al. 2014)	Hospitalised patients NHS Hospitals UK	Closing a bay or ward promptly (within 3 days of the first case occurring) in an outbreak of norovirus, the duration of the outbreak is shorter compared with the outbreaks where closure is not prompt.
(Harris et al. 2013)	Hospitalised patients NHS Hospitals UK	Increasing barriers to movement between bays by closing affected bays promptly would be effective in preventing further spread.
(Heijne et al. 2012)	Patients with mental health conditions Psychiatric wards Netherlands	All social activities were cancelled to limit patient-to-patient transmission and health- care workers were instructed to wear gloves to limit health-care-workers-to-patient transmission. Healthcare workers were also instructed to limit cross-contact between wards
(Hoffmann et al. 2013)	Patients and staff University hospital, Munich, Germany	Rigorous hygienic measures, including disinfection procedures and closure of wards helped contain the outbreak
(Johnston et al. 2007)	Patients and staff Hospital (JHH) Baltimore,	Aggressive infection-control measures, including closure of units and thorough disinfection using sodium hypochlorite,

	USA	were required to terminate the outbreak
Reference	**Healthcare setting /Country**	**Infection control strategies**
(Kanerva et al. 2009)	Patients and staff Tertiary care hospital Finland	Cohorting and contact isolation, hand hygiene, temporary closure of the wards, All touch surfaces cleaned with chlorine disinfectant, Gloves, aprons and surgical masks were used
(Mattner, Guyot & Henke-Gendo 2015)	Hospitalised patients University and teaching hospitals Germany	Constant surveillance for new cases of diarrhoea and vomiting and timely adherence to contact precautions for all exposed persons is crucial in outbreak control, as is the need for extended microbiological testing
(Munir et al. 2014)	Hospitalised children Paediatric hospitals in Atlanta USA	Rapid NoV detection system, and strict hospital hygiene practices.
(Nenonen et al. 2014)	Hospitalised patients University Hospital Sweden	The high nucleotide similarity between the NoV GII.4 strains from patients and their hospital room environment provided molecular evidence of GII.4 dispersal in the air and dust; therefore, environment cleaning is essential
(Nguyen & Middaugh 2012)	Older residents Long-term care facilities USA	ill staff excluded from work for 72 h after resolution of symptoms, hand washing with soap and water, and intensive environmental cleaning with bleach or products effective against feline caliciviruses from an environmental protection agency-approved list (http://www.epa.gov/oppad001/list_g_NoV.pdf).
(Ohwaki et al. 2009)	Adults and older residents Hospital and attached LTCF Japan	Disinfection of doorknobs and floors by chlorine and monthly collection of stool samples from kitchen workers. In addition, employees were instructed to stay at home for a week if they were having symptoms
(Partridge et al. 2012)	Hospitalised Adults and older adults A teaching hospital UK	Affected patients and their contacts were isolated or cohorted and clinical areas closed. Briefly, if isolated cases developed within a bay then that bay would be closed until 72 h beyond the last loose stool or vomit of any patient. The bay would then undergo thorough cleaning with hypochlorite and change of curtains. If more than one bay was affected within a clinical area, or if staff were affected, the whole ward would be closed until 72 h beyond last symptoms. Cohort wards were created on an ad hoc basis to facilitate cleaning and re-opening of other areas. Twice daily cleaning with 0.1% hypochlorite was instituted during outbreaks with particular attention paid to toilets, commodes and frequently touched areas such as door handles and rails.
(Rao et al. 2009)	Hospitalised Adults and older adults Tertiary care facility & LTCF USA	Isolation, cancelled congregate activities, and diverted patients to alternate hospitals. Removed alcohol-based hand hygiene products from the facility and encouraged soap and water hand-washing Environmental services staff used a chlorine-based disinfectant to clean rooms. Staff not return to work until 48 hours after complete resolution of symptoms.
(Sheahan et al. 2015)	Hospitalised children Inpatient paediatric unit of tertiary care hospital USA	Patients isolation with contact precautions (Gown, Gloves, soup and water hand washing, daily communication, enhanced cleaning of entire floor twice, staff education, restriction of visitors
(Simon et al. 2006)	Hospitalised children with cancer Paediatric oncology unit, Germany	Hand hygiene with a disinfectant until diagnostic assays turn negative Paediatric oncology patients must be closely monitored -they face a greater risk of NV-related complications.
(Sukhrie et al. 2012)	Hospitalised Adults and older adults Tertiary care hospital and nursing homes Netherlands	Healthcare workers should not resume work until 2–3 days after clinical recovery/
(Tseng et al. 2011)	Patients with mental illness	Multiple infection-control measures were implemented; A

	Psychiatric Unit Taiwan.	cohort programme, Standard precautions including wearing gowns, masks, gloves, head caps and shoe caps were universally implemented when HCWs entered the contaminated areas. Vomitus and faecal spillage were soaked with 0.5% (5000 ppm) bleach for at least 30 min and then flushed into the sanitary sewer. Hand hygiene practices: wash hands hourly, 75% alcohol solution for hand washing; alcohol solution was made available to visitors ; washing of hands with soap, chlorhexidine, and water after completing work and before meals. Environment-cleaning measures: clean and disinfect the beds, windows, and chairs of their private rooms with 0.05% bleach daily Education programme; restrictions placed on visiting staff and related HCWs to reduce the frequency and number of staff in daily ward rounds HCWs were placed on sick leave for at least 72 h after their last symptoms,
(Zheng et al. 2015)	Older residents Aged care facility China	Isolated the asymptomatic case, and promptly blocked the cross-transmission between the attendants and the elderly and between attendants and other types of workers. It is necessary to analyze the stool samples from all staff (symptomatic and asymptomatic) and to pay attention to staff education on hand washing and disinfecting faeces and vomitus appropriately.

Discussion

The purpose of this literature review was to examine the current epidemiology (Review Question 1) and latest evidence on transmission pathways (Review Question 2) and infection prevention and control measures for Norovirus Gastroenteritis (review question 3). This review included 33 observational studies for the Review Question 1 and 2 and nine studies for the Review Question 3. Due to limited number of comparative observational studies for the Review Question 3, this review examined 33 observational studies relevant to Question 1 and 2 and identified 24 (73%) studies that discussed infection control strategies used during the NoV outbreaks in healthcare settings. The Review Questions 1 and 2 included 33 observational studies (14 cohort studies, one observational comparative study, two case control studies, five case series and 11 cross sectional studies) which were Level III and IV with moderate quality. Observational studies are considered as appropriate study designs to address issues regarding prevalence and incidence (JBI 2014). For the Review Question 3, the gold standard study design is a randomised controlled trial (RCT), however, this literature review failed to find a RCT or other research designs including cluster RCTs, non-randomised controlled trials (Non-RCTs), controlled before and after studies and interrupted time series studies (ITS). In the absence of above research studies, other quantitative research designs were considered and Review Question 3 included six observational studies and three experimental controlled laboratory designs of moderate quality.

Overall, NoV genogroup II are the most common strains reported in most of the outbreaks worldwide (Ahmed et al. 2014; Cho et al. 2015). In this review, 17 studies (81%) identified that NoV genotype GII.4 caused the majority of clinical outbreaks in healthcare settings during the past decade. This finding is consistent with many other studies conducted around the word and norovirus strains over the years show emergent strains replacing those previously dominant resulting in new global epidemics (Greig & Lee 2012). Based on nine observational studies conducted in four long-term aged care facilities, two aged care facilities attached to the major hospitals and in three public hospitals, it appears that NoV GII.4 predominated in older adults. Franck et al. (2014) conducted a Cohort study involving 3,846 patients and revealed an association between an age ≥60 years and infection with NoV GII.4 in patients from community and health care settings. It seems that older adults are more susceptible to NoV GII.4 infection, which could partly explain why most NoV infections in health care settings are caused by this genotype.

NoV infection generally has a shorter incubation (24–48 h) and is characterized by acute onset of nausea, vomiting, abdominal cramps, and non-bloody diarrhoea (Cheng, VCC et al. 2011; Cummins & Ready 2016). This review identified 10 observational studies that examined clinical features of patients with norovirus gastroenteritis in outbreaks. The review found that the prevalence of diarrhoea (range: 61%-97%) and vomiting (range: 46%-98%) was higher in adults and older adults, whereas the prevalence of vomiting (82%) was higher in children. The mean duration of symptoms is 2-3 days. Careful examination of clinical symptom especially vomiting is very important to determine the NoV outbreaks as Kaplan et al. (1982) developed criteria to define norovirus outbreaks, including incubation period of 24-48 h, stool culture negative for bacterial pathogens, vomiting in >50% of cases and duration of illness lasting for 12-60 h. In this review, two studies used Kaplan criteria for the identification of norovirus-associated outbreaks (Nguyen & Middaugh 2012; Tsang et al. 2008), however only one study reported details of the NoV detection using the Kaplan criteria. Except one study, all other 32 observational studies used real-time RT-PCR to detect the NoV and some studies

used ELISA in addition to real-time RT-PCR. In case of the unavailability of a rapid and accurate diagnostic assay, Kaplan criteria may be useful in determining NoV outbreaks.

Based on available data from nine observational studies (27%), this review identified that transmission for NoV infections in healthcare setting mainly occur by the faecal–oral route, either through person to person contact or through exposure to contaminated food. Determination of transmission pathways are varied and only two studies reported that NoV infection was hospital-acquired if there was an interval of at least five days between hospital admission and initial diagnostic sampling (Beersma et al. 2009; Franck et al. 2015). It appears that genotype GII.4 is more often associated with transmission mediated by person-to‑person contact than with other types of transmission. Five observational studies suggested that there is a possibility of viral transmission via aerosols that were likely to be generated during severe vomiting, although there is no data or determination criteria reported to support this assumption except one study which detected airborne dispersal of NoV in dust particles (Nenonen et al. 2014). Cheng, et al. (2006) recommended surgical masks for staff in the ward areas in order to minimize the possibility of viral transmission via aerosols. Prolonged viral shedding was reported in four observational studies (12%) and patients may shed NoVs more than 21 days after the resolution of symptoms, possibly acting as a possible source for nosocomial transmission. However, no data has been reported on ongoing transmission or secondary cases. NoV shedding is noticeable among children and older adults and prolonged viral shedding has been reported in paediatric oncology patients infected with NoV (median 23 days; range 3-140 days) (Simon et al. 2006). Consistent with the above findings, a recent systematic review found that prolonged viral shedding among both staff and residents mostly related to older age (Petrignani et al. 2015).

This review examined the NoV infection prevention and control strategies used during NoV outbreaks in healthcare settings. The review considered the effectiveness of hand sanitizers, the effectiveness of ward or bay closures and environmental cleaning using nine studies including six observational studies (Level III- IV) and three experimental controlled laboratory designs. Based on the findings of five included studies (55.5%), no reliable conclusion can be made on the effectiveness of alcohol-based hand sanitizer for the prevention and control of NoV infection in healthcare settings. According to Park et al. (2010), 90% Ethanol or 90% Isopropanol may be effective against NoV, however it is not clear whether lower concentrations (50 to 70%) of alcohols, which are widely used in commercial sanitizers, are effective against human NoV. However in combination of other infection control strategies, alcohol based hand rub may be useful in controlling nosocomial transmission of norovirus (Cheng et al. 2011). In the past, ward closure was considered as a central control measure for managing hospital outbreaks of norovirus, however this review found that entire ward closure may not always be necessary, and that more efficient control may be achieved by closure of bays. If implemented, this approach needs to occur promptly and early (within three days of the first case becoming ill) in an outbreak in combination with adequate infection control strategies. This review found a Pre and Post-test study which was conducted to assess the efficiency of cleaning using 10 000 ppm Actichlor plus and identify any NoV contamination in the environment, however it is difficult to determine the effectiveness of Actichlor plus cleaning agents (Morter et al. 2011).

In addition to above nine studies, this review examined 33 observational studies to identify NoV infection prevention and control strategies in healthcare settings. Although there is no evaluation

data relevant to the effectiveness of interventions, 24 (73%) studies provide infection control strategies used during outbreaks. Early detection and rapid diagnostic testing allowing immediate implementation of control measures was noted in 4/89 studies (4.5%). The restriction of movements of patients, staff and visitors is frequently reported as a measure to control the spread of an outbreak (24/89 studies; (27%). Patient isolation strategies (9/89 studies; 10.1%) may be difficult due to a lack of isolation rooms, however cohorting of symptomatic patients (6/89; 6.7%) and restricting of staff, patients, visitors (9/89; 10%) may minimise potential transmissions of NoV. Environmental cleaning (26/89 studies; 29.2%) was considered as an important intervention for the prevention and control of NoV infection in healthcare settings. Environmental decontamination with solutions of hypochlorite at 1000–5000 ppm was suggested (7/89 studies; 7.9%) and intensive environmental cleaning with bleach or chlorine also suggested in 5/89 studies (5.6%) with particular attention to frequently touched areas such as toilets and door handles. Following the outbreak, the ward and used equipment should be thoroughly cleaned using combined detergent/hypochlorite product and a change of curtains is recommended before the ward is re-opened (Danial et al. 2011; Partridge et al. 2012).

Hand washing/hygiene (13/89 studies; 14.5%) is considered as the single most effective measure for preventing infections (Huang, Stewardson & Grayson 2014), however conflicting recommendations were noted regarding the use of alcohol hand sanitizers. Rao et al. (2009) suggested removing alcohol-based hand hygiene products from the facility and encouraged soap and water hand-washing, while Tseng et al. (2011) recommended the use of 75% alcohol solution for hand washing.. The Australian Guidelines for the Prevention and Control of Infection in Healthcare (2010) recommended that hand hygiene should be performed using soap and water when Clostridium difficile or non-enveloped viruses such as norovirus (NHMRC 2010) are identified. The increased use of personal protective equipment incorporated into standard precautions (5/89; 5.6%) and staff education on infection control strategies (4/89 studies; 4.5%) were frequently reported as control measures. Exclusion of ill staff for 2–5 days following final symptoms was reported as effective in controlling transmission of infection (7/89 studies; 7.9%). The Australian Guidelines for the Prevention and Control of Infection in Healthcare (2010) recommended that healthcare workers should not return to work until diarrhoea and vomiting have ceased for two days (NHMRC 2010) and that healthcare workers should comply with appropriate hand hygiene methods and stringent infection prevention and control practices upon return to work, because of possible prolonged viral shedding. It can be concluded that a combination of infection control strategies such as early detection and rapid diagnostic testing, immediate implementation of infection control measures, including isolation/cohorting of infected patients, hand hygiene, proper environmental cleaning and staff education can be effective in controlling NoV outbreaks in healthcare settings. However due to the widespread prevalence of NoV infections, the need for specific prevention strategies is becoming apparent.

The literature search was limited to English language publication since 2006. Lack of high quality comparative studies on the effectiveness of infection control strategies led to the inclusion of lower level evidence from observational studies therefore findings should be generalised to the clinical setting with caution. High quality comparative studies are needed to evaluate the effectiveness of infection control strategies in order to make meaningful recommendations for clinical practice.

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