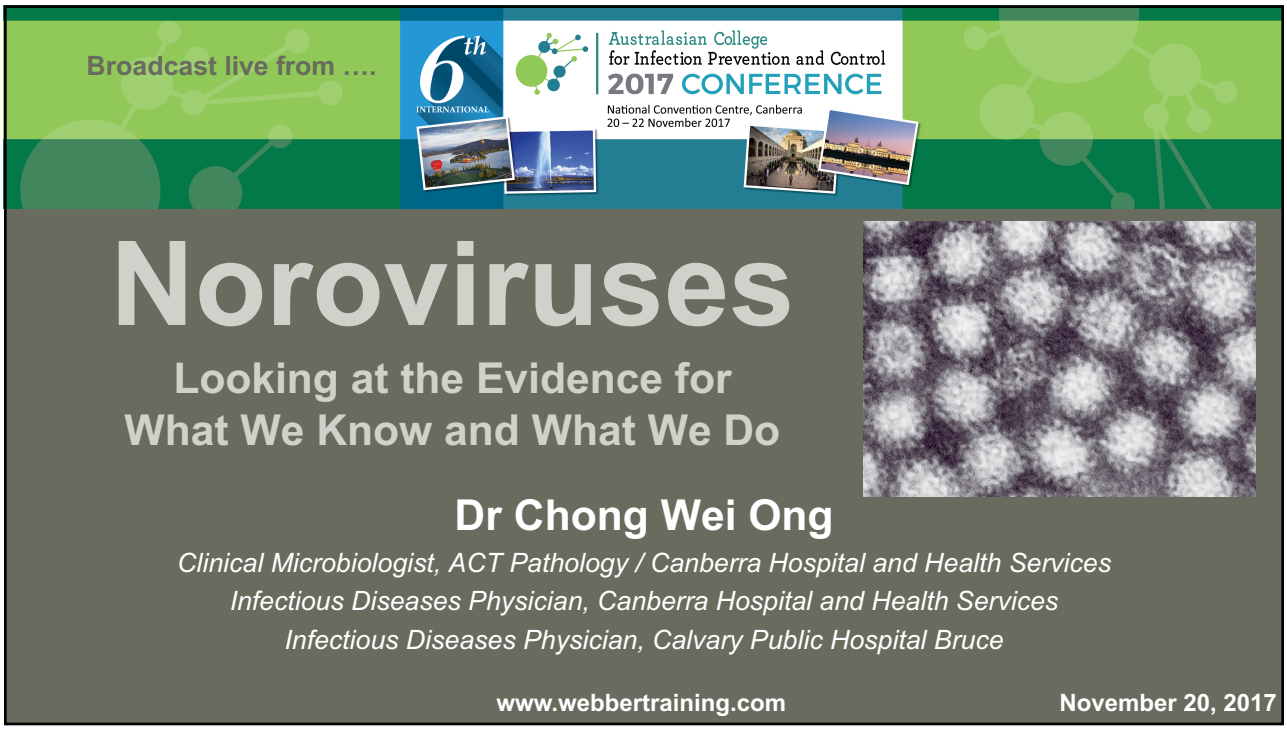
Noroviruses - Looking at the Evidence for What We Know and What We Do
Dr Chong Wei Ong, Canberra Hospital and Health Services
Broadcast live from the 2017 conference of the Australasian College of Infection Control



DISCLOSURE

I have no conflicts of interest to declare.

A Webber Training Teleclass
www.webbertraining.com

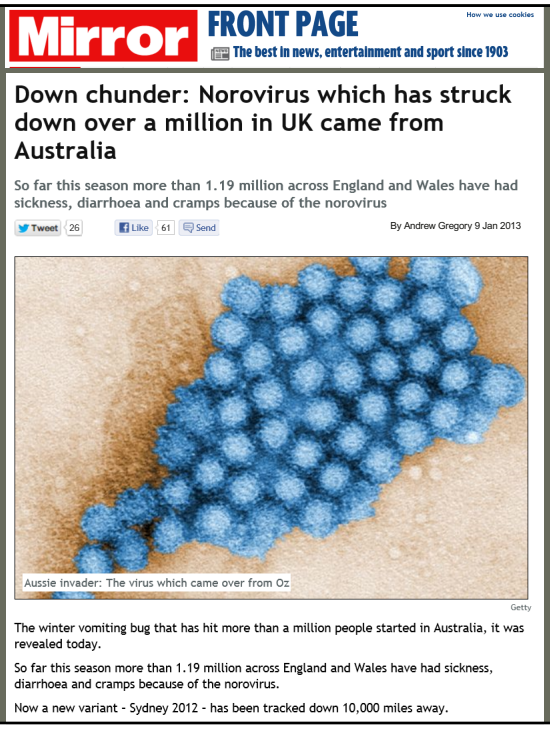
Background

- about 18% of all cases of acute gastroenteritis worldwide
- about 50% of all gastroenteritis outbreaks worldwide
- 677 million cases in 2010, over 200 000 deaths
- infects persons of all **ages**
- sporadic vs outbreaks
- "winter vomiting illness"

Ahmed SM et al. Lancet Infect Dis. 2014 Aug;14(8):725-730.
Pires SM et al. PLoS One. 2015 Dec 3;10(12):e0142927.
Patel M. J Clin Virol 2009;44:1-8.
CDC. MMWR 2011;60(No. RR-3):1-15.

- Incubation period : 12–48 h
- Nausea, vomiting, abdominal cramps, myalgias, and non-bloody diarrhea, fever [<50%]
- Mild to severe
- Resolution in 2–3 days [up to 4–6 days in hospitalized patients, the elderly and children < age 11 years of age]

CDC. MMWR 2011;60(No. RR-3):1-15.
Glass R et al. N Engl J Med 361:1776-1785.
Rockx B et al. Clin Infect Dis 2002;35:246–53.
Lopman B et al. Clin Infect Dis 2004;39:318–24.



Mirror FRONT PAGE
The best in news, entertainment and sport since 1903

Down chunder: Norovirus which has struck down over a million in UK came from Australia

So far this season more than 1.19 million across England and Wales have had sickness, diarrhoea and cramps because of the norovirus

By Andrew Gregory 9 Jan 2013

Aussie invader: The virus which came over from Oz

Getty

The winter vomiting bug that has hit more than a million people started in Australia, it was revealed today.

So far this season more than 1.19 million across England and Wales have had sickness, diarrhoea and cramps because of the norovirus.

Now a new variant - Sydney 2012 - has been tracked down 10,000 miles away.

New strain "GII.4-Sydney (Mar 2012)" goes worldwide

Jul 2012 – Jan 2013 :

813 outbreaks reported

– 720 (89%) ward/bay closures or restrictions to admissions

HPA. Weekly update of norovirus activity. 30 Jan 2013. Health Protection Agency, UK.
Gregory A. Daily mirror. 9 Jan 2013. http://www.mirror.co.uk/news/technology-science/science/norovirus-came-from-australia-and-has-struck-down-1526563. Accessed 8 Feb 2013.

Outbreak management measures

- Strict hand hygiene
- PPE use (gown/gloves/mask/goggles)
- Enhanced Environmental cleaning and disinfection
- Isolation / exclusion [until 48 hrs after last diarrhoeal stool]
  - Hospital patients : contact / droplet precautions
  - Visitor : restrictions
  - Staff : cohorting / exclusion
- Facility / ward closures
- Food safety measures

CDNA. Guidelines for the public health management of gastroenteritis outbreaks due to norovirus or suspected viral agents in Australia 2010. Commonwealth of Australia.
Barclay L et al. Clin Microbiol Infect 2014; 20:731.

Evidence challenges

PubMed search (1 Nov 2017)
“norovirus”
5194 papers

Infection control measures for norovirus: a systematic review of outbreaks in semi-enclosed settings

J.P. Harris [a,*], B.A. Lopman [a], S.J. O'Brien [b]

Journal of Hospital Infection (2010) **74**, 1–9

- assess the evidence for effectiveness of control measures
- 72 outbreaks reported in 47 papers
- differences experienced whether control measures were implemented or not

- 'We found **no evidence that implementing infection control measures affected the duration of outbreaks, or the attack rates** either overall (all settings combined) or within particular settings.'
- CONCLUSION : '**Sound infection control procedures are key to controlling norovirus outbreaks** but unfortunately, the present body of the **published literature does not provide an evidence-base** for the value of specific measures.'

GUIDELINE FOR THE PREVENTION AND CONTROL OF NOROVIRUS GASTROENTERITIS OUTBREAKS IN HEALTHCARE SETTINGS

Taranisia MacCannell, PhD, MSc[1]; Craig A. Umscheid, MD, MSCE[2]; Rajender K. Agarwal, MD, MPH[2]; Ingi Lee, MD, MSCE[2]; Gretchen Kuntz, MSW, MSLIS[2];Kurt B. Stevenson, MD, MPH[3] and the Healthcare Infection Control Practices Advisory Committee (HICPAC)[4]

[1] Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, GA

[2] Center for Evidence-based Practice
University of Pennsylvania Health System
Philadelphia, PA

[3] Division of Infectious Diseases
The Ohio State University,
Columbus, OH

OCTOBER 2011

CDC. https://www.cdc.gov/infectioncontrol/guidelines/norovirus/index.html. Accessed 24 Oct 2017.
MacCannell T. et al. Infect Control Hosp Epidemiol. 2011 Oct;32(10):939-69.

HICPAC Categorization Scheme for Recommendations

Rank	Description
Category IA	A **strong recommendation** supported by **high to moderate quality evidence** suggesting net clinical benefits or harms.
Category IB	A **strong recommendation** supported by **low-quality evidence** suggesting net clinical benefits or harms, or an accepted practice (e.g., aseptic technique) supported by low to very low-quality evidence.
Category IC	A **strong recommendation** required by state or federal **regulation**.
Category II	A **weak recommendation** supported by **any quality evidence** suggesting a tradeoff between clinical benefits and harms.
Recommendation for further research	An unresolved issue for which there is low to very low-quality evidence with uncertain tradeoffs between benefits and harms.

CDC. https://www.cdc.gov/infectioncontrol/guidelines/norovirus/index.html. Accessed 24 Oct 2017.
MacCannell T. et al. Infect Control Hosp Epidemiol. 2011 Oct;32(10):939-69.

HICPAC Categorization Scheme for Recommendations

Rank		Description
Category IA	1	A **strong recommendation** supported by **high to moderate quality evidence** suggesting net clinical benefits or harms.
Category IB	27	A **strong recommendation** supported by **low-quality evidence** suggesting net clinical benefits or harms, or an accepted practice (e.g., aseptic technique) supported by low to very low-quality evidence.
Category IC	6	A **strong recommendation** required by state or federal **regulation**.
Category II	19	A **weak recommendation** supported by **any quality evidence** suggesting a tradeoff between clinical benefits and harms.
Recommendation for further research	8	An unresolved issue for which there is low to very low-quality evidence with uncertain tradeoffs between benefits and harms.

CDC. https://www.cdc.gov/infectioncontrol/guidelines/norovirus/index.html. Accessed 24 Oct 2017.
MacCannell T. et al. Infect Control Hosp Epidemiol. 2011 Oct;32(10):939-69.

Human noroviruses – 'uncultivable'

- Biology / pathogenesis / transmission – infectivity of particles
- Immune responses
- Diagnostic tests – significance of RNA detection
- Disinfectants / Virucidal agents
- Treatment / Antiviral drugs
- Vaccine

Research & application issues

- Observational or descriptive studies
  - not controlled
  - each outbreak is different
  - ethics of RCT
- Multiple interventions
- Heterogeneity of settings
- Incomplete adherence to control measures
- Basic science technical difficulties
- Applicability of basic science to clinical setting

Evidence challenges

- **A**dequacy (**A**bsence)
- **A**ntagonism
- **A**pplicability

Selected topics

- Hand hygiene
- Isolation / exclusion
- Personal protective equipment

Hand hygiene

Alcohol-based hand rub

or

soap and water?

Method of evaluating reduction in infectivity

In general :

Virus culture with/without hand sanitizer

BUT

Human norovirus (HuNoV) "cannot" be cultured

- Human norovirus (HuNoV)
  - Quantitative RNA by RT-PCR with/without hand sanitizer
    - Presence of RNA does not necessarily mean infectivity
    - Sanitizers target capsid
  - Virus culture with/without hand sanitizer using surrogate (Feline Calicivirus FCV vs Murine Norovirus MNV)
    - Correlation between FCV and MNV variable
    - Correlation to RT-PCR poor

Sattar S et al. PLoS One 2011;6:e17340.
Park G et al. J Food Prot 2010; 2232-2238.
Kampf G et al. Clin Microbiol Rev 2004;17:863-893.

Alcohol-based hand rub (ABHR) v. Soap / water

- Finger pad testing – genomic copies determined by RT-PCR

	MuNoV1	HuNoV GI.4	HuNoV GII.4
Soap and water 30 sec	>5 $\log_{10}$	>6 $\log_{10}$	4 $\log_{10}$
Propanol hand-rub 30 sec	>1.2 $\log_{10}$	>2.6 $\log_{10}$	>3.3 $\log_{10}$

- "Washing hands with soap and water is better than using alcohol-based hand disinfectants in removing noroviruses from hands."

Tuladhar E et al. J Hosp Infect. 2015 Jul;90(3):226-34.

In vitro comparison

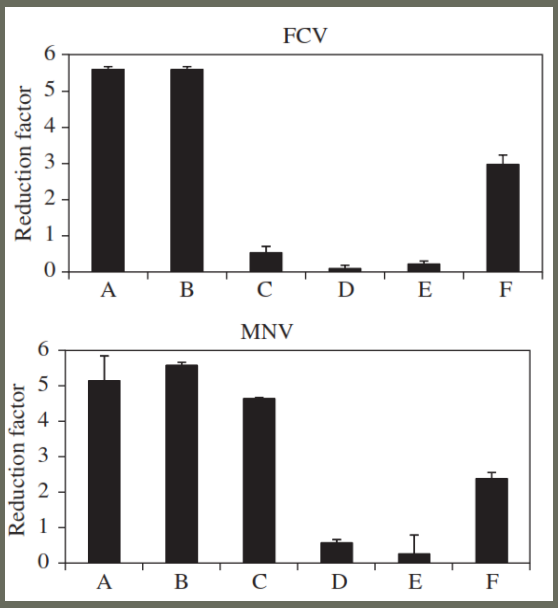
Tube suspension test :

ALCOHOL

A 45% ethanol
B 55% ethanol
C 90% ethanol

SOAP

D 1% triclosan soap
E 4% chlorhexidine soap
F Povidone iodine (0.8%) soap



Steinmann J et al. J Hosp Infect. 2012;82:277.

Use of alcohol-based hand sanitizers as a risk factor for norovirus outbreaks in long-term care facilities in northern New England: December 2006 to March 2007

Am J Infect Control 2011;39:296-301.

David D. Blaney, MD, MPH,[a,b] Elizabeth R. Daly, MPH,[b] Kathryn B. Kirkland, MD,[c] Jon Eric Tongren, PhD, MSPH,[a,d] Patsy Tassler Kelso, PhD,[e] and Elizabeth A. Talbot, MD[b,c]
Atlanta, Georgia; Concord and Hanover, New Hampshire; Augusta, Maine; and Burlington, Vermont

- Survey
  - 91 of 160 facilities (60%) responded
  - 61 facilities reported 73 outbreaks; 29 confirmed as norovirus
  - Self-report : no objective data on hand hygiene practices

Facilities reporting that staff were ***equally or more likely to use ABHS than soap and water*** for routine hand hygiene had **higher odds of a confirmed norovirus outbreak** than facilities with staff ***less likely to use ABHS*** (adjusted odds ratio, **6.06**; 95% confidence interval: 1.44-33.99).

This study suggests that preferential use of ABHS over soap and water for routine hand hygiene might be associated with *increased risk of norovirus* outbreaks in LTCFs.

Blaney D et al. Am J Infect Control 2011;39:296-301.

- Cross sectional study : association, not causation
- Multivariate analysis failed to take into account hand hygiene compliance
- Alternate hypothesis for association : better infection control = better detection
  - univariate analysis: having an IC practitioner associated with greater likelihood of confirmed HuNoV outbreak

"Researchers have the responsibility to draw valid conclusions from their studies."

Longtin Y et al. Am J Infect Control 2011; doi:10.1016/j.ajic.2011.05.002

Jury still out???

- WHO
  - "WHO experts recommend the use of alcohol-based handrubs during outbreaks of noroviral gastroenteritis."
- CDC
  - "... hand washing with soap and running water ... reduce norovirus contamination ... whereas hand sanitizers might serve as an effective adjunct ... but should not be considered a substitute..."

WHO. 2017. http://www.who.int/gpsc/tools/faqs/system_change/en/ Accessed 31 Oct 2017.
CDC. MMWR 2011;60(No. RR-3):1-15.

- NHMRC
  - "Hand hygiene should be performed using soap and water when *Clostridium difficile* or non-enveloped viruses such as norovirus are known or suspected to be present and gloves have not been worn."

NHMRC. Australian Guidelines for the Prevention and Control of Infection in Healthcare 2010. Commonwealth of Australia.

Isolation and exclusion

Should infected patients be isolated?

When should infected patients be removed from isolation?

When should infected staff be allowed back to work?

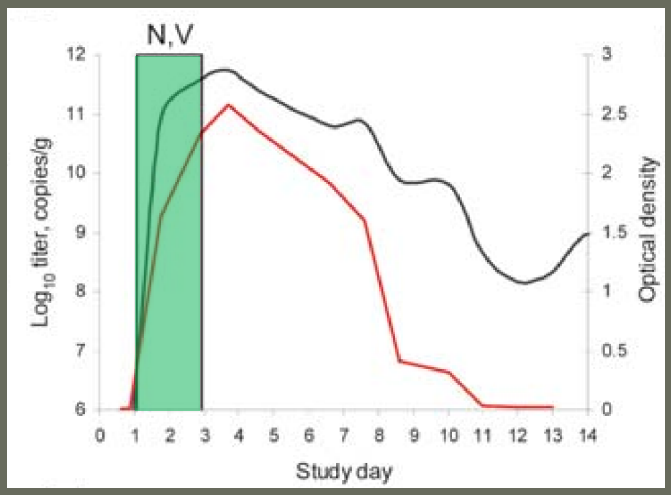
Norovirus infections in a tertiary care centre - individual cases do not necessarily lead to an outbreak

- Monitored exposed asymptomatic patients next to infectious patients for symptom development
- Of 102 patients exposed to 94 infectious patients only 11 patients developed typical norovirus symptoms - secondary attack rate only 10.8%
- **CONCLUSIONS:**

1. Patient-to-patient transmission is potentially overestimated
2. Future prevention strategies should consider personal risk factors of exposed patients

Kampmeier S et al. J Clin Virol. 2016 Nov;84:39-41.

- Peak viral shedding
  - –3 days post-symptom onset



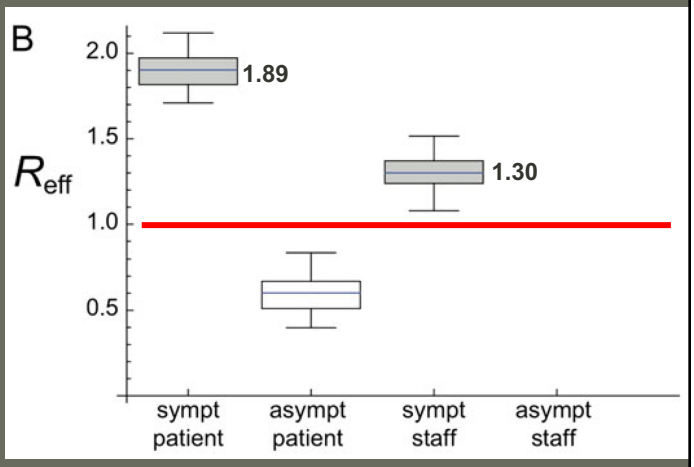
Atmar R et al. Emerg Inf Dis 2008;14:1553-1557.

- Asymptomatic shedding
  - –After symptomatic infection
    - Median 28 days [range 13-56 days] (months or years in immunosuppressed)
  - –Before symptomatic infection
    - 3 to 14 hr before symptom onset
  - –During asymptomatic infection
    - Prevalence : 1.0% to 49.2 %
    - ?? lower viral loads than symptomatic infection

Atmar R et al. Emerg Inf Dis 2008;14:1553-1557.
Utsumi T et al. Infect Genet Evol. 2017 Aug 24;55:1-7.
Rockx B et al. Clin Infect Dis 2002;35:246-53.
Barclay L et al. Clin Microbiol Infect 2014; 20:731.
Phillips G et al. BMC Infect Dis 2009;63.
Robilotti E et al. Clin Microbiol Rev 2015;28:134.

Nosocomial Transmission of Norovirus Is Mainly Caused by Symptomatic Cases

- Netherlands; 5 nosocomial outbreaks; n = 28
- Enhanced sampling – 65 extra cases (with and without symptoms; patients and staff)
- Shedding kinetics – prediction of infection onset
- Modelling of transmission pathways and reproduction numbers



Sukhrie FH et al. Clin Infect Dis. 2012 Apr;54(7):931-7.

Chronic Norovirus Infections

- Primary Immunodeficiency
  - Common Variable Immune deficiency
  - Severe Combined Immune deficiency
- Haematologic malignancies
- Stem Cell Transplantation
- Solid Organ Cancers
- Solid Organ transplant recipients
- HIV infection (advanced)

Bok K et al. Open Forum Infect Dis. 2016 Sep 8;3(3):ofw169.
Van Beek J et al. Clin Microbiol Infect. 2017 Apr;23(4):265.e9-265.e13.
Wingfield T et al. J Clin Virol. 2010 Nov;49(3):219-22.

Patient	Diagnosis	Shedding (days)	Genotype (variant)
A	PID/Hyper IgM, stem cell transplant	939	GII.4 (Apeldoorn 2007)
D	HIV/carcinoma CD4 = 8	205	GII.4 (New Orleans 2009)
E	PID/SCID	554	GII.4 (New Orleans 2009)
H	PID/CVID	641	GII.4 (New Orleans 2009)
I	Leukemia/ALL	417	GII.4 (New Orleans 2009)
M	PID/IRAK4 deficiency	385	GII.4 (not assigned)
O	PID/PLAID	304	GII.4 (not assigned)
P	PID/SCID	677	GII.2

NOROVIRUS SHEDDING DURATION

PID / SCT / Haem and solid organ cancer :
Median 485.5 (range 205 – 939)

Solid Organ Transplant :
Median 218 (range 32 – 1164) days

Bok K et al. Open Forum Infect Dis. 2016 Sep 8;3(3):ofw169.
Van Beek J et al. Clin Microbiol Infect. 2017 Apr;23(4):265.e9-265.e13.

Personal Protective Equipment

Should masks be worn by healthcare staff during patient care?

Organization / country	CDC USA	NHMRC Australia [current]	CDC USA [current]	Norovirus Working Party UK [current]
Year	2007	2010	2011	2012
Infection control Precautions	Standard	Contact + Droplet (if faecally incontinent)	Standard [sporadic] Contact [outbreak]	"Contact"
Remarks	Contact - if incontinent; Mask use if cleaning heavily soiled area	Mask use if patient symptomatic	Mask use if anticipated facial splash especially from vomiting patient	Mask only if there is a risk of droplets or aerosols

CDC. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings.
NHMRC. Australian Guidelines for the Prevention and Control of Infection in Healthcare 2010. Commonwealth of Australia.
MacCannell T. et al. Infect Control Hosp Epidemiol. 2011 Oct;32(10):939-69.
Health Protection Agency et al. Guidelines for the management of norovirus outbreaks in acute and community health and social care settings, 2012.

Person-to-person transmission

- Contact with faeces or vomitus
  - Direct contact
  - Fomites / environmental contamination
  - Aerosolisation / droplets

CDC. MMWR 2011;60(No. RR-3):1-15.

Airborne Norovirus

- 48 air samples collected during norovirus outbreaks in 8 healthcare facilities – 47% positive for virus

Location (air sample)	Positive / Total samples (%)	Range of Norovirus GII, Genomes/m3
Patients' rooms	14 / 26 (54%)	1.46×10^1–2.35×10^3
Nurses' stations	3 / 6 (50%)	1.35×10^1–1.22×10^2
Hallway/common areas	6 /16 (38%)	1.54×10^1–5.43×10^2

- HCW may inhale up to 60 copies of virus during a 5-minute stay in room – then ingest – may be sufficient to cause disease
- **Consider use of full airborne precautions**

Bonifait L et al. Clin Infect Dis. 2015 Aug 1;61(3):299-304.

CONCLUSION

- Much of what we do is based on low quality or 'difficult' evidence
- Guidelines are useful but don't get dogmatic
- More research is needed – well-designed to answer questions; not simply ad hoc
  - Basic science (cultivable)
  - Interventions
- Until then, follow guidelines plus use new data
- Lots of common sense!

Discussion paper

Infection control: Evidence-based common sense

Stephanie J. Dancer [a,b,*]

Infection, Disease & Health (2016) **21**, 147–153

- When compared against classical sciences, infection control is very much the '**new kid-on-the-block**'.
- …activities directed by infection prevention and control are more likely to reflect **'common sense' rather than robust evidence**…
- Common sense, however defined, **eventually turns into scientific evidence** at some stage but this progression relies upon continued accumulation, evaluation and integration of evidence by professionals and policy makers.

Thank you

chong-wei.ong@act.gov.au

Noroviruses - Looking at the Evidence for What We Know and What We Do
Dr Chong Wei Ong, Canberra Hospital and Health Services
Broadcast live from the 2017 conference of the Australasian College of Infection Control