

# Infection Control

## Evidence Update

Autumn 2017  
(Quarterly)



Respecting everyone  
Embracing change  
Recognising success  
Working together  
**Our hospitals.**



## Lunchtime Drop-in Sessions

*All sessions last one hour*

### November (13.00-14.00)

Thu 2nd	Literature searching
Fri 10th	Critical Appraisal
Mon 13th	Statistics
Tue 21st	Literature searching
29 <sup>th</sup> Wed	Critical Appraisal

### December (12.00-13:00)

7 <sup>th</sup> Thu	Statistics
15 <sup>th</sup> Fri	Literature Searching

## Your Outreach Librarian – Sarah Barrett

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## Updates

<p><b>NICE</b> National Institute for Health and Care Excellence</p>
<p><b><u><a href="#">Bronchiolitis in children</a></u></b>          Everything NICE has said on diagnosing and managing bronchiolitis in children in an interactive flowchart          NICE Pathway Published June 2015 Last updated July 2017</p> <p><b><u><a href="#">Flu vaccination: increasing uptake</a></u></b>          In development [GID-PHG96] Expected publication date: 10 January 2018          NICE guideline In development</p>
<p> <b>Cochrane Library</b></p>
<p>McCallum GB, Plumb EJ, Morris PS, Chang AB. <b><u><a href="#">Antibiotics for persistent cough or wheeze following acute bronchiolitis in children</a></u></b>. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD009834. DOI: 10.1002/14651858.CD009834.pub3.</p> <p>Nelson RL, Suda KJ, Evans CT. <b><u><a href="#">Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults</a></u></b>. Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD004610. DOI: 10.1002/14651858.CD004610.pub5.</p>
<p><b>UpToDate®</b>          OpenAthens login required. Register here: <a href="https://openathens.nice.org.uk/">https://openathens.nice.org.uk/</a></p>
<p><b><u><a href="#">Clostridium difficile infection: Prevention and control</a></u></b></p> <p>Authors: <a href="#">L Clifford McDonald, MD</a>; <a href="#">Preeta K Kutty, MD, MPH</a></p>

Literature review current through: Sep 2017. | This topic last updated: Jul 25, 2017.

[Bronchiolitis in infants and children: Treatment, outcome, and prevention](#)

Authors: [Pedro A Piedra, MD](#); [Ann R Stark, MD](#)

Literature review current through: Sep 2017. | This topic last updated: Aug 01, 2017.

[Bronchiolitis in adults](#)

Author: [Talmadge E King, Jr, MD](#)

Literature review current through: Sep 2017. | This topic last updated: Sep 14, 2017.

[Respiratory syncytial virus infection: Prevention](#)

Authors: [Frederick E Barr, MD](#); [Barney S Graham, MD, PhD](#)

Literature review current through: Sep 2017. | This topic last updated: Sep 14, 2017.

[Overview of control measures for prevention of surgical site infection in adults](#)

Authors: [Deverick J Anderson, MD, MPH](#); [Daniel J Sexton, MD](#)

Literature review current through: Sep 2017. | This topic last updated: Oct 24, 2017.

[Seasonal influenza in children: Prevention and treatment with antiviral drugs](#)

Author: [Flor M Munoz, MD, MSc](#)

Literature review current through: Sep 2017. | This topic last updated: Oct 20, 2017.

[Seasonal influenza in children: Prevention with vaccines](#)

Author: [Flor M Munoz, MD, MSc](#)

Literature review current through: Sep 2017. | This topic last updated: Oct 09, 2017.

[Norovirus](#)

Authors: [David O Matson, MD, PhD](#); [Miguel G O'Ryan, MD](#); [Neil R Blacklow, MD](#)

Literature review current through: Sep 2017. | This topic last updated: Jul 25, 2017.

## Recent Database Articles

Below is a selection of articles recently added to the healthcare databases, grouped in the following categories:

- **C Difficile**
- **Bronchiolitis**
- **RSV**
- **Surgical Site Infection**
- **Influenza**
- **Norovirus**

If you would like any of the following articles in full text, or if you would like a more focused search on your own topic, then get in touch:

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### C Difficile

#### 1. A systematic review of Clostridium difficile infection following reversal of ileostomy.

**Author(s):** Harries, R L; Ansell, J; Codd, R J; Williams, G L

**Source:** Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland; Oct 2017; vol. 19 (no. 10); p. 881-887

**Publication Type(s):** Journal Article

**Abstract:**AIMThe incidence of Clostridium difficile infection (CDI) has been reported to be as high as 4% following ileostomy reversal. CDI can be associated with significant morbidity. A systematic review on this subject has not been previously reported; our aim was to review the literature to establish incidence and to evaluate the factors that may contribute to an increased risk of CDI following ileostomy reversal.METHODA systematic review of Ovid, Embase and Medline was undertaken. Search terms included C. difficile, reversal of ileostomy and ileostomy closure. Articles were included where at least one case of C. difficile-associated diarrhoea following reversal of defunctioning ileostomy was reported. Data extraction for articles was performed by two authors, using predefined data fields. The primary outcome measure was incidence of CDI amongst patients undergoing ileostomy reversal. Secondary outcomes were defunctioning time, antibiotic regime, acid suppression, time to onset of symptoms and study conclusions including colectomy and mortality rate.RESULTSEleven articles were included (five case reports and six cohort studies). The overall incidence of CDI was 1.8% (242/13 728). The mean defunctioning time was 8.7 months (range 6-12). A variety of antibiotic regimes were described. Mean time to onset of symptoms was 6 days (range 3-14). Use of acid suppression, colectomy or mortality rate were frequently not reported.CONCLUSIONCDI should be recognized as a potentially life-threatening complication of ileostomy closure. Careful consideration should be given to peri-operative antibiotic regime, acid suppression, timing of reversal and appropriate preoperative counselling of patients.

## 2. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis.

**Author(s):** Baur, David; Gladstone, Beryl Primrose; Burkert, Francesco; Carrara, Elena; Foschi, Federico; Döbele, Stefanie; Tacconelli, Evelina

**Source:** The Lancet. Infectious diseases; Sep 2017; vol. 17 (no. 9); p. 990-1001

**Publication Type(s):** Meta-analysis Journal Article Review

Available at [The Lancet. Infectious diseases](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:**BACKGROUND Antibiotic stewardship programmes have been shown to reduce antibiotic use and hospital costs. We aimed to evaluate evidence of the effect of antibiotic stewardship on the incidence of infections and colonisation with antibiotic-resistant bacteria. METHODS For this systematic review and meta-analysis, we searched PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Web of Science for studies published from Jan 1, 1960, to May 31, 2016, that analysed the effect of antibiotic stewardship programmes on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infections in hospital inpatients. Two authors independently assessed the eligibility of trials and extracted data. Studies involving long-term care facilities were excluded. The main outcomes were incidence ratios (IRs) of target infections and colonisation per 1000 patient-days before and after implementation of antibiotic stewardship. Meta-analyses were done with random-effect models and heterogeneity was calculated with the I<sup>2</sup> method. FINDINGS We included 32 studies in the meta-analysis, comprising 9 056 241 patient-days and 159 estimates of IRs. Antibiotic stewardship programmes reduced the incidence of infections and colonisation with multidrug-resistant Gram-negative bacteria (51% reduction; IR 0.49, 95% CI 0.35-0.68; p<0.0001), extended-spectrum  $\beta$ -lactamase-producing Gram-negative bacteria (48%; 0.52, 0.27-0.98; p=0.0428), and methicillin-resistant *Staphylococcus aureus* (37%; 0.63, 0.45-0.88; p=0.0065), as well as the incidence of *C difficile* infections (32%; 0.68, 0.53-0.88; p=0.0029). Antibiotic stewardship programmes were more effective when implemented with infection control measures (IR 0.69, 0.54-0.88; p=0.0030), especially hand-hygiene interventions (0.34, 0.21-0.54; p<0.0001), than when implemented alone. Antibiotic stewardship did not affect the IRs of vancomycin-resistant enterococci and quinolone-resistant and aminoglycoside-resistant Gram-negative bacteria. Significant heterogeneity between studies was detected, which was partly explained by the type of interventions and co-resistance patterns of the target bacteria. INTERPRETATION Antibiotic stewardship programmes significantly reduce the incidence of infections and colonisation with antibiotic-resistant bacteria and *C difficile* infections in hospital inpatients. These results provide stakeholders and policy makers with evidence for implementation of antibiotic stewardship interventions to reduce the burden of infections from antibiotic-resistant bacteria. FUNDING German Center for Infection Research.

## 3. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection.

**Author(s):** Quraishi, M N; Widlak, M; Bhala, N; Moore, D; Price, M; Sharma, N; Iqbal, T H

**Source:** Alimentary pharmacology & therapeutics; Sep 2017; vol. 46 (no. 5); p. 479-493

**Publication Type(s):** Journal Article Review

**Abstract:**BACKGROUND *Clostridium difficile* infection (CDI) is the commonest nosocomial cause of diarrhoea. Faecal microbiota transplantation (FMT) is an approved treatment for recurrent or refractory CDI but there is uncertainty about its use. AIM To evaluate the efficacy of FMT in treating recurrent and refractory CDI and investigate outcomes from modes of delivery and preparation. METHODS A systematic review and meta-analysis was performed. MEDLINE, EMBASE,

CINAHL, Cochrane Library, trial registers and conference proceedings were searched. Studies on FMT in recurrent and refractory CDI were included. The primary outcome was clinical resolution with subgroup analyses of modes of delivery and preparation. Random effects meta-analyses were used to combine data. RESULT Thirty seven studies were included; seven randomised controlled trials and 30 case series. FMT was more effective than vancomycin (RR: 0.23 95%CI 0.07-0.80) in resolving recurrent and refractory CDI. Clinical resolution across all studies was 92% (95%CI 89%-94%). A significant difference was observed between lower GI and upper GI delivery of FMT 95% (95%CI 92%-97%) vs 88% (95%CI 82%-94%) respectively (P=.02). There was no difference between fresh and frozen FMT 92% (95%CI 89%-95%) vs 93% (95%CI 87%-97%) respectively (P=.84). Administering consecutive courses of FMT following failure of first FMT resulted in an incremental effect. Donor screening was consistent but variability existed in recipient preparation and volume of FMT. Serious adverse events were uncommon. CONCLUSION Faecal microbiota transplantation is an effective treatment for recurrent and refractory Clostridium difficile infection, independent of preparation and route of delivery.

#### **4. A randomized controlled trial of probiotics for Clostridium difficile infection in adults (PICO).**

**Author(s):** Barker, Anna K; Duster, Megan; Valentine, Susan; Hess, Timothy; Archbald-Pannone, Laurie; Guerrant, Richard; Safdar, Nasia

**Source:** The Journal of antimicrobial chemotherapy; Aug 2017

**Publication Type(s):** Journal Article

**Abstract:** Background Clostridium difficile is the most common cause of hospital-acquired infections, responsible for >450 000 infections annually in the USA. Probiotics provide a promising, well-tolerated adjunct therapy to standard C. difficile infection (CDI) treatment regimens, but there is a paucity of data regarding their effectiveness for the treatment of an initial CDI. Objectives We conducted a pilot randomized controlled trial of 33 participants from February 2013 to February 2015 to determine the feasibility and health outcomes of adjunct probiotic use in patients with an initial mild to moderate CDI. Methods The intervention was a 28 day, once-daily course of a four-strain oral probiotic capsule containing Lactobacillus acidophilus NCFM, Lactobacillus paracasei Lpc-37, Bifidobacterium lactis Bi-07 and B. lactis BI-04. The control placebo was identical in taste and appearance. Registered at clinicaltrials.gov: trial registration number = NCT01680874. Results Probiotic adjunct therapy was associated with a significant improvement in diarrhoea outcomes. The primary duration of diarrhoea outcome (0.0 versus 1.0 days; P = 0.039) and two exploratory outcomes, total diarrhoea days (3.5 versus 12.0 days; P = 0.005) and rate of diarrhoea (0.1 versus 0.3 days of diarrhoea/stool diary days submitted; P = 0.009), all decreased in participants with probiotic use compared with placebo. There was no significant difference in the rate of CDI recurrence or functional improvement over time between treatment groups. Conclusions Probiotics are a promising adjunct therapy for treatment of an initial CDI and should be further explored in a larger randomized controlled trial.

#### **5. An updated Meta-Analysis of controlled observational studies: proton-pump inhibitors and risk of Clostridium difficile infection.**

**Author(s):** Cao, Fei; Chen, Chunxiang; Wang, Min; Liao, Hairong; Wang, Meixiang; Hua, Shuizhen; Huang, Bin; Xiong, Yan; Zhang, Jieyu; Xu, Yanliang

**Source:** The Journal of hospital infection; Aug 2017

**Publication Type(s):** Journal Article Review

**Abstract:** BACKGROUND Attention has recently been directed toward a plausible link between Clostridium difficile infection (CDI) and proton-pump inhibitors (PPIs). However, the results of

studies on the association between CDI and PPI remain controversial. **METHODS** We searched the literature from their inception to December 2016 without restriction of language. We included all controlled observational studies examining the association between acid suppressive therapy and CDI. **RESULTS** Pooled analysis of 50 studies showed a significant association between PPI use and risk of developing CDI, OR 1.26, (1.12-1.39) as compared with non-users. When stratified by study patients, the relative risk of hospital-acquired CDI and community-associated CDI were 1.29(1.14-1.44) and 1.17(0.74-1.59). After restricting the studies according to hospital department, the relative risks of hospital-acquired CDI in ICUs and general wards were 1.43(0.74-2.11) and 1.29(1.13-1.45). By implementing cumulative meta-analysis, it was clear that earlier trials of CDI conducted in the early 2000s demonstrated a high degree of heterogeneity and a high percentage of negative results. Since 2011, the overall association between PPI use and risk of developing CDI has remained relatively stable within an effect size between OR 1.20 and 1.26. **CONCLUSION** Our findings indicate a significant associated risk of incident CDI among PPI users, especially in general ward patients. The totality of evidence, when given using cumulative meta-analysis, showed that further trials are unlikely to overturn this positive result. Therefore establishing a guideline for the use of PPI may help in the future with the control of CDI.

## **6. Faecal microbiota transplantation for *Clostridium difficile*-associated diarrhoea: a systematic review of randomised controlled trials.**

**Author(s):** Moayyedi, Paul; Yuan, Yuhong; Baharith, Harith; Ford, Alexander C

**Source:** The Medical journal of Australia; Aug 2017; vol. 207 (no. 4); p. 166-172

**Publication Type(s):** Journal Article

**Abstract:** **OBJECTIVES** Faecal microbiota transplantation (FMT) has emerged as a useful approach for treating *Clostridium difficile*-associated diarrhoea (CDAD). Randomised controlled trials (RCTs) have recently evaluated its effectiveness, but systematic reviews have focused on evidence from case series. We therefore conducted a systematic review and meta-analysis of RCTs evaluating the effectiveness of FMT for treating CDAD. **STUDY DESIGN** We included RCTs that primarily recruited adults with CDAD and compared the effectiveness of FMT with that of placebo, antibiotic therapy, or autologous stool transplantation, or compared different preparations or modes of delivery of FMT. Dichotomous symptom data were pooled to calculate a relative risk (RR) of CDAD persisting after therapy, and the number needed to treat (NNT). **DATA SOURCES** MEDLINE, EMBASE, and the Cochrane Controlled Trials Register and Database of Systematic Reviews were searched to 6 February 2017. **DATA SYNTHESIS** We identified ten RCTs that evaluated the treatment of a total of 657 patients with CDAD. Five RCTs compared FMT with placebo (including autologous FMT) or vancomycin treatment (total of 284 patients); FMT was statistically significantly more effective (RR, 0.41; 95% CI, 0.22-0.74; NNT, 3; 95% CI, 2-7). Heterogeneity across studies was significant ( $I^2 = 61\%$ ); this heterogeneity was attributable to the mode of delivery of FMT, and to the therapy being more successful in European than in North American trials. The other five RCTs evaluated different approaches to FMT therapy. Frozen FMT preparations were as efficacious as fresh material in one RCT, but the numbers of patients in the remaining RCTs were too small to allow definitive conclusions. **CONCLUSIONS** Moderate quality evidence from RCT trials indicates that FMT is more effective in patients with CDAD than vancomycin or placebo. Further investigations are needed to determine the best route of administration and FMT preparation.

## **7. Is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation in patients with recurrent or refractory *Clostridium difficile* infection: A meta-analysis?**

**Author(s):** Tang, Guihua; Yin, Wen; Liu, Wenen



**Source:** Diagnostic microbiology and infectious disease; Aug 2017; vol. 88 (no. 4); p. 322-329

**Publication Type(s):** Journal Article Review

**PubMedID:** 28602517

**Abstract:** Fecal microbiota transplantation (FMT) is a remarkably efficacious therapy for recurrent or refractory *Clostridium difficile* infection (CDI), but not standardized. This work is to determine whether frozen FMT is as effective as fresh FMT. Meta-analysis showed that frozen FMT was as effective as fresh FMT, both pooled first effective rate (65.0% (95% CI 57.0-73.0%) vs. 65.0% (95% CI 57.0-73.0%),  $P=0.962$ ) and pooled second effective rate (95.0% (95% CI 91.0-99.0%) vs. 95.0% (95% CI 92.0-99.0%),  $P=0.880$ ). In conclusion, among patients with recurrent or refractory CDI, frozen FMT is as effective as fresh FMT. Considering potential advantages of performing frozen FMT, it is a reasonable option to select frozen FMT.

### **8. Polyethylene glycol intestinal lavage in addition to usual antibiotic treatment for severe *Clostridium difficile* colitis: a randomised controlled pilot study.**

**Author(s):** McCreery, Greig; Jones, Philip M; Kidane, Biniam; DeMelo, Vanessa; Mele, Tina; ERASE C. *difficile* (Early Rescue from Acute SEvere *Clostridium difficile*) Trials Group

**Source:** BMJ open; Jul 2017; vol. 7 (no. 7); p. e016803

**Publication Type(s):** Journal Article

Available at [BMJ open](#) - from HighWire - Free Full Text

Available at [BMJ open](#) - from Europe PubMed Central - Open Access

**Abstract:** INTRODUCTION *Clostridium difficile* infections (CDI) are common, costly and potentially life threatening. Most CDI will respond to antibiotic therapy, but 3%-10% of all patients with CDI will progress to a severe, life-threatening course. Complete removal of the large bowel is indicated for severe CDI. However, the 30-day mortality following surgical intervention for severe CDI ranges from 20% to 70%. A less invasive approach using surgical faecal diversion and direct colonic lavage with polyethylene glycol (PEG) and vancomycin has demonstrated a relative mortality reduction of approximately 50%. As an alternative to these operative approaches, we propose to treat patients with bedside intestinal lavage with PEG and vancomycin instillation via nasojejunal tube, in addition to usual antibiotic management. Preliminary data collected by our research group are encouraging. METHODS AND ANALYSIS We will conduct a 1-year, single-centre, pilot randomised controlled trial to study this new treatment strategy for patients with severe CDI and additional risk factors for fulminant or complicated infection. After informed consent, patients with severe-complicated CDI without immediate indication for surgery will be randomised to either usual antibiotic treatment or usual antibiotic treatment with the addition of 8 L of PEG lavage via nasojejunal tube. This pilot trial will evaluate our eligibility and enrolment rate, protocol compliance and adverse event rates and provide further data to inform a more robust sample size calculation and protocol modifications for a definitive multicentre trial design. Based on historical data, we anticipate enrolling approximately 24 patients during the 1-year pilot study period. As a pilot study, data will be reported in aggregate. Between-group differences will be assessed in a blinded fashion for evidence of harm, and to further refine our sample size calculation. ETHICS AND DISSEMINATION This study protocol has been reviewed and approved by our local institutional review board. Results of the pilot trial and subsequent main trial will be submitted for publication in a peer-reviewed journal. TRIAL REGISTRATION NUMBER NCT02466698; Pre-results.

### 9. Magnitude and direction of the association between *Clostridium difficile* infection and proton pump inhibitors in adults and pediatric patients: a systematic review and meta-analysis.

**Author(s):** Oshima, Tadayuki; Wu, Liping; Li, Min; Fukui, Hirokazu; Watari, Jiro; Miwa, Hiroto

**Source:** Journal of gastroenterology; Jul 2017

**Publication Type(s):** Journal Article

**Abstract:**BACKGROUND *Clostridium difficile* infection (CDI) is a cause of increased morbidity and health care costs among hospitalized patients. Proton pump inhibitors (PPIs) are mainly used for the treatment of acid-related upper gastrointestinal diseases. The aim of the study was to assess the risks associated with initial and recurrent CDI in adult and pediatric patients treated with PPIs. METHODS A systematic search was performed using PubMed (Medline), Embase, and Web of Science with the following search terms: ("proton pump inhibitor," "PPI," or "acid suppression") AND ("infection," "diarrhea," "diarrhoea," "colitis," or "disease") AND ("*Clostridium difficile*"). Meta-analysis was performed using Revman5.3 software. Pooled odds ratios (ORs) presented as standard plots with 95% confidence intervals (CIs) were determined. RESULTS Sixty-seven eligible studies were selected. PPI use was significantly associated with risk of CDI (OR 2.34, 95% CI 1.94-2.82;  $P < 0.00001$ ). Pooled data from twelve studies demonstrated a significant association between PPI use and recurrent CDI (OR 1.73, 95% CI 1.39-2.15;  $P = 0.02$ ). Subgroup analysis revealed significant associations between PPI use and an increased incidence of CDI among adult (OR 2.30, 95% CI 1.89-2.80;  $P < 0.00001$ ) and pediatric (OR 3.00, 95% CI 1.44-6.23;  $P < 0.00001$ ) patients. CONCLUSIONS PPI use was associated with CDI in adult and pediatric patients, and with recurrent CDI. Although many risk factors are associated with the occurrence and recurrence of CDI, consideration should be given to not administering PPIs at any age if they are unnecessary.

### 10. Susceptibilities of clinical *Clostridium difficile* isolates to antimicrobials: a systematic review and meta-analysis of studies since 1970.

**Author(s):** Khanafer, N; Daneman, N; Greene, T; Simor, A; Vanhems, P; Samore, M; Brown, K A

**Source:** Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases; Jul 2017

**Publication Type(s):** Journal Article Review

**Abstract:**OBJECTIVES Although exposure to antibiotics can cause *Clostridium difficile* infection, certain antibiotics are used to treat *C. difficile*. Measurements of antimicrobial *C. difficile* activity could help to identify antibiotic risk and emergent resistance. Here, we describe publication patterns relating to *C. difficile* susceptibilities and estimate minimum inhibitory concentrations (MIC) for antibiotic classes in the published literature between January 1970 and June 2014. METHODS We queried PUBMED and EMBASE for studies reporting antibiotic *C. difficile* MIC in English or French. We used mixed-effects models to obtain pooled estimates of antibiotic class median MIC (MIC<sub>50</sub>), 90th percentile of MIC (MIC<sub>90</sub>), and MIC<sub>90</sub>:MIC<sub>50</sub> ratio. RESULTS Our search identified 182 articles that met our inclusion criteria, of which 27 were retained for meta-analysis. Aminoglycosides (MIC<sub>50</sub> 120 mg/L, 95% CI 62-250), 3rd (MIC<sub>50</sub> 75 mg/L, 95% CI 39-130) and 2nd generation cephalosporins (MIC<sub>50</sub> 64 mg/L, 95% CI 27-140) had the least *C. difficile* activity. Rifamycins (MIC<sub>50</sub> 0.034 mg/L, 95% CI 0.012-0.099) and tetracyclines (MIC<sub>50</sub> 0.29 mg/L, 95% CI 0.054-1.7) had the highest level of activity. The activity of 3rd generation cephalosporins was more than three times lower than that of 1st generation agents (MIC<sub>50</sub> 19 mg/L, 95% CI 7.0-54). Time-trends in MIC<sub>50</sub> were increasing for carbapenems (70% increase per 10 years) while decreasing for tetracyclines (51% decrease per 10 years). CONCLUSIONS We found a 3500-fold variation in antibiotic *C. difficile* MIC<sub>50</sub>, with aminoglycosides as the least active agents and rifamycins as the most active. Further research is needed to determine how in vitro measures can help assess patient *C. difficile* risk and guide antimicrobial stewardship.

## Bronchiolitis

### 1. Modifiable risk factors associated with bronchiolitis.

**Author(s):** Nenna, Raffaella; Cutrera, Renato; Frassanito, Antonella; Alessandroni, Claudia; Nicolai, Ambra; Cangiano, Giulia; Petrarca, Laura; Arima, Serena; Caggiano, Serena; Ullman, Nicola; Papoff, Paola; Bonci, Enea; Moretti, Corrado; Midulla, Fabio

**Source:** Therapeutic advances in respiratory disease; Oct 2017; vol. 11 (no. 10); p. 393-401

**Publication Type(s):** Journal Article

**Abstract:**BACKGROUND We sought to clarify possibly modifiable risk factors related to pollution responsible for acute bronchiolitis in hospitalized infants. METHODS For this observational study, we recruited 213 consecutive infants with bronchiolitis (cases: median age: 2 months; age range: 0.5-12 months; boys: 55.4%) and 213 children aged <3 years (controls: median age: 12 months; age range: 0.5-36 months; boys: 54.5%) with a negative medical history for lower respiratory tract diseases hospitalized at 'Sapienza' University Rome and IRCCS Bambino Gesù Hospital. Infants' parents completed a standardized 53-item questionnaire seeking information on social-demographic and clinical characteristics, indoor pollution, eating habits and outdoor air pollution. Multivariate logistic regression analyses were run to assess the independent effect of risk factors, accounting for confounders and effect modifiers. RESULTS In the 213 hospitalized infants the questionnaire identified the following risk factors for acute bronchiolitis: breastfeeding  $\geq 3$  months (OR: 2.1, 95% confidence interval [CI]: 1.2-3.6), presence of older siblings (OR: 2.8, 95% CI: 1.7-4.7),  $\geq 4$  cohabitants (OR: 1.5, 95% CI: 1.1-2.1), and using seed oil for cooking (OR: 1.7, 95% CI: 1.2-2.6). Having renovated their home in the past 12 months and concurrently being exposed daily to smoking, involving more than 11 cigarettes and two or more smoking cohabitants, were more frequent factors in cases than in controls ( $p = 0.021$  and  $0.05$ ), whereas self-estimated proximity to road and traffic was similar in the two groups. CONCLUSIONS We identified several risk factors for acute bronchiolitis related to indoor and outdoor pollution, including inhaling cooking oil fumes. Having this information would help public health authorities draw up effective preventive measures - for example, teach mothers to avoid handling their child when they have a cold and eliminate exposure to second-hand tobacco smoke.

### 2. Clinical definition of respiratory viral infections in young children and potential bronchiolitis misclassification.

**Author(s):** Megalaa, Rosemary; Perez, Geovanny F; Kilaikode-Cheruveettara, Sasikumar; Kotwal, Nidhi; Rodriguez-Martinez, Carlos E; Nino, Gustavo

**Source:** Journal of investigative medicine : the official publication of the American Federation for Clinical Research; Sep 2017

**Publication Type(s):** Journal Article

**Abstract:** Viral respiratory infections are often grouped as a single respiratory syndrome named 'viral bronchiolitis', independently of the viral etiology or individual risk factors. Clinical trials and guidelines have used a more stringent definition of viral bronchiolitis, including only the first episode of wheezing in children less than 12 months of age without concomitant respiratory comorbidities. There is increasing evidence suggesting that this definition is not being followed by pediatric care providers, but it is unclear to what extent viral respiratory infections are currently misclassified as viral bronchiolitis using standard definitions. We conducted a retrospective analysis of hospitalized young children ( $\leq 3$  years) due to viral respiratory infections. Bronchiolitis was defined as the first wheezing episode less than 12 months of age. Demographic variables and comorbidities were obtained by electronic medical record review. The study comprised a total of 513 hospitalizations

(n=453). Viral bronchiolitis was diagnosed in 144 admissions (28.1%). Notably, we identified that the majority of children diagnosed with bronchiolitis (63%) were misclassified as they had prior episodes of wheezing. Many children with bronchiolitis misclassification had significant comorbidities, including prematurity (51%), neuromuscular conditions (9.8%), and congenital heart disease (9.8%). Misclassification of bronchiolitis is a common problem that may lead to inappropriate management of viral respiratory infections in young children. A comprehensive approach that takes into consideration viral etiology and individual risk factors may lead to a more accurate clinical assessment of this condition and would potentially prevent bronchiolitis misclassification.

### **3. Immune and inflammatory response in bronchiolitis due to respiratory Syncytial Virus and Rhinovirus infections in infants.**

**Author(s):** Vandini, Silvia; Calamelli, Elisabetta; Faldella, Giacomo; Lanari, Marcello

**Source:** Paediatric respiratory reviews; Sep 2017; vol. 24 ; p. 60-64

**Publication Type(s):** Journal Article Review

**Abstract:** Bronchiolitis is a common disease in infancy, mostly due to Respiratory Syncytial Virus and Rhinovirus. In addition to acute infection, viral bronchiolitis is responsible for sequelae including recurrent wheezing and asthma. The analysis of the viral characteristics and of the pathogenesis of the infection shows differences between the two viruses that may be helpful for the development of therapies and preventive strategies.

### **4. Continuous Positive Airway Pressure in Bronchiolitis: A Randomized Controlled Trial.**

**Author(s):** Lal, Sandeep Narayan; Kaur, Jaspreet; Anthwal, Pooja; Bahl, Pinky; Puliyeel, Jacob M

**Source:** Indian pediatrics; Sep 2017

**Publication Type(s):** Journal Article

**Abstract:** OBJECTIVE To evaluate the efficacy of nasal continuous positive airway pressure (nCPAP) in decreasing respiratory distress in bronchiolitis. DESIGN Randomized controlled trial. SETTING Tertiary-care hospital in New Delhi, India. PARTICIPANTS 72 infants (age <1y) hospitalized with a clinical diagnosis of bronchiolitis were randomized to receive standard care, or nCPAP in addition to standard care, in the first hour after admission. 23 parents refused to give consent for participation. 2 infants did not tolerate nCPAP. INTERVENTION The study was continued for an hour. If nCPAP was not tolerated or the distress increased the infant was switched to standard care. Analysis was done on intention to treat basis. MAIN OUTCOME MEASURES Change in respiratory rate, Silverman-Anderson score and a Modified Pediatric Society of New Zealand Severity Score were compared between the 2 groups after 1 hour of treatment. RESULTS 14 out of 32 in nCPAP group had change in respiratory rate  $\geq 10$ , while 5 out of 35 had change in respiratory rate  $\geq 10$  with standard care ( $P=0.008$ ). The mean (SD) change in respiratory rate following nCPAP was 8.03 (5.8), while with standard care it was 5.11 (3.98) ( $P=0.018$ ). Mean (SD) change in Silverman-Anderson score following nCPAP was 0.78 (0.87), while with standard care it was 0.39 (0.73) ( $P=0.029$ ). Mean (SD) change in Modified Pediatric Society of New Zealand Severity Score following nCPAP was 2.5 (3.01) compared to 1.08 (1.3) ( $P=0.012$ ) with standard care. CONCLUSION nCPAP helped reduce respiratory distress significantly compared to standard care.

## 5. Viral bronchiolitis in young infants: new perspectives for management and treatment.

**Author(s):** Caballero, Mauricio T; Polack, Fernando P; Stein, Renato T

**Source:** Jornal de pediatria; Aug 2017

**Publication Type(s):** Journal Article Review

Available at [Jornal de pediatria](#) - from EBSCO (MEDLINE Complete)

**Abstract:**OBJECTIVEThe aim of this review was to address advances in management and treatment of acute viral bronchiolitis in infants.SOURCESA systematic review search was made including all articles published in English between 2010 and 2017, and available in the electronic databases PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) and specialized register of the Acute Respiratory Infections Group (Cochrane review group). The following MESH terms in English were included, using different Boolean operators for the search strategy: "bronchiolitis, viral," "diagnosis," "epidemiology," "etiology," "therapy," "virology," "prevention and control," "respiratory syncytial virus, human." Additional filters were used.SUMMARY OF FINDINGSFew effective interventions are recommended for the management of RSV bronchiolitis in young infants. The main goal is to ensure an adequate oxygen supplementation and fluid balance whenever deemed necessary. Hypertonic saline nebulization is helpful only for hospitalized infants. Numerous antiviral drugs and specific vaccines for RSV are under evaluation and foretell advances in disease management in the near future.CONCLUSIONA number of promising new technologies are advancing in the field. Until new interventions became feasible, early detection and modification of preventable risk factors is essential to improve outcomes.

## 6. Antibiotics for persistent cough or wheeze following acute bronchiolitis in children.

**Author(s):** McCallum, Gabrielle B; Plumb, Erin J; Morris, Peter S; Chang, Anne B

**Source:** The Cochrane database of systematic reviews; Aug 2017; vol. 8 ; p. CD009834

**Publication Type(s):** Research Support, Non-u.s. Gov't Meta-analysis Journal Article Review

**Abstract:**BACKGROUNDBronchiolitis is a common acute respiratory condition with high prevalence worldwide. This clinically diagnosed syndrome is manifested by tachypnoea (rapid breathing), with crackles or wheeze in young children. In the acute phase of bronchiolitis ( $\leq 14$  days), antibiotics are not routinely prescribed unless the illness is severe or a secondary bacterial infection is suspected. Although bronchiolitis is usually self-limiting, some young children continue to have protracted symptoms (e.g. cough and wheezing) beyond the acute phase and often re-present to secondary care.OBJECTIVESTo compare the effectiveness of antibiotics versus controls (placebo or no treatment) for reducing or treating persistent respiratory symptoms following acute bronchiolitis within six months of acute illness.SEARCH METHODSWe searched the following databases: the Cochrane Airways Group Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), Embase (Ovid), the World Health Organization (WHO) trial portal, the Australian and New Zealand Clinical Trials Registry, and ClinicalTrials.gov, up to 26 August 2016.SELECTION CRITERIAWe included randomised controlled trials (RCTs) comparing antibiotics versus controls (placebo or no treatment) given in the post-acute phase of bronchiolitis ( $> 14$  days) for children younger than two years with a diagnosis of bronchiolitis.DATA COLLECTION AND ANALYSISTwo review authors independently assessed studies against predefined criteria, and selected, extracted, and assessed data for inclusion. We contacted trial authors for further information.MAIN RESULTSIn this review update, we added one study with 219 children. A total of two RCTs with 249 children ( $n = 240$  completed) were eligible for inclusion in this review. Both studies contributed to our primary and secondary outcomes, but we assessed the quality of evidence for our three primary outcomes as low, owing to the small numbers of studies and participants; and high attrition in one of the studies. Data show no significant differences between treatment groups for our primary outcomes: proportion of children ( $n = 249$ ) who had persistent

symptoms at follow-up (odds ratio (OR) 0.69, 95% confidence interval (CI) 0.37 to 1.28; fixed-effect model); and number of children (n = 240) rehospitalised with respiratory illness within six months (OR 0.54, 95% CI 0.05 to 6.21; random-effects model). We were unable to analyse exacerbation rate because studies used different methods to report this information. Data showed no significant differences between treatment groups for our secondary outcome: proportion of children (n = 240) with wheeze at six months (OR 0.47, 95% CI 0.06 to 3.95; random-effects model). One study reported bacterial resistance, but only at 48 hours (thus with limited applicability for this review). Another study reported adverse events from which all children recovered and remained in the study.

**AUTHORS' CONCLUSIONS** Current evidence is insufficient to inform whether antibiotics should be used to treat or prevent persistent respiratory symptoms in the post-acute bronchiolitis phase. Future RCTs are needed to evaluate the efficacy of antibiotics for reducing persistent respiratory symptoms. This is particularly important in populations with high acute and post-acute bronchiolitis morbidity (e.g. indigenous populations in Australia, New Zealand, and the USA).

### **7. The role of viruses in post-bronchiolitis wheezing/asthma development-a systematic review and meta-analysis**

**Author(s):** Makrinioti H.; Bush A.; Xepapadaki P.; Malietzis G.; Johnston S.; Tsolia M.; Papaevangelou V.; Papadopoulos N.

**Source:** Allergy: European Journal of Allergy and Clinical Immunology; Aug 2017; vol. 72 ; p. 492

**Publication Type(s):** Conference Abstract

**Abstract:** Introduction: Acute viral infection is a leading cause of severe wheezing during infancy and one of the most frequent causes of hospitalization in children less than 2 years old. The incidence of childhood asthma has risen within the last years. There is increasing evidence that acute viral infection during infancy can be directly linked to the development and/or incidence of childhood asthma. Whether viral induced acute wheeze causes later asthma, or is merely a marker of an asthmatic predisposition is unclear. So for example, severe respiratory syncytial virus (RSV) is considered by some, but by no means all, to be causative of later asthma. Objectives: to investigate the association between specific viruses detected in infants with acute bronchiolitis and the development of pre-school wheezing and/or school-age asthma Results: Infants suffering with RSV-bronchiolitis were not more likely to develop asthma as compared to infants suffering with rhinovirus (RV) bronchiolitis (OR 0.63; 95%CI (0.33-1.23)) P = .072) Also, RSV is strongly associated with both persistent wheezing and asthma when compared with no bronchiolitis (healthy individuals) (OR 3.63 and P < .001, OR 3.41 and P < .001), but, the risk of RSV is no different to that of other viruses (OR 0.81 and P = .76) for wheezing, and indeed is less strongly associated with asthma (OR 0.42 and P < .001) Conclusions: Both RV and RSV are associated with the development of asthma. RV is much more strongly associated with subsequent asthma when compared with other viruses (RSV included), whilst RSV did not have a greater association with asthma development than other viruses (RV included).

### **8. Bronchiolitis in Infants and Children.**

**Author(s):** Schaller, Alexandra; Galloway, Carl S

**Source:** South Dakota medicine : the journal of the South Dakota State Medical Association; Jun 2017; vol. 70 (no. 6); p. 274-277

**Publication Type(s):** Journal Article

Available at [South Dakota medicine : the journal of the South Dakota State Medical Association](#) - from EBSCO (MEDLINE Complete)

**Abstract:** Bronchiolitis is among the most common illnesses in infants and children, and is the most common cause for hospitalization in infants in the U.S. This illness can be caused by many viruses, most commonly respiratory syncytial virus. It is diagnosed clinically by history and physical exam findings, with a narrow role for ancillary testing. Management is supportive, with medications demonstrating limited utility in multiple studies. Preventive measures include hand hygiene, breastfeeding, avoiding tobacco smoke exposure, and isolation precautions for hospitalized patients. Palivizumab prophylaxis is recommended for infants with qualifying high risk conditions. Recent evidence-based clinical practice guidelines have been published by the American Academy of Pediatrics to guide diagnosis, treatment, and prevention of bronchiolitis.

## 9. Reviewing the guidelines: Management of acute viral bronchiolitis

**Author(s):** Da Silva Filho L.V.R.F.

**Source:** Pediatric Pulmonology; Jun 2017; vol. 52

**Publication Type(s):** Conference Abstract

**Abstract:** Acute viral bronchiolitis is one of the most common reasons for hospital admission in childhood, with increasing incidence in the last decades 1. While the overall mortality is relatively low, its high incidence results in a very high burden, especially for low-income populations 2. The main etiologic agent is respiratory syncytial virus (RSV), although several other viruses, such as rhinovirus, influenza, parainfluenza, adenovirus and metapneumovirus are identified in these patients 3. Risk factors for severe bronchiolitis include preterm delivery or chronic diseases such as congenital heart disease, Down syndrome, chronic lung diseases and neuromuscular diseases - all of which are associated with a higher risk of hospitalization, need of mechanical ventilation and death 4. Treatment of several diseases has changed dramatically in the last 50 years, but this is not the case for bronchiolitis. Although there have been hundreds of trials of drugs such as bronchodilators, steroids, antibiotics and other therapeutic strategies such as nebulized hypertonic saline and chest physiotherapy, they all lack evidence of significant benefit. Therefore, treatment of acute viral bronchiolitis remains mainly supportive 5. Treatment guidelines are published periodically, with the most recent being the 2014 North American Clinical Practice Guideline from the American Academy of Pediatrics 6, and the 2015 British Clinical Guideline, commissioned by the National Institute for Health and Care Excellence (NICE) 7. The AAP Guidelines designated recommendation levels to illustrate quality of evidence and balance for benefit and harm anticipated by its application in clinical practice. The NICE guidelines adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, incorporating health economics for some topics. The wording used in the recommendations (for example, words such as 'offer' and 'consider') denoted the certainty with which the recommendation was made (the strength of the recommendation). Both guidelines had several recommendations of treatments to avoid, in a genuine attempt to reduce unnecessary interventions administered to children with bronchiolitis. The basic principle of "Primum non nocere" is prevailing. The AAP guideline is significantly shorter and more objective, focusing also on immunoprophylaxis and prevention of viral contamination between patients and caregivers. The NICE guidelines are much more extensive and detailed, containing details of the trials used for evidence-based recommendations, resulting in a document of more than 300 pages. Main Recommendations and Comments: \* The diagnosis and assessment of severity of bronchiolitis is made by history and physical examination - assessment of risk must also take into account age, history of prematurity or other underlying conditions such as cardiopulmonary disease, immunodeficiency or neuromuscular diseases. \* Consider the diagnosis in children younger than 2 years of age with a history of upper respiratory tract symptoms (coryza), that get worse and affect the lower respiratory tract (persistent cough, wheeze and/or crackles on chest auscultation and signs of increased work of breathing (tachypnea and/or chest retractions). \* Radiographic or other laboratory studies are not routinely indicated. \* Hospital admission must be

considered for children presenting: \* apnea (observed or reported). \* persistent oxygen saturation of less than 92% when breathing air.\*\* inadequate oral fluid intake. \* persisting severe respiratory distress (grunting, marked chest retractions, or a respiratory rate >70 breaths/minute). \* The AAP Guidelines recommend 90% as the cutoff value for pulse oximetry (see below). \* Continuous pulse oximetry is not indicated for patients admitted to the Hospital \* Do not use any of the following to treat bronchiolitis in children: \* salbutamol \* ipratropium bromide \* systemic or inhaled corticosteroids \* adrenaline (nebulized) \* a combination of systemic corticosteroids and nebulized adrenaline \* nebulized hypertonic saline (AAP guidelines state that it may be used for patients admitted to the Hospital) \* oral montelukast \* antibiotics \* Do not perform chest physiotherapy on children with bronchiolitis (NICE guidelines state that it may be indicated for children with comorbidities such as spinal muscular atrophy). \* Regarding nasal (upper airway suctioning), only the NICE guidelines recommend: \* "Do not routinely perform upper airway suctioning in children with bronchiolitis." \* "Consider upper airway suctioning in children who have respiratory distress or feeding difficulties because of upper airway secretions." \* "Perform upper airway suctioning in children with bronchiolitis presenting with apnea even if there are no obvious upper airway secretions." \* Oxygen supplementation is indicated for children with hypoxemia, but the consensus state different cutoff values for oxyhemoglobin saturation: \* AAP guidelines: "Clinicians may choose not to administer supplemental oxygen if the oxyhemoglobin saturation exceeds 90% in infants and children with a diagnosis of bronchiolitis." \* NICE guidelines: "Give oxygen supplementation to children with bronchiolitis if their oxygen saturation is persistently less than 92%." \* Nasogastric or intravenous fluids may be indicated for infants who cannot maintain hydration orally (less than 50-75% of the regular amount). \* Non-invasive ventilation (continuous positive airway pressure - CPAP) should be considered in children who have impending respiratory failure. The inclusion of bronchodilators in the list of "Do not use drugs" was surprising and certainly very controversial among pediatricians and pediatric pulmonologists. The previous AAP guidelines published in 2006<sup>8</sup> recommended a "carefully monitored trial" of bronchodilators for children with bronchiolitis, which seemed to be the breach for physicians to prescribe it. While bronchodilator use was definitely not associated with a reduction in hospital admission rates or length of stay, the belief that it could transiently improve respiratory mechanics may be the reason why it was prescribed to more than half of the admitted patients with bronchiolitis<sup>9</sup>. Regarding oxygen supplementation, which is undoubtedly helpful and indicated for hypoxemic children, the new cutoff value of 90% of oxyhemoglobin saturation and the possibility of avoiding continuous pulse oximetry monitoring proposed in the AAP guidelines are both very impactful. While a slightly different value was recommended in the NICE guidelines (pulse oximetry of at least 92%), both guidelines support the idea of reducing pulse oximetry role as a decision making indicator for admission or discharge of the hospital. A very interesting study carried out recently by Dr. Schuh and colleagues from Toronto<sup>10</sup> reinforces this view. They randomized children with moderate to severe bronchiolitis presenting to the emergency department to either having true oximetry values versus values that were artificially increased by 3 percentage points showed to the attending physician. Patients who had falsely elevated oximetry values were less likely to be hospitalized within 72 hours or receive active hospital care for more than 6 hours than those with unaltered oximetry readings. No difference was seen in the frequency of complications or unscheduled visits<sup>10</sup>. Implementing these guidelines will be challenging in several parts of the world, but they signal a new attitude of minimizing interventions and reducing the role of pulse oximetry as the main indicator of severity. This could be of significant impact for admission rates and length of stay, reducing costs and the burden of bronchiolitis for children and their families.



### **10. Azithromycin administered at the time of severe bronchiolitis has a protective effect on subsequent wheezing in infants**

**Author(s):** Pinto L.A.; Jones M.H.; Pitrez P.M.; Stein R.T.

**Source:** Pediatric Pulmonology; Jun 2017; vol. 52

**Publication Type(s):** Conference Abstract

**Abstract:** Purpose A significant proportion of infants develop recurrent wheezing after an acute viral bronchiolitis (AB) event. Despite extensive research, clinical trials could not show any intervention with a relevant clinical impact on AB. However, at least one recent study has demonstrated a prolonged protection for recurrent wheeze and lower respiratory morbidity in infants treated with azithromycin during an acute respiratory syncytial virus (RSV) bronchiolitis. The aim of the present study was to test the hypothesis that administration of Azithromycin during an AB event reduces subsequent wheezing and hospital re-admissions. Methods This is a secondary analysis of a randomized, double-blinded, placebo-controlled trial, including unpublished data on wheezing and hospitalizations during the initial 6 months following admission for acute viral bronchiolitis. The study was performed in a tertiary University hospital in Southern Brazil. Participants were infants (< 12 months of age) hospitalized with AB. Patients were randomized to receive either Azithromycin or placebo, administered orally, for 7 days. Assessment of clinical data included length of hospital stay and identification of respiratory viruses, described in a previous publication. In addition, secondary data from the initial study were registered in a follow-up during 6 months after the AB episode in order to identify recurrent wheezing and hospital readmissions. Families were contacted by telephone at 3 and 6 months after the initial acute event and responded to a standardized questionnaire. Results Eighty-three patients were included (Azithromycin group, n = 46; placebo group, n = 37). Kaplan-Meier analysis showed wheezing was significantly reduced in the Azithromycin group (P =0.022). Acute events which were positive for RSV (n = 38) or not by RSV (n = 30) had a significant reduction for subsequent wheezing in both subgroups. Hospital re-admission during the period of follow-up was not significantly different between the two groups. Conclusion Azithromycin significantly reduces the risk of subsequent wheezing between 0 and 6 months after hospital admission due to acute viral bronchiolitis irrespective of the presence of respiratory syncytial virus. Considering the important clinical impact of our findings and the risk of increased use of macrolides in this group of patients, further studies should try to better define which infants could be better responders to macrolides and whether severity is also a factor associated with efficacy of treatment.

### **11. Systematic review and meta-analysis of the efficacy and safety of combined epinephrine and corticosteroid therapy for acute bronchiolitis in infants**

**Author(s):** Kua K.P.; Lee S.W.H.

**Source:** Frontiers in Pharmacology; Jun 2017; vol. 8

**Publication Type(s):** Short Survey

Available at [Frontiers in Pharmacology](#) - from Europe PubMed Central - Open Access

**Abstract:** Objective: To evaluate the effectiveness of combined epinephrine and corticosteroid therapy for acute bronchiolitis in infants. Methods: Four electronic databases (MEDLINE, EMBASE, CINAHL, and CENTRAL) were searched from their inception to February 28, 2017 for studies involving infants aged less than 24 months with bronchiolitis which assessed the use of epinephrine and corticosteroid combination therapy. The methodological quality of the included studies was assessed using the Cochrane Collaboration's Risk of Bias Tool. A random-effects meta-analysis was used to pool the effect estimates. The primary outcomes were hospital admission rate and length of hospital stay. Results: Of 1,489 citations identified, 5 randomized controlled trials involving 1,157 patients were included. All studies were of high quality and low risk of bias. Results of the meta-analysis

showed no significant differences in the primary outcomes. Hospitalization rate was reduced by combinatorial therapy of epinephrine and corticosteroid in only one out of five studies, whereas pooled data indicated no benefit over epinephrine plus placebo. Clinical severity scores were significantly improved in all five RCTs when assessed individually, but no benefit was observed compared to epinephrine monotherapy when the data were pooled together. Pooled data showed that combination therapy was more effective at improving oxygen saturation level (mean difference: -0.70; 95% confidence interval: -1.17 to -0.22,  $p = 0.004$ ). There was no difference in the risk of serious adverse events in infants treated with the combined epinephrine and corticosteroid therapy. Conclusions: Combination treatment of epinephrine and dexamethasone was ineffective in reducing hospital admission and length of stay among infants with bronchiolitis.

## RSV

### 1. Prolonged viral replication and longitudinal viral dynamic differences among respiratory syncytial virus infected infants.

**Author(s):** Brint, Monica E; Hughes, Joshua M; Shah, Aditya; Miller, Chelsea R; Harrison, Lisa G; Meals, Elizabeth A; Blanch, Jacqueline; Thompson, Charlotte R; Cormier, Stephania A; DeVincenzo, John P

**Source:** Pediatric research; Nov 2017; vol. 82 (no. 5); p. 872-880

**Publication Type(s):** Journal Article

**Abstract:**Background Longitudinal respiratory syncytial virus (RSV) dynamics have not been well studied despite the existence of factors favoring prolonged RSV replication including high mutation rates allowing rapid evolution and potential escape from immune control. We therefore measured viral load in previously RSV-naive infants over prolonged time spans. Methods During 2014-2015, quantitative nasal aspirates were collected from 51 RSV-PCR+ infants. Multiple parallel assessments of viral loads were quantified at each collected time point using a well-validated real-time quantitative reverse transcriptase polymerase chain reaction assay. After observing viral load rebound phenomenon in some infants, the viral dynamics of 27 infants with sufficient longitudinal viral load data points were analyzed using the pre-defined criteria for viral rebound. Additional analyses were performed comparing age with viral rebound, viral clearance rates, and viral load area-under-the-curve (AUCVL). Results The 51 infants (303 nasal aspirate samples; mean of 5.9 per patient) exhibited slower than expected viral clearance. Lower age trended toward slower viral clearance and greater AUCVL. Six infants had detectable viral loads  $\geq 1$  month after symptom onset. Ten of twenty-seven evaluable subjects exhibited viral rebound and this rebound was age-dependent ( $P=0.0259$ ). All but one rebounder were  $<70$  days old. Conclusion Infants struggle to control primary RSV infections allowing prolonged viral replication and previously undescribed viral rebound; likely representing viral mutational immune escape.

### 2. Respiratory Syncytial Virus Infection Control Challenges with a Novel Polymerase Chain Reaction Assay in a Tertiary Medical Center.

**Author(s):** Sendi, Parham; Egli, Adrian; Dangel, Marc; Frei, Reno; Tschudin-Sutter, Sarah; Widmer, Andreas F

**Source:** Infection control and hospital epidemiology; Oct 2017 ; p. 1-7

**Publication Type(s):** Journal Article

**Abstract:**OBJECTIVES To evaluate host characteristics, mode of infection acquisition, and infection control procedures in patients with a positive respiratory syncytial virus (RSV) test result after the introduction of the GenXpert Influenza/RSV polymerase chain reaction (PCR) assay. DESIGN Retrospective cohort study. PATIENTS Adults with a positive PCR test result for RSV who were

hospitalized in a tertiary academic medical center between January 2015 and December 2016 were included in this study. Our infection control policy applies contact isolation precautions only for immunocompromised patients. **METHODS** Patients were identified through 2 databases, 1 consisting of patients isolated because of RSV infection and 1 with automatically collected laboratory results. Baseline and clinical characteristics were collected through a retrospective medical chart review. The rate of and clinical factors associated with healthcare-associated RSV infections were evaluated. **RESULTS** In total, 108 episodes in 106 patients hospitalized with a positive Xpert RSV test result were recorded during the study period. Among them, 11 episodes were healthcare-associated infections (HAIs) and 97 were community-acquired infections (CAIs). The mean length of hospital stay (LOS, 40.2 vs 11.2 days), the mean number of room switches (3.5 vs 1.7) and ward switches (1.5 vs 0.4), and the mean numbers of contact patients (9.9 vs 3.8) were significantly longer and higher in the HAI group than in the CAI group ( $P < .0001$ ). Surveillance of microbiology records and clinical data did not reveal evidence for a cluster or an epidemic during the 2-year observation period. **CONCLUSIONS** The introduction of a rapid molecular diagnostic test systematically applied to patients with influenza-like illness may challenge current infection control policies. In our study, patients with HAIs had a prolonged hospital stay and a high number of contact patients, and they switched rooms and wards frequently.

### **3. Cost-utility analysis of Palivizumab for Respiratory Syncytial Virus infection prophylaxis in preterm infants: update based on the clinical evidence in Spain.**

**Author(s):** Sanchez-Luna, M; Burgos-Pol, R; Oyagüez, I; Figueras-Aloy, J; Sánchez-Solís, M; Martínón-Torres, F; Carbonell-Estrany, X

**Source:** BMC infectious diseases; Oct 2017; vol. 17 (no. 1); p. 687

**Publication Type(s):** Journal Article

Available at [BMC infectious diseases](#) - from BioMed Central

Available at [BMC infectious diseases](#) - from Europe PubMed Central - Open Access

Available at [BMC infectious diseases](#) - from EBSCO (MEDLINE Complete)

**Abstract:**BACKGROUND This study aimed at estimating the efficiency of palivizumab in the prevention of Respiratory Syncytial Virus (RSV) infection and its sequelae in preterm infants (32day 1-35day 0 weeks of gestational age -wGA-) in Spain. **METHODS** A decision-tree model was developed to compare health benefits (Quality Adjusted Life Years-QALYs) and costs of palivizumab versus a non-prophylaxis strategy over 6 years. A hypothetical cohort of 1,000 preterm infants, 32day 1-35day 0 wGA (4.356 kg average weight) at the beginning of the prophylaxis (15 mg/kg of palivizumab; 3.88 average number of injections per RSV season) was analysed. The model considered the most recent evidence from Spanish observational and epidemiological studies on RSV infection: the FLIP II study provided hospital admission and Intensive Care Unit (ICU) admission rates; in-hospital mortality rate was drawn from an epidemiological study from 2004 to 2012; recurrent wheezing rates associated to RSV infection from SPRING study were adjusted by the evidence on the palivizumab effect from clinical trials. Quality of life baseline value, number of hospitalized infants and the presence of recurrent wheezing over time were granted to estimate QALYs. National Health Service and societal perspective (included also recurrent wheezing indirect cost) were analysed. Total costs (€, 2016) included pharmaceutical and administration costs, hospitalization costs and recurrent wheezing management annual costs. A discount rate of 3.0% was applied annually for both costs and health outcomes. **RESULTS** Over 6 years, the base case analysis showed that palivizumab was associated to an increase of 0.0731 QALYs compared to non-prophylaxis. Total costs were estimated in €2,110.71 (palivizumab) and €671.68 (non-prophylaxis) from the National Health System (NHS) perspective, resulting in an incremental cost utility ratio (ICUR) of €19,697.69/QALYs gained (prophylaxis vs non-prophylaxis). Results derived from the risk-factors population subgroups

analysed were in line with the total population results. From the societal perspective, the incremental cost associated to palivizumab decreased to an €1,253.14 (ICUR = €17,153.16€/QALYs gained for palivizumab vs non-prophylaxis). One-way and probabilistic sensitivity analyses confirmed the robustness of the model. **CONCLUSION** The prophylaxis with palivizumab is efficient for preventing from RSV infections in preterm infants 32day 1-35day 0 wGA in Spain.

#### **4. Development of a High-Throughput Respiratory Syncytial Virus Fluorescent Foci-Based Microneutralization Assay.**

**Author(s):** Shambaugh, Cindy; Azshirvani, Sarieh; Yu, Li; Pache, Jared; Lambert, Stacie L; Zuo, Fengrong; Esser, Mark T

**Source:** Clinical and vaccine immunology : CVI; Oct 2017

**Publication Type(s):** Journal Article

**Abstract:** Neutralizing antibodies specific for respiratory syncytial virus (RSV) represent a major protective mechanism against RSV infection as demonstrated by the efficacy of the immune-prophylactic monoclonal antibody, Palivizumab, in preventing RSV associated lower respiratory tract infections in premature infants. Accordingly, the RSV neutralization assay has become a key functional method to assess the neutralizing activity of serum antibodies in pre-clinical animal models, epidemiology studies and clinical trials. In this study, we qualified a 24-hour, RSV A green fluorescent protein (GFP) fluorescent foci assay-based microneutralization (RSVA FFA-MN) method that requires no medium exchange or pre or post-infection processing to detect GFP-expressing RSV-A2 infected cells using a high-content imaging system for automated image acquisition and foci enumeration. The RSVA FFA-MN was shown to be sensitive with a limit of detection (LOD) and limit of quantitation (LOQ) of 1:10 or 3.32 log<sub>2</sub>, linear over a range of 4.27 to 9.65 log<sub>2</sub> IC<sub>50</sub>, and precise with intra- and inter-assay coefficients of variation of <21%. This precision allows the choice of a statistically justified 3-fold rise seroresponse cutoff criteria. The repeatability and robustness of this method was demonstrated by including a pooled human serum sample in every assay as a positive control (PC). Over 3 years of testing between two laboratories, this PC generated data within 2.5 standard deviations of the mean 98.7% of the time (n=1720). This high-throughput and reliable RSV microneutralization assay has proven useful for testing sera from pre-clinical vaccine candidate evaluation studies, epidemiology studies and both pediatric and adult vaccine clinical trials.

#### **5. Palivizumab Prophylaxis Against Respiratory Syncytial Virus Infection in Children with Immunocompromised Conditions or Down Syndrome: A Multicenter, Post-Marketing Surveillance in Japan.**

**Author(s):** Kashiwagi, Tomoko; Okada, Yukiko; Nomoto, Ken

**Source:** Paediatric drugs; Sep 2017

**Publication Date:** Sep 2017

**Publication Type(s):** Journal Article

**PubMedID:** 28895096

**Abstract:** **OBJECTIVE** The aim of this study was to assess the safety and effectiveness of palivizumab for the prevention of lower respiratory tract infection (LRI) caused by respiratory syncytial virus (RSV) in children with immunocompromised conditions or Down syndrome. **METHODS** In this multicenter, post-marketing surveillance study (December 2013 to December 2015), children aged ≤24 months with immunocompromised conditions or Down syndrome (without hemodynamically significant congenital heart disease) receiving palivizumab immunoprophylaxis during two RSV seasons were observed until 30 days after the final palivizumab injection. Safety [adverse events

(AEs), serious AEs (SAEs), adverse drug reactions (ADRs), serious ADRs (SADRs)] and effectiveness (frequency, incidence, and duration of hospitalization due to RSV infections) were assessed. RESULTS Of 304 patients receiving palivizumab, 167 (54.9%) had immunocompromised conditions, and 138 (45.4%) had Down syndrome; 260 (85.5%) completed palivizumab immunoprophylaxis. The annual mean ( $\pm$ standard deviation) number of doses was 5.3 ( $\pm$ 2.4) per season. Overall, 220 AEs occurred in 99 patients (32.6%), including 89 SAEs in 53 patients (17.4%). Of these, 33 AEs in 25 patients (8.22%) were considered ADRs, and 13 ADRs in 11 patients (3.62%) were considered SADRs. In four patients, five SADRs (nephroblastoma and asthma in the same patient, septic shock, device-related infection, and drug-induced liver injury) were previously unreported; however, none were considered drug-related. During the observation period, five RSV infections occurred and two patients required hospitalization. CONCLUSION Palivizumab was generally safe and effective for the prevention of LRI caused by RSV in newborns, infants, and children with immunocompromised conditions or Down syndrome up to the age of 24 months.

## 6. Chronologic Age at Hospitalization for Respiratory Syncytial Virus Among Preterm and Term Infants in the United States.

**Author(s):** Parikh, Rohan C; McLaurin, Kimmie K; Margulis, Andrea V; Mauskopf, Josephine; Ambrose, Christopher S; Pavilack, Melissa; Candrilli, Sean D

**Source:** Infectious diseases and therapy; Sep 2017

**Publication Type(s):** Journal Article

Available at [Infectious diseases and therapy](#) - from Europe PubMed Central - Open Access

**Abstract:** INTRODUCTION Respiratory syncytial virus (RSV) is the leading cause of hospitalization among infants in the United States, and the risk for RSV hospitalizations is greater for infants born preterm. Recent studies in preterm and term infants have shown that RSV hospitalization rates vary considerably depending on infant chronologic age. This study sought to aggregate the data available from published literature and from nationally representative databases of US infant hospitalizations to generate a composite description of the effect of young chronologic age on RSV hospitalizations among US preterm and term infants by individual month of age. METHODS Data describing the relative incidence of RSV hospitalizations by individual month of chronologic age during the first year of life were obtained from recently published studies, the 2006-2011 National Inpatient Sample databases, and the 2006 and 2009 Kids Inpatient Databases. RESULTS All data sources showed that  $\geq$ 20% of infant RSV hospitalizations occurred in the second month of life and  $>$ 50% and  $>$ 75% of RSV hospitalizations were observed during the first 3 and 6 months of life, respectively. These findings were consistent for both preterm and term infants. CONCLUSION Data from multiple sources demonstrate that the greatest risk of RSV hospitalization occurs during the first 6 months of life among US preterm and term infants. Strategies to prevent infant RSV hospitalizations should be targeted to infants during the first months of life. FUNDING AstraZeneca.

## 7. Product review on the monoclonal antibody palivizumab for prevention of respiratory syncytial virus infection.

**Author(s):** Resch, Bernhard

**Source:** Human vaccines & immunotherapeutics; Sep 2017; vol. 13 (no. 9); p. 2138-2149

**Publication Type(s):** Journal Article

**Abstract:** Respiratory syncytial virus (RSV) accounts for about 20% of all respiratory infections in children below the age of 5 y. It is associated with up to 63% of all acute respiratory infections and up to 81% of all viral lower respiratory tract infections causing hospitalization in infants and young

children. RSV leads to seasonal epidemics between November and April in the northern hemisphere. Most severe infections (RSV accounts for 50 to 80% of all cause bronchiolitis) affect infants younger than 6 months of age and high-risk infants including those born preterm with or without bronchopulmonary dysplasia and those with hemodynamically significant congenital heart disease up to an age of 24 months. Palivizumab, a highly potent RSV-neutralizing monoclonal antibody (Mab), has been licensed in 1998 for prophylactic use to prevent RSV associated hospitalizations in high-risk infants. This Mab is given by monthly intramuscular injection at a dose of 15 mg/kg over the RSV season (up to 5 times). Palivizumab proved to be safe and well-tolerated in this population. Concerns have been raised regarding cost-effectiveness of palivizumab and thus, palivizumab prophylaxis is mainly limited to selected high-risk infants for the first RSV season. Long-lasting Mabs will be the next future approach in the prophylaxis of RSV hospitalization until a vaccine is developed.

### **8. A safe and efficient BCG vectored vaccine to prevent the disease caused by the human Respiratory Syncytial Virus.**

**Author(s):** Rey-Jurado, Emma; Soto, Jorge; Gálvez, Nicolás; Kalergis, Alexis M

**Source:** Human vaccines & immunotherapeutics; Sep 2017; vol. 13 (no. 9); p. 2092-2097

**Publication Type(s):** Journal Article

**Abstract:**The human Respiratory Syncytial Virus (hRSV) causes lower respiratory tract infections including pneumonia and bronchiolitis. Such infections also cause a large number of hospitalizations and affects mainly newborns, young children and the elderly worldwide. Symptoms associated with hRSV infection are due to an exacerbated immune response characterized by low levels of IFN- $\gamma$ , recruitment of neutrophils and eosinophils to the site of infection and lung damage. Although hRSV is a major health problem, no vaccines are currently available. Different immunization approaches have been developed to achieve a vaccine that activates the immune system, without triggering an unbalanced inflammation. These approaches include live attenuated vaccine, DNA or proteins technologies, and the use of vectors to express proteins of the virus. In this review, we discuss the host immune response to hRSV and the immunological mechanisms underlying an effective and safe BCG vectored vaccine against hRSV.

### **9. Immune and inflammatory response in bronchiolitis due to respiratory Syncytial Virus and Rhinovirus infections in infants.**

**Author(s):** Vandini, Silvia; Calamelli, Elisabetta; Faldella, Giacomo; Lanari, Marcello

**Source:** Paediatric respiratory reviews; Sep 2017; vol. 24 ; p. 60-64

**Publication Type(s):** Journal Article Review

**Abstract:**Bronchiolitis is a common disease in infancy, mostly due to Respiratory Syncytial Virus and Rhinovirus. In addition to acute infection, viral bronchiolitis is responsible for sequelae including recurrent wheezing and asthma. The analysis of the viral characteristics and of the pathogenesis of the infection shows differences between the two viruses that may be helpful for the development of therapies and preventive strategies.

### **10. Palivizumab: The Effects of Prophylactic Immunization on the Occurrence of Infections Caused by the Respiratory Syncytial Virus.**

**Author(s):** Raguz, Marjana Jerkovic; Brzica, Jerko; Grgic, Ivana

**Source:** Klinische Padiatrie; Sep 2017; vol. 229 (no. 5); p. 281-285

**Publication Type(s):** Journal Article

**Abstract:**Aim The aim of this research is to analyze the characteristics of children immunized during immunization season, and their readmission to hospital due to infections of the respiratory tract in the period from 2008 to 2016. Method The retrospective cohort study included 101 children. The test group consists of infants who met the strict criteria for immunization. The national guidance was determined on the basis of earlier research and recommendations by the AAP. All the children who had been readmitted for hospitalization were quickly tested for RSV. Results Of this total, 47 children were preterm children (46.5%), 43 (42.5%) were children with CHD, and 11 (11%) exhibited other individual risk factors (gestational age 33-34 weeks, neurological disorders, respiratory anomalies, multi-organ anomalies). 25 (24%) patients of the immunized study population readmitted the ward due to respiratory infections. Of these, 50% were under the age of 6 months and were treated for less than a week on average. Upon readmission, a quick test to diagnose for RSV infections was conducted, which was negative for all of the previously immunized children. Conclusion Palivizumab represents an effective prevention to avoid RSV infections, that significantly contributes to mortality for children at risk, especially in developing countries.

**11. Determining the outcomes of interventions to prevent respiratory syncytial virus disease in children: what to measure?**

**Author(s):** Karron, Ruth A; Zar, Heather J

**Source:** The Lancet. Respiratory medicine; Aug 2017

**Publication Type(s):** Journal Article Review

**Abstract:**Respiratory syncytial virus (RSV) is the most common cause of viral acute lower respiratory tract illness (LRTI) in young children, and a major cause of hospital admissions and health-care utilisation globally. Substantial efforts have been made to develop RSV vaccines and vaccine-like monoclonal antibodies to prevent acute RSV LRTI. Prevention of acute disease could improve long-term lung health, with potential effects on wheezing, asthma, and chronic lung disease. This Personal View describes assessments that should be initiated during clinical trials and continued after licensure to fully evaluate the effect of RSV preventive interventions. These assessments include recording the incidence of RSV-specific LRTI and all-cause LRTI through two RSV seasons, and assessment of the prevalence and severity of recurrent wheezing or asthma in children aged up to 6 years. Standardised assessments in diverse settings are needed to fully determine the effect of interventions for the prevention of RSV disease.

**12. Respiratory Syncytial Virus: The Influence of Serotype and Genotype Variability on Clinical Course of Infection.**

**Author(s):** Vandini, Silvia; Biagi, Carlotta; Lanari, Marcello

**Source:** International journal of molecular sciences; Aug 2017; vol. 18 (no. 8)

**Publication Type(s):** Journal Article Review

Available at [International journal of molecular sciences](#) - from Europe PubMed Central - Open Access

**Abstract:**Respiratory syncytial virus (RSV) belongs to the recently defined Pneumoviridae family, Orthopneumovirus genus. It is the leading cause of acute bronchiolitis and one of the most common causes of infant viral death worldwide, with infection typically occurring as recurrent seasonal epidemics. There are two major RSV subtypes, A and B, and multiple genotypes, which can coexist during RSV epidemic season every year and result in different disease severity. Recently, new RSV genomic sequences and analysis of RSV genotypes have provided important data for understanding

RSV pathogenesis. Novel RSV strains do spread rapidly and widely, and a knowledge of viral strain-specific phenotypes may be important in order to include the more virulent strains in future therapeutical options and vaccine development. Here we summarize recent literature exploring genetic and molecular aspects related to RSV infection, their impact on the clinical course of the disease and their potential utility in the development of safe and effective preventive and therapeutic strategies.

### **13. Respiratory-syncytial-virus- and rhinovirus-related bronchiolitis in children aged <2 years in an English district general hospital.**

**Author(s):** Paul, S P; Mukherjee, A; McAllister, T; Harvey, M J; Clayton, B A; Turner, P C

**Source:** The Journal of hospital infection; Aug 2017; vol. 96 (no. 4); p. 360-365

**Publication Type(s):** Journal Article

**Abstract:**BACKGROUND Bronchiolitis is the most common reason for hospitalization in young children. In addition to respiratory syncytial virus (RSV), other viruses have been increasingly implicated. Guidance on testing has also changed. AIM To compare clinicopathological outcomes in young children admitted with bronchiolitis due to RSV in comparison with rhinovirus (RV), and identify associated risk/epidemiological factors. METHODS Children aged less than two years admitted to hospital with a clinical diagnosis of bronchiolitis with positive results for either RSV or RV were included in this study. Polymerase-chain-reaction-negative cases using an extended respiratory virus panel served as a control group. Retrospective data were collected on sex, risk factors, respiratory support, intravenous fluids and antibiotics. Outcomes such as length of stay (LOS) and need for transfer to the high-dependency unit/paediatric intensive care unit were included. FINDINGS Two hundred and twenty-seven out of 437 nasopharyngeal aspirate samples were positive for either RSV (N = 162) or RV (N = 65). The median age of cases was three months and 75% had at least one risk factor. Risk factors were higher in the RV group (P = 0.004). RV accounted for the majority of cases outside the RSV season (P < 0.01). RV-associated bronchiolitis had a longer LOS (more than seven days) (P < 0.05) and increased need for chest X-rays and/or antibiotics (P < 0.05). Use of intravenous fluids and respiratory support were higher in the RV group, but the difference was not significant. CONCLUSIONS RV is the second most common pathogen associated with bronchiolitis and is isolated all year round. This may be important in those with risk factors resulting in prolonged LOS. Further research is necessary to establish the exact role of RV in this common condition, particularly outside the traditional RSV season.

### **14. Consecutive yearly outbreaks of respiratory syncytial virus in a haemato-oncology ward and efficacy of infection control measures.**

**Author(s):** Inkster, T; Ferguson, K; Edwardson, A; Gunson, R; Soutar, R

**Source:** The Journal of hospital infection; Aug 2017; vol. 96 (no. 4); p. 353-359

**Publication Type(s):** Journal Article

**Abstract:**BACKGROUND Respiratory syncytial virus (RSV) causes significant respiratory tract infection in immunosuppressed patients. AIM To describe two consecutive yearly outbreaks of RSV in our haemato-oncology ward. METHODS Haematology patients presenting with respiratory symptoms were screened by polymerase chain reaction for viral respiratory pathogens using a saline gargle. FINDINGS None of our patients had undergone bone marrow transplant but all had underlying haematological malignancies. Eight patients were affected in the first outbreak (mortality rate: 37.5%) and 12 patients were affected in the second (mortality rate: 8.3%). Extensive infection control measures were implemented in both outbreaks and were successful in preventing further



cross-transmission. **CONCLUSION** There was significant learning from both outbreaks and actions implemented with the aim of reducing the likelihood and impact of future outbreaks.

### **15. Respiratory syncytial virus: prospects for new and emerging therapeutics.**

**Author(s):** Jorquera, Patricia A; Tripp, Ralph A

**Source:** Expert review of respiratory medicine; Aug 2017; vol. 11 (no. 8); p. 609-615

**Publication Type(s):** Journal Article

**Abstract:** **INTRODUCTION** Respiratory syncytial virus (RSV) is the major cause of lower respiratory tract infections (LRTI) in infants, the elderly, and the immunocompromised. Although the development of a RSV vaccine has been a priority for >50 years, there is still no vaccine available. Treatment of RSV LRTI has remained mostly supportive, i.e. hydration and oxygenation. Palivizumab and ribavirin are the only options currently available for prevention and treatment of RSV infection, but evidence suggests that they are not fully effective. This creates a significant unmet medical need for new therapeutics for prevention and treatment of RSV worldwide. **Areas covered:** This article reviews the antiviral drugs and monoclonal antibodies (mAb) for RSV that are in different stages of clinical development. **Expert commentary:** Over the last 10 years, new antiviral drugs and mAb have shown clinical promise against RSV, and may become available in the coming years. Although the RSV fusion protein has been the most popular target for inhibitors and mAbs, new approaches targeting other viral proteins have shown promising results. To overcome the emergence of RSV escape mutants, combination antiviral therapy may be explored in the future.

### **16. Discovery of a Prefusion Respiratory Syncytial Virus F-Specific Monoclonal Antibody That Provides Greater In Vivo Protection than the Murine Precursor of Palivizumab.**

**Author(s):** Zhao, Min; Zheng, Zi-Zheng; Chen, Man; Modjarrad, Kayvon; Zhang, Wei; Zhan, Lu-Ting; Cao, Jian-Li; Sun, Yong-Peng; McLellan, Jason S; Graham, Barney S; Xia, Ning-Shao

**Source:** Journal of virology; Aug 2017; vol. 91 (no. 15)

**Publication Type(s):** Journal Article

**Abstract:** Palivizumab, a humanized murine monoclonal antibody that recognizes antigenic site II on both the prefusion (pre-F) and postfusion (post-F) conformations of the respiratory syncytial virus (RSV) F glycoprotein, is the only prophylactic agent approved for use for the treatment of RSV infection. However, its relatively low neutralizing potency and high cost have limited its use to a restricted population of infants at high risk of severe disease. Previously, we isolated a high-potency neutralizing antibody, 5C4, that specifically recognizes antigenic site  $\emptyset$  at the apex of the pre-F protein trimer. We compared in vitro and in vivo the potency and protective efficacy of 5C4 and the murine precursor of palivizumab, antibody 1129. Both antibodies were synthesized on identical murine backbones as either an IgG1 or IgG2a subclass and evaluated for binding to multiple F protein conformations, in vitro inhibition of RSV infection and propagation, and protective efficacy in mice. Although 1129 and 5C4 had similar pre-F protein binding affinities, the 5C4 neutralizing activity was nearly 50-fold greater than that of 1129 in vitro. In BALB/c mice, 5C4 reduced the peak titers of RSV 1,000-fold more than 1129 did in both the upper and lower respiratory tracts. These data indicate that antibodies specific for antigenic site  $\emptyset$  are more efficacious at preventing RSV infection than antibodies specific for antigenic site II. Our data also suggest that site  $\emptyset$ -specific antibodies may be useful for the prevention or treatment of RSV infection and support the use of the pre-F protein as a vaccine antigen. **IMPORTANCE** There is no vaccine yet available to prevent RSV infection. The use of the licensed antibody palivizumab, which recognizes site II on both the pre-F and post-F proteins, is restricted to prophylaxis in neonates at high risk of severe RSV disease. Recommendations for using passive immunization in the general population or for therapy in immunocompromised

persons with persistent infection is limited because of cost, determined from the high doses needed to compensate for its relatively low neutralizing potency. Prior efforts to improve the in vitro potency of site II-specific antibodies did not translate to significant in vivo dose sparing. We isolated a pre-F protein-specific, high-potency neutralizing antibody (5C4) that recognizes antigenic site Ø and compared its efficacy to that of the murine precursor of palivizumab (antibody 1129) matched for isotype and pre-F protein binding affinities. Our findings demonstrate that epitope specificity is an important determinant of antibody neutralizing potency, and defining the mechanisms of neutralization has the potential to identify improved products for the prevention and treatment of RSV infection.

## Surgical site infection

### 1. The Benefits of a Wound Protector in Preventing Incisional Surgical Site Infection in Elective Open Digestive Surgery: A Large-Scale Cohort Study.

**Author(s):** Itatsu, Keita; Yokoyama, Yukihiro; Sugawara, Gen; Kamiya, Satoaki; Terasaki, Masaki; Morioka, Atsushi; Iyomasa, Shinsuke; Shirai, Kazuhisa; Ando, Masahiko; Nagino, Masato

**Source:** World journal of surgery; Nov 2017; vol. 41 (no. 11); p. 2715-2722

**Publication Type(s):** Journal Article

**Abstract:**BACKGROUNDThe objective of this study was to evaluate the benefits of wound protectors (WPs) in preventing incisional surgical site infection (I-SSI) in open elective digestive surgery using data from a large-scale, multi-institutional cohort study.METHODSPatients who had elective digestive surgery for malignant neoplasms between November 2009 and February 2011 were included. The protective value of WPs against I-SSI was evaluated.RESULTSA total of 3201 patients were analyzed. A WP was used in 1022 patients (32%). The incident rate of I-SSI (not including organ/space SSI) was 9%. In the univariate and the multivariate analyses for perioperative risk factors for I-SSI, the use of WP was an independent favorable factor that reduced the incidence of I-SSI (odds ratio 0.73, 95% confidence interval 0.55-0.98. P = 0.038). The subgroup forest plot analyses revealed that WP reduced the risk of I-SSI only in patients aged 74 years or younger, males, non-obese patients (body mass index <25 kg/m<sup>2</sup>), patients with an American Society of Anesthesiologists score of 1/2, patients with a previous history of laparotomy, non-smokers, and patients who underwent colon and rectum operations. In patients who underwent colorectal surgery, the postoperative hospital stay was significantly shorter in patients with WP than those without WP (median 13 vs. 15 days, P = 0.040). In terms of the depth of SSI, WP only prevented superficial I-SSI and did not reduce the incidence of deep I-SSI.CONCLUSIONSWP is a useful device for preventing superficial I-SSI in open elective digestive surgery.TRIAL REGISTRATION NUMBERUMIN000004723.

### 2. Outcomes Associated With a Five-Point Surgical Site Infection Prevention Bundle in Women Undergoing Surgery for Ovarian Cancer.

**Author(s):** Lippitt, Melissa H; Fairbairn, Melissa Gerardi; Matsuno, Rayna; Stone, Rebecca L; Tanner, Edward J; Wick, Elizabeth C; Angarita, Ana C; Roche, Kara Long; Levinson, Kimberly L; Bergstrom, Jennifer E; Sinno, Abdulrahman K; Curless, Melanie S; Wethington, Stephanie; Temkin, Sarah M; Efron, Jonathan; Hobson, Deborah; Fader, Amanda N

**Source:** Obstetrics and gynecology; Oct 2017; vol. 130 (no. 4); p. 756-764

**Publication Type(s):** Journal Article Evaluation Studies

Available at [Obstetrics and gynecology](#) - from Ovid (Journals @ Ovid)

**Abstract:**OBJECTIVETo identify risk factors for surgical site infection and to define rates associated with cytoreductive surgery before and after implementation of an infection prevention

bundle. **METHODS** We conducted a prospective quality improvement study. Patients who underwent ovarian, fallopian tube, or peritoneal cancer cytoreductive surgery at an academic tertiary care center from April 2014 to April 2016 were prospectively enrolled. Patient demographics, surgical variables, and surgical site infection rates were compared with a historical cohort after introduction of a 5-point infection prevention bundle, including: 1) preoperative and intraoperative skin preparation with 4% chlorhexidine and intraoperative vaginal preparation with 4% chlorhexidine; 2) preoperative use of oral antibiotics and mechanical bowel preparation; 3) appropriate timing of intraoperative antibiotics; 4) adoption of enhanced sterile surgical techniques for colon procedures and incisional closure; and 5) perioperative incision management. **RESULTS** During the study period, 219 women underwent surgery: 91 prebundle and 128 treated in the postbundle period. Stage, body mass index, proportion of patients undergoing colon or upper abdominal surgery, and estimated blood loss were not different between the cohorts. Overall, the surgical site infection rate prebundle was 18 (20%); this was reduced to four (3%) postbundle (odds ratio [OR] 0.13, 95% CI 0.037-0.53;  $P < .001$ ). Patients who underwent a colon resection prebundle had an infection rate of 14 (33%) compared with three (7%) in the postbundle group (OR 0.14, 95% CI 0.037-0.53;  $P < .001$ ). Additionally, rates of surgical site infection-related hospital readmission were also lower in the postbundle (4/128 [3%]) compared with the prebundle group (12/91 [13%];  $P = .005$ ). **CONCLUSION** Infection is common after ovarian cancer cytoreductive surgery. Implementation of a 5-point surgical site infection prevention bundle in women undergoing ovarian cancer operations was associated with dramatically decreased infection rates and lower hospital readmission rates.

### 3. Vancomycin Powder Regimen for Prevention of Surgical Site Infection in Complex Spine Surgeries.

**Author(s):** Van Hal, Michael; Lee, Joon; Laundermilch, Dann; Nwasike, Chinedu; Kang, James

**Source:** Clinical spine surgery; Oct 2017; vol. 30 (no. 8); p. E1062

**Publication Type(s):** Journal Article

**Abstract:** **STUDY DESIGN** In total, 496 patients of a single surgeon cohort examining the surgical-site infection (SSI) rates with the addition of vancomycin powder in both diabetic and revision spine surgery cases. A historical control group of 652 patients were compared from the same surgeon over an earlier time period before the inception of using vancomycin powder prophylaxis. **OBJECTIVE** The objective of this study was to describe and compare the rates of infection in high-risk patient populations while using vancomycin powder. **SUMMARY OF BACKGROUND DATA** Vancomycin powder may not decrease an already low rate of infection. Therefore, use of vancomycin powder in high-risk patients with a higher rate of infection would potentially show benefit of vancomycin powder. **MATERIALS AND METHODS** In total, 496 patient charts were collected from a database of cases. Patients were included in the cohort if they had revision spinal operation or if they were diabetic. Patients in the time period July 2010 to August 2013 were included in the vancomycin protocol where 1 g of vancomycin powder was added to the wound before wound closure. Cases were considered positive if there was a positive culture or if there was sufficient clinical suspicion to treat. As a control to this cohort, 692 charts were reviewed from a earlier time period of the same surgeon and institution. **RESULTS** In total, 28 patients of 496 (5.6%) patients in the cohort returned to the operating room for seroma, hematoma, draining wound, or infection. Sixteen of these patients (16/496, 3.2%) had a culture positive infection or were treated as an infection. This rate was significantly lower than the historical rate before the protocol. **CONCLUSIONS** Although vancomycin does seem to be useful in decreasing SSIs, it is not a panacea. SSIs in high-risk patients were not completely eliminated by the vancomycin protocol.

#### 4. Structure, process, and outcome quality of surgical site infection surveillance in Switzerland

**Author(s):** Kuster S.P.; Eisenring M.-C.; Sax H.; Troillet N.

**Source:** Infection Control and Hospital Epidemiology; Oct 2017; vol. 38 (no. 10); p. 1172-1181

**Publication Type(s):** Article

**Abstract:**OBJECTIVE To assess the structure and quality of surveillance activities and to validate outcome detection in the Swiss national surgical site infection (SSI) surveillance program. DESIGN Countrywide survey of SSI surveillance quality. SETTING 147 hospitals or hospital units with surgical activities in Switzerland. METHODS Site visits were conducted with on-site structured interviews and review of a random sample of 15 patient records per hospital: 10 from the entire data set and 5 from a subset of patients with originally reported infection. Process and structure were rated in 9 domains with a weighted overall validation score, and sensitivity, specificity, positive predictive value, and negative predictive value were calculated for the identification of SSI. RESULTS Of 50 possible points, the median validation score was 35.5 (range, 16.25-48.5).

#### 5. Intraoperative wound irrigation to prevent surgical site infection after laparotomy (IOWISI): study protocol for a randomized controlled trial.

**Author(s):** Mueller, Tara C; Nitsche, Ulrich; Kehl, Victoria; Schirren, Rebekka; Schossow, Beate; Goess, Ruediger; Friess, Helmut; Reim, Daniel; IOWISI Study Group

**Source:** Trials; Sep 2017; vol. 18 (no. 1); p. 410

**Publication Type(s):** Journal Article

Available at [Trials](#) - from BioMed Central

Available at [Trials](#) - from Europe PubMed Central - Open Access

Available at [Trials](#) - from EBSCO (MEDLINE Complete)

**Abstract:**BACKGROUND Postoperative surgical site infection (SSI) is one of the most common hospital infections and contributes substantially to postoperative morbidity and mortality. In addition, SSIs dramatically increase the treatment cost and length of hospital stay. Following visceral surgery by laparotomy, SSI rates are especially high (14-25%). Therefore, measures to prevent SSI in this field are urgently needed. Prophylactic intraoperative wound irrigation (IOWI) of the subcutaneous soft tissue before skin closure hypothetically represents an easy and economical option to reduce SSI rates and is already frequently used in clinical practice. However, there are currently no definite recommendations on the use of IOWI since high-level evidence supporting its use is lacking. Consequently, clinical practice varies widely. Antiseptic polyhexanide (PHX)-based solutions are approved for soft-tissue wound irrigation in surgery but have not been specifically evaluated in randomized clinical trials for the prevention of SSI following laparotomy for visceral surgery. METHODS/DESIGN The IOWISI trial is a multicentre, randomized, observer- and patient-blinded clinical trial with three parallel treatment groups, comparing IOWI with a 0.04% PHX solution to no irrigation (test 1) or saline (test 2) before skin closure after laparotomy for visceral surgery (contamination level II-IV). The primary endpoint of the trial is the SSI rate within 30 days postoperatively. Statistical analysis of the primary endpoint measure will be based on the intention-to-treat population. The global level of significance is set at 2.5% for test 1 and 5% for test 2 and the sample size (n = 540) is determined to assure a power of 94% (test 1) and 85% (test 2). DISCUSSION The IOWISI trial will provide high-level evidence as a basis for clinical recommendations regarding the use of IOWI with PHX or saline and will potentially impact on future clinical guidelines and practice. The pragmatic trial design guarantees high external validity. TRIAL REGISTRATION Registered at the German Clinical Trials Register, DRKS00012251. Registered on 3 July 2017.

## 6. Reducing Surgical Site Infection with Negative-Pressure Wound Therapy After Open Abdominal Surgery: A Prospective Randomized Controlled Study.

**Author(s):** Li, P-Y; Yang, D; Liu, D; Sun, S-J; Zhang, L-Y

**Source:** Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society; Sep 2017; vol. 106 (no. 3); p. 189-195

**Publication Type(s):** Journal Article

**Abstract:**BACKGROUND AND AIMSSurgical site infection, in particular superficial incision infection, is a common type of complication following abdominal surgery. Negative-pressure wound therapy has been confirmed to reduce the incidence of surgical site infection in various surgeries, but there are few prospective randomized studies into its application to abdominal surgery.MATERIAL AND METHODSA prospective randomized controlled study was conducted in which patients with abdominal surgery and open surgery were randomly divided into a negative-pressure wound therapy experimental group and a gauze-covering control group. Information about demographic data, type of surgery, surgical sites, incision treatment outcomes, surgical site infection factors, and follow-up was recorded.RESULTSFrom May 2015 to December 2015, 71 patients were enrolled in this study, including 33 in the experimental group and 38 in the control group. There were 10 cases of incision complications, all superficial infections, with an incidence of 14.1%. The surgical site infection incidence was statistically different between the experimental and control groups (3.0% vs 23.7%,  $p = 0.031$ ). Multivariate logistic regression analysis showed that incision length  $\geq 20$  cm increased the surgical site infection incidence (odds ratio value of 15.576,  $p = 0.004$ ) and that the application of negative-pressure wound therapy reduced the surgical site infection incidence (odds ratio value of 0.073,  $p = 0.029$ ).CONCLUSIONNegative-pressure wound therapy can reduce the incidence of surgical site infection in open abdominal surgery.

## 7. Effect of post-cesarean delivery oral cephalexin and metronidazole on surgical site infection among obese women: A randomized clinical trial

**Author(s):** Valent A.M.; Dearmond C.; Masters H.R.; Boldt M.; Defranco E.; Evans A.T.; Warshak C.R.; Houston J.M.; Reddy S.; Gold A.

**Source:** JAMA - Journal of the American Medical Association; Sep 2017; vol. 318 (no. 11); p.1026-1034

**Publication Type(s):** Article

Available at [JAMA - Journal of the American Medical Association](#) - from EBSCO (MEDLINE Complete)

**Abstract:**IMPORTANCE: The rate of obesity among US women has been increasing, and obesity is associated with increased risk of surgical site infection (SSI) following cesarean delivery. The optimal perioperative antibiotic prophylactic regimen in this high-risk population undergoing cesarean delivery is unknown. OBJECTIVE: To determine rates of SSI among obese women who receive prophylactic oral cephalexin and metronidazole vs placebo for 48 hours following cesarean delivery. DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind clinical trial comparing oral cephalexin and metronidazole vs placebo for 48 hours following cesarean delivery for the prevention of SSI in obese women (prepregnancy BMI  $\geq 30$ ) who had received standard intravenous preoperative cephalosporin prophylaxis. Randomization was stratified by intact vs rupture of membranes prior to delivery. The study was conducted at the University of Cincinnati Medical Center, Cincinnati, Ohio, an academic and urban setting, between October 2010 and December 2015, with final follow-up through February 2016. INTERVENTIONS: Participants were randomly assigned to receive oral cephalexin, 500 mg, and metronidazole, 500 mg ( $n = 202$  participants), vs identical-appearing placebo ( $n = 201$  participants) every 8 hours for a total of 48 hours following cesarean delivery. MAIN OUTCOMES AND MEASURES: The primary outcome was SSI, defined as any superficial incisional, deep incisional, or organ/space infections within 30 days after cesarean

delivery. RESULTS: Among 403 randomized participants who were included (mean age, 28 [SD, 6] years; mean BMI, 39.7 [SD, 7.8]), 382 (94.6%) completed the trial. The overall rate of SSI was 10.9% (95% CI, 7.9%-14.0%). Surgical site infection was diagnosed in 13 women (6.4%) in the cephalexin-metronidazole group vs 31 women (15.4%) in the placebo group (difference, 9.0% [95% CI, 2.9%-15.0%]; relative risk, 0.41 [95% CI, 0.22-0.77]; P = .01). There were no serious adverse events, including allergic reaction, reported in either the antibiotic group or the placebo group.

CONCLUSIONS AND RELEVANCE: Among obese women undergoing cesarean delivery who received the standard preoperative cephalosporin prophylaxis, a postoperative 48-hour course of oral cephalexin and metronidazole, compared with placebo, reduced the rate of SSI within 30 days after delivery. For prevention of SSI among obese women after cesarean delivery, prophylactic oral cephalexin and metronidazole may be warranted. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01194115.

### **8. A novel risk severity score to predict pediatric spine surgical site infection in patients with cerebral palsy ranges from 0.88% to 23.3%**

**Author(s):** Matsumoto H.; Hung Meng C.; Vitale M.; Franzone J.; Troy M.; Glotzbecker M.; Striano B.; Flynn J.; Skaggs D.; Roye D.

**Source:** Developmental Medicine and Child Neurology; Sep 2017; vol. 59 ; p. 58-59

**Publication Type(s):** Conference Abstract

Available at [Developmental medicine and child neurology](#) - from Wiley Online Library Free Content - NHS

**Abstract:**Background and Objective(s): Cerebral palsy (CP) is one of the most common childhood disabilities, and up to 67% reportedly have comorbid scoliosis. Surgical treatment of scoliosis, especially neuromuscular etiologies like CP, is associated with high levels of complications. In particular, surgical site infections (SSI) lead to significant physical and financial burden on the patient, caregivers, healthcare system, and society as a whole. Therefore, the purpose of this study was to develop a risk severity scoring (RSS) system to predict SSI in children with CP undergoing spinal surgery. Study Design: Prognostic - Multicenter retrospective cohort study. Study Participants & Setting: Consecutive samples of patients with CP and undergoing surgical procedure for scoliosis were retrospectively reviewed from 4 tertiary centers. Materials/Methods: This multicenter retrospective cohort study determined the risk factors for SSI in patients with CP following surgical scoliosis correction. Inclusion criteria were pediatric patients with CP and history of index spinal fusions and revisions. Patients were identified from 4 academic institutions between January 2006 and December 2011. Data collected include patient characteristics such as demographics, etiology, comorbidities, preop labs. SSI was defined as infection within 90 days of surgery, as per the Centers for Disease Control. Results: In total, 255 patients with CP were identified. Of these, 146 (57%) were male and 109 (43%) were female. The mean age at surgery was 14.5 years. The overall SSI risk was 11.7%. Regression analysis showed that ambulatory status (OR 5.0, p<0.05), behavioral disorder/delay (OR 1.1), revision surgery (OR 1.1), and hemoglobin<14 g/dL (OR 1.1) were prognostic of SSI. The RSS model predicted SSI risk of 0.88% when none of these factors were present, and 23.3% when all factors were present. The predictive ability of the RSS was 71%, which demonstrates good discriminatory ability. Conclusions/Significance: This study shows that patients with CP experience high risk of SSI (11.7%) subsequent to spinal surgery. A RSS to predict the probability of SSI developing within 90 days after spinal surgery was created. The CP RSS is a significant addition to a surgeon's arsenal for predicting SSI risk following spine surgery. It facilitates perioperative planning discussions among the clinical team as well as between patient and family members. It allows for fair comparisons of surgical outcomes among different medical centers, based on patients' risk factors. By identifying patients with high risk of SSI, preoperative optimization

can help reduce SSI incidence. This has the potential to improve patient outcomes, reduce health care costs associated with SSI, and serves as a stepping stone for future research.

### **9. Wound Healing and Anti-inflammatory Effects of Topical Hyaluronic Acid Injection in Surgical-Site Infection Caused by Staphylococcus aureus**

**Author(s):** Park J.H.; Park E.J.; Yi H.S.

**Source:** International Journal of Lower Extremity Wounds; Sep 2017; vol. 16 (no. 3); p. 202-207

**Publication Type(s):** Article

**Abstract:** Surgical-site infection (SSI) is a common postoperative complication, primarily caused by Staphylococcus aureus. S aureus produces hyaluronidase which degrades hyaluronic acid (HA). HA prevents bacterial proliferation and has anti-inflammatory effects to promote wound healing. We evaluated the effect of HA injection with systemic antibiotics for prevention and treatment of SSIs caused by S aureus. An open wound was created on the dorsum of 40 rats. The wound bed was sutured with S aureus inoculated thread. The test group was injected with HA (HA group), and the control group received a subcutaneous injection of normal saline (NS group). All groups were then treated with intraperitoneal cefazolin injection. The sutures were removed 2 days after the procedure. Gross pathology, bacterial count, and wound histology were assessed at days 2, 4, 6, and 8 postprocedure. The HA group showed a significant reduction in the wound area compared with the control group on gross pathology (at days 8 postprocedure, 36.54% +/- 6.12% vs 50.59% +/- 5.50%, P

### **10. Variable Case Detection and Many Unreported Cases of Surgical-Site Infection Following Colon Surgery and Abdominal Hysterectomy in a Statewide Validation**

**Author(s):** Calderwood M.S.; Huang S.S.; Keller V.; Kazerouni N.N.; Janssen L.; Bruce C.B.

**Source:** Infection Control and Hospital Epidemiology; Sep 2017; vol. 38 (no. 9); p. 1091-1097

**Publication Type(s):** Article

**Abstract:** OBJECTIVE To assess hospital surgical-site infection (SSI) identification and reporting following colon surgery and abdominal hysterectomy via a statewide external validation METHODS Infection preventionists (IPs) from the California Department of Public Health (CDPH) performed on-site SSI validation for surgical procedures performed in hospitals that voluntarily participated. Validation involved chart review of SSI cases previously reported by hospitals plus review of patient records flagged for review by claims codes suggestive of SSI. We assessed the sensitivity of traditional surveillance and the added benefit of claims-based surveillance. We also evaluated the positive predictive value of claims-based surveillance (ie, workload efficiency). RESULTS Upon validation review, CDPH IPs identified 239 SSIs following colon surgery at 42 hospitals and 76 SSIs following abdominal hysterectomy at 34 hospitals. For colon surgery, traditional surveillance had a sensitivity of 50% (47% for deep incisional or organ/space [DI/OS] SSI), compared to 84% (88% for DI/OS SSI) for claims-based surveillance. For abdominal hysterectomy, traditional surveillance had a sensitivity of 68% (67% for DI/OS SSI) compared to 74% (78% for DI/OS SSI) for claims-based surveillance. Claims-based surveillance was also efficient, with 1 SSI identified for every 2 patients flagged for review who had undergone abdominal hysterectomy and for every 2.6 patients flagged for review who had undergone colon surgery. Overall, CDPH identified previously unreported SSIs in 74% of validation hospitals performing colon surgery and 35% of validation hospitals performing abdominal hysterectomy. CONCLUSIONS Claims-based surveillance is a standardized approach that hospitals can use to augment traditional surveillance methods and health departments can use for external validation.

### **11. Multi-Institution Analysis of Infection Control Practices Identifies the Subset Associated with Best Surgical Site Infection Performance: A Texas Alliance for Surgical Quality Collaborative Project.**

**Author(s):** Davis, Catherine H; Kao, Lillian S; Fleming, Jason B; Aloia, Thomas A; Texas Alliance for Surgical Quality Collaborative

**Source:** Journal of the American College of Surgeons; Aug 2017

**Publication Type(s):** Journal Article

**Abstract:**BACKGROUND In an effort to reduce surgical site infection (SSI) rates, a large number of infection control practices (ICPs), including operating room attire policies, have been recommended. However, few have proven benefits and many are costly, time-consuming, and detrimental to provider morale. The goal of this multi-institution study was to determine which ICPs are associated with lower postoperative SSI rates. STUDY DESIGN Twenty American College of Surgeons NSQIP and Texas Alliance for Surgical Quality-affiliated hospitals completed this Quality Improvement Assessment Board-approved study. Surgeon champions at each hospital ranked current surgery, anesthesia, and nursing adherence to 38 separate ICPs in 6 categories (attire, preoperative, intraoperative, preoperative, intraoperative, antibiotics, postoperative, and reporting) on 4-point scales for general surgery cases. These data were compared with the risk-adjusted general surgery SSI odds ratios contained in the July 2016 American College of Surgeons NSQIP hospital-level, risk-adjusted reports. Compliance rates were compared between the 7 best (median SSI odds ratio, 0.64; range, 0.56 to 0.70) and 7 worst (median SSI odds ratio, 1.16; range, 0.94 to 1.65) performers using ANOVA. RESULTS Nearly all hospitals reported maximal adherence to hair removal with clippers (Surgical Care Improvement Project measure Inf-6) and to best-practice prophylactic antibiotic metrics (Surgical Care Improvement Project measure Inf-1-3). Variable adherence was identified across many ICPs and more frequent compliance with 8 ICPs correlated with lower SSI odds ratios, including preoperative shower; skin preparation technique; using clean instruments, gowns, and gloves for wound closure and dressing changes; and transparent internal reporting of SSI data. Operating room attire ICPs, including coverage of nonscrubbed provider head and arm hair, did not correlate with SSI rates. CONCLUSION This analysis suggests that the subset of ICPs that focus on perioperative patient skin and wound hygiene and transparent display of SSI data, not operating room attire policies, correlated with SSI rates. Implementation of this subset of evidence-based ICPs may improve SSI rates at lower-performing hospitals.

### **12. Comparison of Superficial Surgical Site Infection Between Delayed Primary Versus Primary Wound Closure in Complicated Appendicitis: A Randomized Controlled Trial.**

**Author(s):** Siribumrungwong, Boonying; Chantip, Anuwat; Noorit, Pinit; Wilasrusmee, Chumpon; Ungpinitpong, Winai; Chotiya, Pradya; Leerapan, Borwornsom; Woratanarat, Patarawan; McEvoy, Mark; Attia, John; Thakkestian, Ammarin

**Source:** Annals of surgery; Aug 2017

**Publication Type(s):** Journal Article

**Abstract:**OBJECTIVE To compare superficial surgical site infection (SSI) rates between delayed primary wound closure (DPC) and primary wound closure (PC) for complicated appendicitis. BACKGROUND SSI is common in appendectomy for complicated appendicitis. DPC is preferentially used over PC, but its efficacy is still controversial. METHODS A multicenter randomized controlled trial was conducted in 6 hospitals in Thailand, enrolling patients with gangrenous and ruptured appendicitis. Patients were randomized to PC (ie, immediately wound closure) or DPC (ie, wound closure at postoperative days 3-5). Superficial SSI was defined by the Center for Disease Control criteria. Secondary outcomes included postoperative pain, length of stay, recovery time, quality of life, and cost of treatment. RESULTS In all, 303 and 304 patients were randomized to PC and



DPC groups, and 5 and 4 patients were lost to follow-up, respectively, leaving 300 and 298 patients in the modified intention-to-treat analysis. The superficial SSI rate was lower in the PC than DPC groups [ie, 7.3% (95% confidence interval 4.4, 10.3) vs 10% (95% CI 6.6, 13.3)] with a risk difference (RD) of -2.7% (-7.1%, 1.9%), but this RD was not significant. Postoperative pain, length of stay, recovery times, and quality of life were nonsignificantly different with corresponding RDs of 0.3 (-2.5, 3.0), -0.1 (-0.5, 0.3), -0.2 (-0.8, 0.4), and 0.02 (-0.01, 0.04), respectively. However, costs for PC were 2083 (1410, 2756) Baht cheaper than DPC (~\$60 USD). CONCLUSION Superficial SSI rates for the PC group were slightly lower than DPC group, but this did not reach statistical significance. Costs were significantly lower for the PC group. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. <http://creativecommons.org/licenses/by-nc-nd/4.0>.

### **13. A Prospective, Randomized, Controlled Clinical Trial to Assess Use of 2% Lidocaine Irrigation to Prevent Abdominal Surgical Site Infection.**

**Author(s):** Quiroga-Garza, Alejandro; Valdivia-Balderas, Juan Manuel; Trejo-Sánchez, Miguel Ángel; Espinosa-Uribe, Abraham Guadalupe; Reyes-Hernández, Cynthia Guadalupe; Elizondo-Omaña, Rodrigo Enrique

**Source:** Ostomy/wound management; Aug 2017; vol. 63 (no. 8); p. 12-21

**Publication Type(s):** Journal Article

**Abstract:** Surgical site infections (SSI) are the third most common nosocomial infection, increasing morbidity and mortality rates of patients as well as their costs of care, but longer-term follow up studies and data are limited. Lidocaine, in addition to being a readily available and accessible local anesthetic, is known to have bacteriostatic properties. A prospective, descriptive, controlled, randomized clinical trial was conducted among patients scheduled to undergo abdominal surgery in the general surgical unit of a Mexican hospital. The purpose of the study was to assess the incidence of SSIs in general and to compare the 30-day postoperative infection outcomes of saline irrigation to saline irrigation followed by 2% lidocaine application before skin closure in wounds grade II to IV per the Centers for Disease Control and Prevention surgical wound classification. All patients received systemic antibiotics before surgery. Eighty-four (84) patients (40 men and 44 women; mean age  $49.02 \pm 19.9$  years, range 18-92 years), 39 in the control and 45 in the experimental group, completed the 30-day follow-up without experiencing nonsurgery-related complications. The overall incidence of SSIs (specifically, seromas and abscesses) was 17.86%; the incidence of abscess formation was 7.14%. The overall incidence of SSIs in the lidocaine group was 8.89% compared to 28.2% in the saline only group ( $P = .02$ ); the relative risk was 1.8 ( $P = .02$ ; 95% CI 1.19-2.74) and 0.45 ( $P = .02$ ; 95% CI 0.19-1.06) in the saline and lidocaine groups, respectively. Hemoglobin and albumin levels were significantly lower in patients who did compared to those who did not develop an SSI ( $P = .02$  and  $.04$ , respectively). No significant SSI rate differences were seen between patients who did and did not have a drain placed. In patients who developed an abscess, *Escherichia coli* was the most prevalent bacteria and present in 40% of collected uid. While carefully controlled clinical studies are needed, lidocaine appears to be a viable option to decrease the incidence of SSI if applied as irrigation before wound closure in patients undergoing abdominal surgery.

#### **14. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017.**

**Author(s):** Berríos-Torres, Sandra I; Umscheid, Craig A; Bratzler, Dale W; et al; Healthcare Infection Control Practices Advisory Committee

**Source:** JAMA surgery; Aug 2017; vol. 152 (no. 8); p. 784-791

**Publication Type(s):** Practice Guideline Journal Article

Available at [JAMA surgery](#) - from EBSCO (MEDLINE Complete)

**Abstract:** Importance The human and financial costs of treating surgical site infections (SSIs) are increasing. The number of surgical procedures performed in the United States continues to rise, and surgical patients are initially seen with increasingly complex comorbidities. It is estimated that approximately half of SSIs are deemed preventable using evidence-based strategies. Objective To provide new and updated evidence-based recommendations for the prevention of SSI. Evidence Review A targeted systematic review of the literature was conducted in MEDLINE, EMBASE, CINAHL, and the Cochrane Library from 1998 through April 2014. A modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of evidence and the strength of the resulting recommendation and to provide explicit links between them. Of 5759 titles and abstracts screened, 896 underwent full-text review by 2 independent reviewers. After exclusions, 170 studies were extracted into evidence tables, appraised, and synthesized. Findings Before surgery, patients should shower or bathe (full body) with soap (antimicrobial or nonantimicrobial) or an antiseptic agent on at least the night before the operative day. Antimicrobial prophylaxis should be administered only when indicated based on published clinical practice guidelines and timed such that a bactericidal concentration of the agents is established in the serum and tissues when the incision is made. In cesarean section procedures, antimicrobial prophylaxis should be administered before skin incision. Skin preparation in the operating room should be performed using an alcohol-based agent unless contraindicated. For clean and clean-contaminated procedures, additional prophylactic antimicrobial agent doses should not be administered after the surgical incision is closed in the operating room, even in the presence of a drain. Topical antimicrobial agents should not be applied to the surgical incision. During surgery, glycemic control should be implemented using blood glucose target levels less than 200 mg/dL, and normothermia should be maintained in all patients. Increased fraction of inspired oxygen should be administered during surgery and after extubation in the immediate postoperative period for patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation. Transfusion of blood products should not be withheld from surgical patients as a means to prevent SSI. Conclusions and Relevance This guideline is intended to provide new and updated evidence-based recommendations for the prevention of SSI and should be incorporated into comprehensive surgical quality improvement programs to improve patient safety.

#### **15. Preoperative chlorhexidine versus povidone-iodine antiseptics for preventing surgical site infection: A meta-analysis and trial sequential analysis of randomized controlled trials.**

**Author(s):** Zhang, Dan; Wang, Xi-Chen; Yang, Zeng-Xi; Gan, Jian-Xin; Pan, Jie-Bin; Yin, Lan-Ning

**Source:** International journal of surgery (London, England); Aug 2017; vol. 44 ; p. 176-184

**Publication Type(s):** Journal Article Review

**Abstract:** BACKGROUND Updated guidelines for surgical site infections (SSIs) suggested that chlorhexidine (CH) or povidone-iodine (PVI) product was equally appropriate to be applied in preoperative disinfection, but which one was optimal remained ambiguous. Moreover, recent studies reported inconsistent results. Thus, an updated meta-analysis was conducted to clarify the superiority of CH or PVI for prevention of SSIs in clean and clean-contaminated surgery. METHODS From the inception to November 2016, Pubmed, Embase, and the Cochrane

library were systematically searched for randomized controlled trials (RCTs) which explored preoperative antiseptics schemes (CH or PVI) for prevention of SSIs in clean and clean-contaminated surgery. Relative risks (RRs) with 95% confidence interval (CI) were calculated using random effects model. Furthermore, subgroup analysis, sensitive analysis, and trial sequential analysis (TSA) were applied to estimate whether overall pooled effect was enough credible and robust. RESULTSThirteen RCTs involving 6997 patients (3352 in CH and 3645 in PVI group) undergoing clean and clean-contaminated surgeries were included in our meta-analysis. Compared with PVI, preoperative CH antiseptics was associated with lower incidence of SSIs (RR, 0.70; 95%CI, 0.60-0.83, I<sup>2</sup> = 0). Additionally, subgroup analysis, sensitive analysis, and TSA indicated that the current available evidence was reliable and robust. CONCLUSIONSCH should be more preferentially recommended for preoperative skin preparation as compared with PVI in clean and clean-contaminated surgery.

### **16. Surgical-site infection in gynecologic surgery: pathophysiology and prevention.**

**Author(s):** Steiner, Holly L; Strand, Eric A

**Source:** American journal of obstetrics and gynecology; Aug 2017; vol. 217 (no. 2); p. 121-128

**Publication Type(s):** Journal Article Review

**Abstract:**Surgical-site infections (SSIs) represent a well-known cause of patient morbidity as well as added health care costs. In gynecologic surgery, particularly hysterectomy, SSIs are often the result of a number of risk factors that may or may not be modifiable. As both the Centers for Medicaid and Medicare Services and the Joint Commission on the Accreditation of Healthcare Organizations have identified SSIs as a patient safety priority, gynecologic surgeons continue to seek out the most effective interventions for SSI prevention. This review studies the epidemiology and pathophysiology of SSIs in gynecologic surgery and evaluates the current literature regarding possible interventions for SSI prevention, both as individual measures and as bundles. Data from the obstetrical and general surgery literature will be reviewed when gynecological data are either unclear or unavailable. Practitioners and hospitals may use this information as they develop strategies for SSI prevention in their own practice.

### **17. Meta-analysis of randomized and quasi-randomized clinical trials of topical antibiotics after primary closure for the prevention of surgical-site infection.**

**Author(s):** Heal, C F; Banks, J L; Lepper, P; Kontopantelis, E; van Driel, M L

**Source:** The British journal of surgery; Aug 2017; vol. 104 (no. 9); p. 1123-1130

**Publication Type(s):** Meta-analysis Comparative Study Journal Article Review

**Abstract:**BACKGROUND Surgical-site infections (SSIs) increase patient morbidity and costs. The aim was to identify and synthesize all RCTs evaluating the effect of topical antibiotics on SSI in wounds healing by primary intention. METHODSThe search included Ovid MEDLINE, Ovid Embase, the Cochrane Wounds Specialized Register, Central Register of Controlled Trials and EBSCO CINAHL from inception to May 2016. There was no restriction of language, date or setting. Two authors independently selected studies, extracted data and assessed risk of bias. When sufficient numbers of comparable trials were available, data were pooled in meta-analysis. RESULTS Fourteen RCTs with 6466 participants met the inclusion criteria. Pooling of eight trials (5427 participants) showed that topical antibiotics probably reduced the risk of SSI compared with no topical antibiotic (risk ratio (RR) 0.61, 95 per cent c.i. 0.42 to 0.87; moderate-quality evidence), equating to 20 fewer SSIs per 1000 patients treated. Pooling of three trials (3012 participants) for risk of allergic contact dermatitis found no clear difference between antibiotics and no antibiotic (RR 3.94, 0.46 to 34.00; very low-quality evidence). Pooling of five trials (1299 participants) indicated that topical antibiotics probably reduce the risk of SSI compared with topical antiseptics (RR 0.49, 0.30 to 0.80; moderate-quality

evidence); 43 fewer SSIs per 1000 patients treated. Pooling of two trials (541 participants) showed no clear difference in the risk of allergic contact dermatitis with antibiotics or antiseptic agents (RR 0.97, 0.52 to 1.82; very low-quality evidence). **CONCLUSION** Topical antibiotics probably prevent SSI compared with no topical antibiotic or antiseptic. No conclusion can be drawn regarding whether they cause allergic contact dermatitis.

### **18. Optimal skin antiseptic agents for prevention of surgical site infection in cesarean section: a meta-analysis with trial sequential analysis**

**Author(s):** Huang H.; Li G.; Wang H.; He M.

**Source:** Journal of Maternal-Fetal and Neonatal Medicine; Aug 2017 ; p. 1-8

**Publication Type(s):** Article In Press

**Abstract:** Purpose: The best choice of antiseptic agent for skin preparation at cesarean section remains controversial. We performed this meta-analysis to assess whether chlorhexidine (CH)-based skin antisepsis was more effective than povidone iodine (PI)-based antisepsis for the prevention of surgical site infection (SSI) after cesarean section. Methods: PubMed, EMBASE, and the Cochrane Library were systematically searched to identify English publications that compared chlorhexidine gluconate (CH) as a skin preparation agent with PI in cesarean section. The primary outcome was SSI rate. Review Manager 5.3 was used to analyze the collected data and trial sequential analysis (TSA) Software 0.9 (Cochrane Collaboration, Oxford, UK) beta was applied to estimate whether the overall pooled outcome was conclusive. Results: Six articles involving 4385 participants were included in this study. The outcomes showed that CH-based skin antisepsis, compared with PI-based antisepsis, was not associated with a decreased overall rate of SSI (risk ratio [RR], 0.74; 95% confidence interval [CI], 0.54-1.02;  $p=0.07$ ). TSA indicated that the current available evidence was inconclusive. There were no differences in adverse skin reactions in the two groups. Conclusions: This study provides evidence that CH-based antisepsis for skin preparation does not show an additional advantage in reducing risk of SSI after cesarean section. However, additional high-quality, randomized clinical trials are needed to confirm these findings.

### **19. Surgical site infection related to use of elastomeric pumps in pectus excavatum repair. Lessons learned from root cause analysis**

**Author(s):** Apelt N.; Bates C.; Brown R.L.; Garcia V.; Schaffzin J.; Mecoli M.; Sadhasivam S.

**Source:** Journal of Pediatric Surgery; Aug 2017; vol. 52 (no. 8); p. 1292-1295

**Publication Type(s):** Article

**Abstract:** Background Pectus excavatum repair (PEX) is among the most painful thoracic procedures performed. Continuous peripheral nerve blockade (CPNB) is known to be efficacious in optimizing pain control while limiting narcotic use in adult thoracic procedures. It was introduced in May 2015 as a bridge to oral pain control in children undergoing PEX. Consequently, the surgical site infection (SSI) rate increased from 2.7% to 27.7%. Methods SSI surveillance followed national guidelines. The abrupt increase prompted root cause analysis and cessation of CPNB use. A dynamic systems model of SSI in PEX was developed. Statistical analysis compared SSI outcomes with and without CPNB. Results From May 2015 to June 2015, 21 PEX were performed; 11 with CPNB. 6 SSIs were observed. Use of CPNB significantly ( $p = 0.008$ ) increased SSI incidence. Haller index, number of bars, usage of Fiberwire, methicillin resistant *S. aureus* colonization and length of stay did not differ. Root cause analysis revealed the proximity of CPNB catheters to the wound, the use of CPNB with implanted hardware and a delayed utilization of CPNB catheters to be of concern. Conclusion Introduction of CPNB coincided with a significant increase in SSI. Further study is needed to assess the safety of CPNB in pediatric PEX. Level of evidence Level III treatment study.

## 20. Post-Caesarean Section Surgical Site Infection Surveillance Using an Online Database and Mobile Phone Technology

**Author(s):** Castillo E.; Wilson D.; McIsaac C.; Kohr R.; MacDougall B.

**Source:** Journal of Obstetrics and Gynaecology Canada; Aug 2017; vol. 39 (no. 8); p. 645

**Publication Type(s):** Article

**Abstract:**Background Obstetric surgical site infections (SSIs) are common and expensive to the health care system but remain under reported given shorter postoperative hospital stays and suboptimal post-discharge surveillance systems. SSIs, for the purpose of this paper, are defined according to the Center for Disease Control and Prevention (1999) as infection incurring within 30 days of the operative procedure (in this case, Caesarean section [CS]). Primary Objective Demonstrate the feasibility of real-life use of a patient driven SSIs post-discharge surveillance system consisting of an online database and mobile phone technology (surgical mobile app - how2trak) among women undergoing CS in a Canadian urban centre. Secondary Objective Estimate the rate of SSIs and associated predisposing factors. Methods Prospective cohort of consecutive women delivering by CS at one urban Canadian hospital. Using surgical mobile app-how2trak-predetermined demographics, comorbidities, procedure characteristics, and self-reported symptoms and signs of infection were collected and linked to patients' incision self-portraits (photos) on postpartum days 3, 7, 10, and 30. Results A total of 105 patients were enrolled over a 5-month period. Mean age was 31 years, 13% were diabetic, and most were at low risk of surgical complications. Forty-six percent of surgeries were emergency CSs, and 104/105 received antibiotic prophylaxis. Forty-five percent of patients (47/105) submitted at least one photo, and among those, one surgical site infection was detected by photo appearance and self-reported symptoms by postpartum day 10. The majority of patients whom uploaded photos did so multiple times and 43% of them submitted photos up to day 30. Patients with either a diagnosis of diabetes or self-reported Asian ethnicity were less likely to submit photos. Conclusions Post-discharge surveillance for CS-related SSIs using surgical mobile app how2trak is feasible and deserves further study in the post-discharge setting.

## 21. Silver-containing dressing for surgical site infection in clean and clean-contaminated operations: a systematic review and meta-analysis of randomized controlled trials.

**Author(s):** Li, Hui-Zi; Zhang, Lei; Chen, Jia-Xi; Zheng, Yang; Zhu, Xiang-Nan

**Source:** The Journal of surgical research; Jul 2017; vol. 215 ; p. 98-107

**Publication Type(s):** Meta-analysis Journal Article Review

**Abstract:**BACKGROUND Silver-containing dressings for the prevention of surgical site infections (SSIs) remained controversial, and accumulating evidence was lacking, so a meta-analysis was conducted to systematically assess the effectiveness and safety of silver-containing dressings for clean and clean-contaminated surgical incisions. METHODSPubmed, Embase, and the Cochrane Library were searched from the inception to February 2016 for randomized controlled trials (RCTs), which explored silver-containing dressings for the prevention of SSIs in clean and clean-contaminated operations. Relative risk (RR) with 95% confidence interval (CI) was pooled using random effects model. Predefined subgroup analyses, sensitivity analyses, and influence analyses were further undertaken. RESULTSNine RCTs totaling 2196 patients (1141 in silver-containing group and 1055 in control group) were included. Silver-containing dressings did not effectively prevent the incidence of SSIs (9 RCTs; RR: 0.92; 95% CI: 0.66-1.29; I<sup>2</sup> = 40%), superficial SSIs (5 RCTs; RR: 0.67; 95% CI: 0.36-1.24; I<sup>2</sup> = 36%), and deep SSIs (5 RCTs; RR: 0.78; 95% CI: 0.41-1.49; I<sup>2</sup> = 0). Subgroup analyses, sensitivity analyses, and influence analyses confirmed the robustness of the pooled estimate. CONCLUSIONSThe current available evidence indicated that silver-containing dressing as

compared with silver-free dressing was not associated with lower incidence of SSIs. Considering the quality of evidence ranking very low, further studies with higher quality should be warranted.

## **22. The role of antimicrobial sutures in preventing surgical site infection.**

**Author(s):** Leaper, D; Wilson, P; Assadian, O; Edmiston, C; Kiernan, M; Miller, A; Bond-Smith, G; Yap, J

**Source:** Annals of the Royal College of Surgeons of England; Jul 2017; vol. 99 (no. 6); p. 439-443

**Publication Type(s):** Meta-analysis Journal Article Review

Available at [Annals of the Royal College of Surgeons of England](#) - from EBSCO (MEDLINE Complete)

**Abstract:**INTRODUCTION Healthcare associated infections (HCAIs) are falling following widespread and enforced introduction of guidelines, particularly those that have addressed antibiotic resistant pathogens such as methicillin resistant Staphylococcus aureus or emergent pathogens such as Clostridium difficile, but no such decline has been seen in the incidence of surgical site infection (SSI), either in the UK, the EU or the US. SSI is one of the HCAIs, which are all avoidable complications of a surgical patient's pathway through both nosocomial and community care. METHODS This report is based on a meeting held at The Royal College of Surgeons of England on 21 July 2016. Using PubMed, members of the panel reviewed the current use of antiseptics and antimicrobial sutures in their specialties to prevent SSI. FINDINGS The group agreed that wider use of antiseptics in surgical practice may help in reducing reliance on antibiotics in infection prevention and control, especially in the perioperative period of open elective colorectal, hepatobiliary and cardiac operative procedures. The wider use of antiseptics includes preoperative showering, promotion of hand hygiene, (including the appropriate use of surgical gloves), preoperative skin preparation (including management of hair removal), antimicrobial sutures and the management of dehisced surgical wounds after infection. The meeting placed emphasis on the level I evidence that supports the use of antimicrobial sutures, particularly in surgical procedures after which the SSI rate is high (colorectal and hepatobiliary surgery) or when a SSI can be life threatening even when the rate of SSI is low (cardiac surgery).

## **23. Risk of surgical site infection, acute kidney injury, and Clostridium difficile infection following antibiotic prophylaxis with vancomycin plus a beta-lactam versus either drug alone: A national propensity-score-adjusted retrospective cohort study**

**Author(s):** Branch-Elliman W.; Strymish J.; Gupta K.; Itani K.M.F.; O'Brien W.J.; Ripollone J.E.; Schweizer M.L.; Perencevich E.

**Source:** PLoS Medicine; Jul 2017; vol. 14 (no. 7)

**Publication Type(s):** Article

Available at [PLoS Medicine](#) - from Public Library of Science (PLoS)

Available at [PLoS Medicine](#) - from Europe PubMed Central - Open Access

Available at [PLoS Medicine](#) - from EBSCO (MEDLINE Complete)

**Abstract:**Background: The optimal regimen for perioperative antimicrobial prophylaxis is controversial. Use of combination prophylaxis with a beta-lactam plus vancomycin is increasing; however, the relative risks and benefits associated with this strategy are unknown. Thus, we sought to compare postoperative outcomes following administration of 2 antimicrobials versus a single agent for the prevention of surgical site infections (SSIs). Potential harms associated with combination regimens, including acute kidney injury (AKI) and Clostridium difficile infection (CDI), were also considered. Methods and findings: Using a multicenter, national Veterans Affairs (VA) cohort, all patients who underwent cardiac, orthopedic joint replacement, vascular, colorectal, and hysterectomy procedures during the period from 1 October 2008 to 30 September 2013 and who received planned manual review of perioperative antimicrobial prophylaxis regimen and manual

review for the 30-day incidence of SSI were included. Using a propensity-adjusted log-binomial regression model stratified by type of surgical procedure, the association between receipt of 2 antimicrobials (vancomycin plus a beta-lactam) versus either single agent alone (vancomycin or a beta-lactam) and SSI was evaluated. Measures of association were adjusted for age, diabetes, smoking, American Society of Anesthesiologists score, preoperative methicillin-resistant *Staphylococcus aureus* (MRSA) status, and receipt of mupirocin. The 7-day incidence of postoperative AKI and 90-day incidence of CDI were also measured. In all, 70,101 procedures (52,504 beta-lactam only, 5,089 vancomycin only, and 12,508 combination) with 2,466 (3.5%) SSIs from 109 medical centers were included. Among cardiac surgery patients, combination prophylaxis was associated with a lower incidence of SSI (66/6,953, 0.95%) than single-agent prophylaxis (190/12,834, 1.48%; crude risk ratio [RR] 0.64, 95% CI 0.49, 0.85; adjusted RR 0.61, 95% CI 0.46, 0.83). After adjusting for SSI risk, no association between receipt of combination prophylaxis and SSI was found for the other types of surgeries evaluated, including orthopedic joint replacement procedures. In MRSA-colonized patients undergoing cardiac surgery, SSI occurred in 8/346 (2.3%) patients who received combination prophylaxis versus 4/100 (4.0%) patients who received vancomycin alone (crude RR 0.58, 95% CI 0.18, 1.88). Among MRSA-negative and -unknown cardiac surgery patients, SSIs occurred in 58/6,607 (0.9%) patients receiving combination prophylaxis versus 146/10,215 (1.4%) patients who received a beta-lactam alone (crude RR 0.61, 95% CI 0.45, 0.83). Based on these associations, the number needed to treat to prevent 1 SSI in MRSA-colonized patients is estimated to be 53, compared to 176 in non-MRSA patients. CDI incidence was similar in both exposure groups. Across all types of surgical procedures, risk of AKI was increased in the combination antimicrobial prophylaxis group (2,971/12,508 [23.8%] receiving combination versus 1,058/5,089 [20.8%] receiving vancomycin alone versus 7,314/52,504 [13.9%] receiving beta-lactam alone). We found a significant association between absolute risk of AKI and receipt of combination regimens across all types of procedures. If the observed association is causal, the number needed to harm for severe AKI following cardiac surgery would be 167. The major limitation of our investigation is that it is an observational study in a predominantly male population, which may limit generalizability and lead to unmeasured confounding. Conclusions: There are benefits but also unintended consequences of antimicrobial and infection prevention strategies aimed at "getting to zero" healthcare-associated infections. In our study, combination prophylaxis was associated with both benefits (reduction in SSIs following cardiac surgical procedures) and harms (increase in postoperative AKI). In cardiac surgery patients, the difference in risk-benefit profile by MRSA status suggests that MRSA-screening-directed prophylaxis may optimize benefits while minimizing harms in this selected population. More information about long-term outcomes and patient and societal preferences regarding risk of SSI versus risk of AKI is needed to improve clinical decision-making.

#### **24. Timing of preoperative antibiotic prophylaxis in 54,552 patients and the risk of surgical site infection**

**Author(s):** De Jonge S.W.; Gans S.L.; Ateman J.J.; Boermeester M.A.; Solomkin J.S.; Dellinger P.E.

**Source:** *Medicine (United States)*; Jul 2017; vol. 96 (no. 29)

**Publication Type(s):** Review

Available at [Medicine \(United States\)](#) - from Europe PubMed Central - Open Access

**Abstract:** The aim of the study was to assess the effect of timing of preoperative surgical antibiotic prophylaxis (SAP) on surgical site infection (SSI) and compare the different timing intervals. The benefit of routine use of SAP prior to surgery has long been recognized. However, the optimal timing has not been defined. For the purpose of developing recommendations for the World Health Organization guideline for SSI prevention, a systematic review and meta-analysis of all relevant evidence was conducted. Major medical databases were searched from 1990 to 2016. The primary outcome was SSI after preoperative-SAP comparing different timing intervals. Adjusted odds ratios

(OR) with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model. Fourteen papers with 54,552 patients were included in this review. In a quantitative analysis, there was no significant difference when SAP was administered 120-60 minutes prior to incision compared to administration 60-0 minutes prior to incision. Studies investigating different timing intervals within the last 60 minutes time frame reported contradictory results. The risk of SSI almost doubled when SAP was administered after first incision (OR:1.89; 95%CI:[1.05-3.40]) and was 5 times higher when administered more than 120 minutes prior to incision (OR5.26; 95%CI:[3.29-8.39]). Administration of antibiotic prophylaxis more than 120 minutes before incision or after incision is associated a higher risk of surgical site infections than administration less than 120 minutes before incision. Within this 120-minute time frame prior to incision, no differential effects could be identified. The broadly accepted recommendation to administer prophylaxis within a 60-minute time frame prior to incision could not be substantiated.

## Influenza

### 1. Estimating influenza vaccine effectiveness: Evolution of methods to better understand effects of confounding in older adults.

**Author(s):** McElhaney, Janet E; Andrew, Melissa K; McNeil, Shelly A

**Source:** Vaccine; Nov 2017; vol. 35 (no. 46); p. 6269-6274

**Publication Type(s):** Journal Article Review

**Abstract:**Older adults are at high risk for serious complications of influenza illness and loss of vaccine-mediated protection. It is increasingly recognized that in addition to age, multiple chronic conditions and associated frailty contribute to the decline in vaccine effectiveness in this population. However, observational studies have been fraught with issues of confounding related to the degree of frailty and functional decline, measures of which are not included in standard administrative health care databases that are used to calculate vaccine effectiveness. This issue has led to the identification of confounding by indication or from "healthy vaccinee" bias, which respectively lead to underestimates or overestimates of influenza vaccine effectiveness. In addition, the sensitivity and specificity of the criteria used to define influenza-like illness declines with increasing age due to atypical presentations of illness and the inability to distinguish between influenza and other respiratory viruses. The test-negative case:control design has emerged as a method to estimate influenza vaccine effectiveness by comparing vaccination rates in those with laboratory-confirmed influenza to those with other acute viral respiratory illnesses. This review provides a perspective on how test-negative case:control study designs and new insights into mechanisms of protection have considerably strengthened influenza vaccination policy decisions for older adults that have historically been undermined by the conclusions of observational studies.

### 2. Influenza vaccines for preventing acute otitis media in infants and children.

**Author(s):** Norhayati, Mohd N; Ho, Jacqueline J; Azman, Mohd Y

**Source:** The Cochrane database of systematic reviews; Oct 2017; vol. 10 ; p. CD010089

**Publication Date:** Oct 2017

**Publication Type(s):** Journal Article Review

**PubMedID:** 29039160

**Abstract:**BACKGROUND Acute otitis media (AOM) is one of the most common infectious diseases in children. It has been reported that 64% of infants have an episode of AOM by the age of six months and 86% by one year. Although most cases of AOM are due to bacterial infection, it is commonly



triggered by a viral infection. In most children AOM is self limiting, but it does carry a risk of complications. Since antibiotic treatment increases the risk of antibiotic resistance, influenza vaccines might be an effective way of reducing this risk by preventing the development of AOM.

**OBJECTIVES**To assess the effectiveness of influenza vaccine in reducing the occurrence of acute otitis media in infants and children.

**SEARCH METHODS**We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, LILACS, Web of Science, the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov (15 February 2017). We also searched the reference lists of included studies to identify any additional trials.

**SELECTION CRITERIA**Randomised controlled trials comparing influenza vaccine with placebo or no treatment in infants and children aged younger than six years. We included children of either sex and of any ethnicity, with or without a history of recurrent AOM.

**DATA COLLECTION AND ANALYSIS**Two review authors independently screened studies, assessed trial quality, and extracted data. We performed statistical analyses using the random-effects and fixed-effect models and expressed the results as risk ratio (RR), risk difference (RD), and number needed to treat for an additional beneficial outcome (NNTB) for dichotomous outcomes, with 95% confidence intervals (CI).

**MAIN RESULTS**We included 11 trials (6 trials in high-income countries and 5 multicentre trials in high-, middle-, and low-income countries) involving 17,123 children aged 6 months to 6 years. Eight trials recruited participants from a healthcare setting. Ten trials (and all four trials that contributed to the primary outcome) declared funding from vaccine manufacturers. Four trials reported adequate allocation concealment, and 10 trials reported adequate blinding of participants and personnel. Attrition was low for eight trials included in the analysis. The primary outcome showed a small reduction in at least one episode of AOM over at least six months of follow-up (4 trials, 3134 children; RR 0.84, 95% CI 0.69 to 1.02; RD -0.04, 95% CI -0.08 to -0.00; NNTB 25, 95% CI 12.5 to 100; low-quality evidence). The subgroup analyses (i.e. number of courses and types of vaccine administered) showed no differences. There was a reduction in the use of antibiotics in vaccinated children (2 trials, 1223 children; RR 0.70, 95% CI 0.59 to 0.83; RD -0.11, 95% CI -0.16 to -0.06; moderate-quality evidence). We were unable to demonstrate whether there was any difference in the utilisation of health care. The use of influenza vaccine resulted in a significant increase in fever (7 trials, 10,615 children; RR 1.15, 95% CI 1.06 to 1.24; RD 0.02, 95% CI 0.00 to 0.04; low-quality evidence), rhinorrhoea (6 trials, 10,563 children; RR 1.17, 95% CI 1.07 to 1.29; RD 0.09, 95% CI 0.01 to 0.16; low-quality evidence), but no difference in pharyngitis. No major adverse events were reported. Differing from the protocol, the original publication of the review included a subgroup analysis of AOM episodes by season, and the secondary outcome 'types of influenza vaccine' was changed to a subgroup analysis. For this update, we removed the subgroup analyses for trial setting, season, and utilisation of health care due to the small number of trials involved. We removed Belshe 2000 from primary and secondary outcomes (courses of vaccine and types of vaccine) because it reported episodes of AOM per person. We did not perform a subgroup analysis by type of adverse event. We have reported each type of adverse event as a separate analysis.

**AUTHORS' CONCLUSIONS**Influenza vaccine results in a small reduction in AOM. The observed reduction in the use of antibiotics needs to be considered in light of current recommended practices aimed at avoiding antibiotic overuse. Safety data from these trials were limited. The benefits may not justify the use of influenza vaccine without taking into account the vaccine efficacy in reducing influenza and safety data. We judged the quality of the evidence to be low to moderate. Additional research is needed.

### **3. The road to a more effective influenza vaccine: Up to date studies and future prospects.**

**Author(s):** Sano, Kaori; Ainai, Akira; Suzuki, Tadaki; Hasegawa, Hideki

**Source:** Vaccine; Sep 2017; vol. 35 (no. 40); p. 5388-5395

**Publication Type(s):** Journal Article Review

Available at [Vaccine](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:**Influenza virus causes an acute respiratory infection in humans. Frequent point mutations in the influenza genome and occasional exchange of genetic segments between virus strains help the virus evade the pre-existing immunity, resulting in epidemics and pandemics. Although vaccination is the most effective intervention, mismatches between circulating viruses and vaccine strains reduce vaccine efficacy. Furthermore, current injectable vaccines induce IgG antibodies in serum (which limit progression of influenza symptoms) but not secretory IgA antibodies in the respiratory mucosa (which prevent virus infection efficiently). Therefore, numerous studies have attempted to improve influenza vaccines. The discovery of broadly neutralizing antibodies has progressed research into antigen design. Studies designed to improve vaccine efficacy by changing the vaccine administration route have also been conducted. A thorough understanding of the mechanisms underlying the action of various vaccines is essential if we are to develop a universal influenza vaccine. Therefore, evaluating the quality and quantity of antibodies induced by vaccines, which determine vaccine efficacy, is critical. However, at present vaccine evaluation relies on hemagglutination inhibition tests, which only measure the quantity of antibody produced. Antibody repertoires comprise a set of antibodies with specific genetic or molecular features that correspond to their functions. Genetically and functionally similar antibodies may be produced by multiple individuals exposed to an identical stimulus. Therefore, it may be possible to evaluate and compare multiple vaccine strategies in terms of the quality and quantity of an antibody response induced by a vaccine by examining antibody repertoires. Recent studies have used single cell expression and high-throughput immunoglobulin sequencing to provide a detailed picture of antibody responses. These novel methods may be critical for detailed characterization of antibody repertoires induced by various vaccination strategies.

#### **4. Perspectives from the society for pediatric research (SPR): Decreased effectiveness of the live attenuated influenza vaccine (LAIV).**

**Author(s):** Gill, Michelle A; Schlaudecker, Elizabeth P

**Source:** Pediatric research; Sep 2017

**Publication Type(s):** Journal Article Review

**Abstract:**Purpose of SPR Perspectives Reviews: Address contemporary scientific issues and controversies by leveraging the expertise of SPR membersIncrease SPR member engagement with the journalPair established and younger SPR members to simultaneously increase interaction between SPR members and create opportunities for mentorship The intranasal Live Attenuated Influenza Vaccine (LAIV), FluMist, has been widely appreciated by pediatricians, parents and children alike for its ease of administration. Concerns regarding lack of effectiveness in recent influenza seasons, however, led to the CDC Advisory Committee on Immunization Practices (ACIP) recommendation to administer inactivated influenza vaccines (IIV), and not LAIV, during the 2016-17 and 2017-18 seasons. Given that data from previous years demonstrated equivalent and even improved efficacy of LAIV compared with IIV, this recent data was surprising, raising many questions about potential mechanisms underlying this change. This review seeks to summarize the history of LAIV studies and ACIP recommendations with a focus on the recent decrease in vaccine effectiveness (VE) and discordant results among studies performed in different countries. Decreased VE for A/H1N1pdm09 viruses represents the most consistent finding across studies, as VE has been low every season these viruses predominated since 2010-11. Potential explanations underlying diminished effectiveness include the hypothesis that prior vaccination, reduced thermostability of A/H1N1pdm09, addition of a fourth virus, or reduced replication fitness of A/H1N1pdm09 strains may have contributed to this phenomenon. Ongoing studies and potential alterations to LAIV formulations provide hope for a return of effective LAIV in future influenza seasons.

## 5. Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection Compared With Reverse Transcriptase Polymerase Chain Reaction: A Systematic Review and Meta-analysis.

**Author(s):** Merckx, Joanna; Wali, Rehab; Schiller, Ian; Caya, Chelsea; Gore, Genevieve C; Chartrand, Caroline; Dendukuri, Nandini; Papenburg, Jesse

**Source:** Annals of internal medicine; Sep 2017; vol. 167 (no. 6); p. 394-409

**Publication Type(s):** Meta-analysis Journal Article Review

Available at [Annals of internal medicine](#) - from EBSCO (MEDLINE Complete)

**Abstract:** Background Rapid and accurate influenza diagnostics can improve patient care. Purpose To summarize and compare accuracy of traditional rapid influenza diagnostic tests (RIDTs), digital immunoassays (DIAs), and rapid nucleic acid amplification tests (NAATs) in children and adults with suspected influenza. Data Sources 6 databases from their inception through May 2017. Study Selection Studies in English, French, or Spanish comparing commercialized rapid tests (that is, providing results in 98%). Forty-six influenza A and 24 influenza B studies presented pediatric-specific data; 35 influenza A and 16 influenza B studies presented adult-specific data. Pooled sensitivities were higher in children by 12.1 to 31.8 percentage points, except for influenza A by rapid NAATs (2.7 percentage points). Pooled sensitivities favored industry-sponsored studies by 6.2 to 34.0 percentage points. Incomplete reporting frequently led to unclear risk of bias. Limitations Underreporting of clinical variables limited exploration of heterogeneity. Few NAAT studies reported adult-specific data, and none evaluated point-of-care testing. Many studies had unclear risk of bias. Conclusion Novel DIAs and rapid NAATs had markedly higher sensitivities for influenza A and B in both children and adults than did traditional RIDTs, with equally high specificities. Primary Funding Source Québec Health Research Fund and BD Diagnostic Systems.

## 6. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: A systematic review and meta-analysis of test-negative design case-control studies.

**Author(s):** Rondy, Marc; El Omeiri, Nathalie; Thompson, Mark G; Levêque, Alain; Moren, Alain; Sullivan, Sheena G

**Source:** The Journal of infection; Sep 2017

**Publication Type(s):** Journal Article Review

**Abstract:** OBJECTIVE Summary evidence of influenza vaccine effectiveness (IVE) against hospitalized influenza is lacking. We conducted a meta-analysis of studies reporting IVE against laboratory-confirmed hospitalized influenza among adults. METHODS We searched Pubmed (January 2009 to November 2016) for studies that used test-negative design (TND) to enrol patients hospitalized with influenza-associated conditions. Two independent authors selected relevant articles. We calculated pooled IVE against any and (sub)type specific influenza among all adults, and stratified by age group (18-64 and 65 years and above) using random-effects models. RESULTS We identified 3411 publications and 30 met our inclusion criteria. Between 2010-11 and 2014-15, the pooled seasonal IVE was 41% (95%CI:34;48) for any influenza (51% (95%CI:44;58) among people aged 18-64y and 37% (95%CI:30;44) among ≥65 years). IVE was 48% (95%CI:37;59), 37% (95%CI:24;50) and 38% (95%CI:23;53) against influenza A(H1N1)pdm09, A(H3N2) and B, respectively. Among persons aged ≥65 year, IVE against A(H3N2) was 43% (95%CI:33;53) in seasons when circulating and vaccine strains were antigenically similar and 14% (95%CI:-3;30) when A(H3N2) variant viruses predominated. CONCLUSIONS Influenza vaccines provided moderate protection against influenza-associated hospitalizations among adults. They seemed to provide low protection among elderly in seasons where vaccine and circulating A(H3N2) strains were antigenically variant.

**Database:** Medline

### 7. Latest recommendations for the 2017-2018 flu season.

**Author(s):** Campos-Outcalt, Doug

**Source:** The Journal of family practice; Sep 2017; vol. 66 (no. 9); p. 570-572

**Publication Type(s):** Practice Guideline

Available at [The Journal of family practice](#) - from EBSCO (MEDLINE Complete)

**Abstract:**This season's vaccine has a new H1N1 component and any vaccine, except the live attenuated virus formulation, is suitable for pregnant women.

### 8. Effectiveness of personal protective measures in reducing pandemic influenza transmission: A systematic review and meta-analysis.

**Author(s):** Saunders-Hastings, Patrick; Crispo, James A G; Sikora, Lindsey; Krewski, Daniel

**Source:** Epidemics; Sep 2017; vol. 20 ; p. 1-20

**Publication Type(s):** Journal Article Review

**Abstract:**The goal of this review was to examine the effectiveness of personal protective measures in preventing pandemic influenza transmission in human populations. We collected primary studies from Medline, Embase, PubMed, Cochrane Library, CINAHL and grey literature. Where appropriate, random effects meta-analyses were conducted using inverse variance statistical calculations. Meta-analyses suggest that regular hand hygiene provided a significant protective effect (OR=0.62; 95% CI 0.52-0.73; I<sup>2</sup>=0%), and facemask use provided a non-significant protective effect (OR=0.53; 95% CI 0.16-1.71; I<sup>2</sup>=48%) against 2009 pandemic influenza infection. These interventions may therefore be effective at limiting transmission during future pandemics. PROSPERO Registration: 42016039896.

### 9. Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial.

**Author(s):** Park, Jin Kyun; Lee, Min Ah; Lee, Eun Young; Song, Yeong Wook; Choi, Yunhee; Winthrop, Kevin L; Lee, Eun Bong

**Source:** Annals of the rheumatic diseases; Sep 2017; vol. 76 (no. 9); p. 1559-1565

**Publication Type(s):** Randomized Controlled Trial Journal Article

Available at [Annals of the rheumatic diseases](#) - from BMJ Journals - NHS

**Abstract:****OBJECTIVE**To investigate whether temporary discontinuation of methotrexate (MTX) improves the efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis (RA).**METHODS**In this prospective randomised parallel-group trial, patients with RA taking stable dose of MTX were randomly assigned at a ratio of 1:1:1:1 to continue MTX (group 1), suspend MTX for 4 weeks before vaccination (group 2), suspend MTX for 2 weeks before and 2 weeks after vaccination (group 3) or suspend MTX for 4 weeks after vaccination (group 4). All participants were vaccinated with trivalent influenza vaccine containing H1N1, H3N2 and B-Yamagata. The primary outcome was frequency of satisfactory vaccine response ( $\geq 4$ -fold titre increase 4 weeks postvaccination). Secondary endpoints included fold change in antibody titres from baseline.**RESULTS**The per-protocol population consisted of 199 patients (n=54, 44, 49 and 52 in groups 1, 2, 3 and 4, respectively). Group 3 achieved higher satisfactory vaccine response against all three antigens than group 1 (51.0% vs 31.5%, p=0.044). The anti-H3N2 antibody fold increase (95% CI) was significantly higher in groups 3 and 4 (12.2 (8.4 to 17.5), p <0.001 and 10.0 (6.8 to 14.8), p=0.043, respectively) than group 1 (5.9 (4.3 to 8.1)). The anti-B-Yamagata antibody responses of

groups 3 and 4 were higher (4.7 (3.3 to 6.7),  $p=0.048$ ; 6.1 (4.2 to 8.8),  $p < 0.001$ , respectively) than group 1 (2.9 (2.2 to 3.8)). RA flare occurred in 24.1%, 21.2%, 34.1% and 38.8% in groups 1, 2, 3 and 4, respectively ( $p=NS$ ). CONCLUSION Temporary MTX discontinuation improves the immunogenicity of seasonal influenza vaccination in patients with RA. TRIAL REGISTRATION Trial registration number is: [www.clinicaltrials.gov](http://www.clinicaltrials.gov), NCT02748785.

#### **10. From Original Antigenic Sin to the Universal Influenza Virus Vaccine.**

**Author(s):** Henry, Carole; Palm, Anna-Karin E; Krammer, Florian; Wilson, Patrick C

**Source:** Trends in immunology; Aug 2017

**Publication Type(s):** Journal Article Review

**Abstract:** Antibody responses are essential for protection against influenza virus infection. Humans are exposed to a multitude of influenza viruses throughout their lifetime and it is clear that immune history influences the magnitude and quality of the antibody response. The 'original antigenic sin' concept refers to the impact of the first influenza virus variant encounter on lifelong immunity. Although this model has been challenged since its discovery, past exposure, and likely one's first exposure, clearly affects the epitopes targeted in subsequent responses. Understanding how previous exposure to influenza virus shapes antibody responses to vaccination and infection is critical, especially with the prospect of future pandemics and for the effective development of a universal influenza vaccine.

#### **11. Live attenuated influenza vaccine (LAIV): recent effectiveness results from the USA and implications for LAIV programmes elsewhere.**

**Author(s):** Pebody, Richard; McMenamin, Jim; Nohynek, Hanna

**Source:** Archives of disease in childhood; Aug 2017

**Publication Type(s):** Journal Article Review

**Abstract:** The USA has a long-standing paediatric influenza vaccination programme, including use of live attenuated influenza vaccine (LAIV). Following US evidence of apparent lack of vaccine effectiveness (VE) of LAIV in 2015/2016, particularly against A(H1N1)pdm09, the USA suspended the use of LAIV in the 2016/2017 season. The UK introduced LAIV for children in 2013/2014 and Finland in 2015/2016. Both countries have since been closely monitoring programme performance. In 2015/2016, the UK and Finland, unlike the USA, found evidence of significant VE of LAIV against laboratory-confirmed influenza. Several studies, however, reported relatively lower VE of LAIV against A(H1N1)pdm09 infection compared with inactivated influenza vaccine, although not for A(H3N2) or B. The reasons for these apparent differences remain under investigation. Both the UK and Finland continue to recommend the use of LAIV in children for the 2017/2018 season and are intensifying further monitoring of their childhood programmes against a range of end-points.

#### **12. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2017-18 Influenza Season.**

**Author(s):** Grohskopf, Lisa A; Sokolow, Leslie Z; Broder, Karen R; Walter, Emmanuel B; Bresee, Joseph S; Fry, Alicia M; Jernigan, Daniel B

**Source:** MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports; Aug 2017; vol. 66 (no. 2); p. 1-20

**Publication Type(s):** Practice Guideline Journal Article

Available at [MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports](#) - from EBSCO (Health Business FullTEXT Elite)

Available at [MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports](#) - from EBSCO (CINAHL with Full Text)

Available at [MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports](#) - from EBSCO (MEDLINE Complete)

**Abstract:** This report updates the 2016-17 recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding the use of seasonal influenza vaccines (MMWR Recomm Rep 2016;65[No. RR-5]). Routine annual influenza vaccination is recommended for all persons aged  $\geq 6$  months who do not have contraindications. A licensed, recommended, and age-appropriate vaccine should be used. For the 2017-18 season, quadrivalent and trivalent influenza vaccines will be available. Inactivated influenza vaccines (IIVs) will be available in trivalent (IIV3) and quadrivalent (IIV4) formulations. Recombinant influenza vaccine (RIV) will be available in trivalent (RIV3) and quadrivalent (RIV4) formulations. Live attenuated influenza vaccine (LAIV4) is not recommended for use during the 2017-18 season due to concerns about its effectiveness against (H1N1)pdm09 viruses during the 2013-14 and 2015-16 seasons. Recommendations for different vaccine types and specific populations are discussed. No preferential recommendation is made for one influenza vaccine product over another for persons for whom more than one licensed, recommended product is available. Updates to the recommendations described in this report reflect discussions during public meetings of ACIP held on October 20, 2016; February 22, 2017; and June 21, 2017. New and updated information in this report includes the following:

- Vaccine viruses included in the 2017-18 U.S. trivalent influenza vaccines will be an A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus (Victoria lineage). Quadrivalent influenza vaccines will contain these three viruses and an additional influenza B vaccine virus, a B/Phuket/3073/2013-like virus (Yamagata lineage).
- Information on recent licensures and labelling changes is discussed, including licensure of Afluria Quadrivalent (IIV4; Seqirus, Parkville, Victoria, Australia); Flublok Quadrivalent (RIV4; Protein Sciences, Meriden, Connecticut); and expansion of the age indication for FluLaval Quadrivalent (IIV4; ID Biomedical Corporation of Quebec, Quebec City, Quebec, Canada), previously licensed for  $\geq 3$  years, to  $\geq 6$  months.
- Pregnant women may receive any licensed, recommended, age-appropriate influenza vaccine.
- Afluria (IIV3; Seqirus, Parkville, Victoria, Australia) may be used for persons aged  $\geq 5$  years, consistent with Food and Drug Administration-approved labeling.
- FluMist Quadrivalent (LAIV4; MedImmune, Gaithersburg, Maryland) should not be used during the 2017-18 season due to concerns about its effectiveness against influenza A(H1N1)pdm09 viruses in the United States during the 2013-14 and 2015-16 influenza seasons.

This report focuses on the recommendations for use of vaccines for the prevention and control of influenza during the 2017-18 season in the United States. A Background Document containing further information and a summary of these recommendations are available at <https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html>. These recommendations apply to licensed influenza vaccines used within Food and Drug Administration-licensed indications, including those licensed after the publication date of this report. Updates and other information are available at CDC's influenza website (<https://www.cdc.gov/flu>). Vaccination and health care providers should check CDC's influenza website periodically for additional information.

### **13. Influenza-like Illness Incidence Is Not Reduced by Influenza Vaccination in a Cohort of Older Adults, Despite Effectively Reducing Laboratory-Confirmed Influenza Virus Infections.**

**Author(s):** van Beek, Josine; Veenhoven, Reinier H; Bruin, Jacob P; van Boxtel, Renée A J; de Lange, Marit M A; Meijer, Adam; Sanders, Elisabeth A M; Rots, Nynke Y; Luytjes, Willem

**Source:** The Journal of infectious diseases; Aug 2017; vol. 216 (no. 4); p. 415-424

**Publication Type(s):** Journal Article Observational Study

**Abstract:**BackgroundData on the relative contribution of influenza virus and other respiratory pathogens to respiratory infections in community-dwelling older adults ( $\geq 60$  years) are needed.MethodsA prospective observational cohort study was performed in the Netherlands during 2 winters. Nasopharyngeal and oropharyngeal swabs were collected during influenza-like illness (ILI) episodes and from controls. Viruses and bacteria were identified by multiplex ligation-dependent probe amplification assay and conventional bacterial culture.ResultsThe ILI incidence in the consecutive seasons was 7.2% and 11.6%, and influenza virus caused 18.9% and 34.2% of ILI episodes. Potential pathogen were detected in 80% of the ILI events with influenza virus, coronaviruses, rhinoviruses, human metapneumovirus, respiratory syncytial virus, parainfluenza viruses, and Haemophilus influenzae being the most common. Influenza vaccination reduced influenza virus infection by 73% (95% confidence interval [CI], 26%-90%) and 51% (95% CI, 7%-74%) in ILI patients. However, ILI incidence was similar between vaccinated (7.6% and 10.8%) and nonvaccinated (4.2% and 11.4%) participants in 2011-2012 and 2012-2013, respectively ( $P > .05$ ).ConclusionsInfluenza virus is a frequent pathogen in older adults with ILI. Vaccination reduces the number of influenza virus infections but not the overall number of ILI episodes: other pathogens fill the gap. We suggest the existence of a pool of individuals with high susceptibility to respiratory infections.Clinical Trials RegistrationNTR3386.

**14. The Importance of Frailty in the Assessment of Influenza Vaccine Effectiveness Against Influenza-Related Hospitalization in Elderly People.**

**Author(s):** Andrew, Melissa K; Shinde, Vivek; Ye, Lingyun; Hatchette, Todd; Haguinet, François; Dos Santos, Gael; McElhaney, Janet E; Ambrose, Ardith; Boivin, Guy; Bowie, William; Chit, Ayman; ElSherif, May; Green, Karen; Halperin, Scott; Iburguchi, Barbara; Johnstone, Jennie; Katz, Kevin; Langley, Joanne; Leblanc, Jason; Loeb, Mark; MacKinnon-Cameron, Donna; McCarthy, Anne; McGeer, Allison; Powis, Jeff; Richardson, David; Semret, Makeda; Stiver, Grant; Trottier, Sylvie; Valiquette, Louis; Webster, Duncan; McNeil, Shelly A; Serious Outcomes Surveillance Network of the Public Health Agency of Canada/Canadian Institutes of Health Research Influenza Research Network (PCIRN) and the Toronto Invasive Bacterial Diseases Network (TIBDN)

**Source:** The Journal of infectious diseases; Aug 2017; vol. 216 (no. 4); p. 405-414

**Publication Type(s):** Multicenter Study Journal Article Observational Study

**Abstract:**BackgroundInfluenza is an important cause of morbidity and mortality among older adults. Even so, effectiveness of influenza vaccine for older adults has been reported to be lower than for younger adults, and the impact of frailty on vaccine effectiveness (VE) and outcomes is uncertain. We aimed to study VE against influenza hospitalization in older adults, focusing on the impact of frailty.MethodsWe report VE of trivalent influenza vaccine (TIV) in people  $\geq 65$  years of age hospitalized during the 2011-2012 influenza season using a multicenter, prospective, test-negative case-control design. A validated frailty index (FI) was used to measure frailty.ResultsThree hundred twenty cases and 564 controls (mean age, 80.6 and 78.7 years, respectively) were enrolled. Cases had higher baseline frailty than controls ( $P = .006$ ). In the fully adjusted model, VE against influenza hospitalization was 58.0% (95% confidence interval [CI], 34.2%-73.2%). The contribution of frailty was important; adjusting for frailty alone yielded a VE estimate of 58.7% (95% CI, 36.2%-73.2%). VE was 77.6% among nonfrail older adults and declined as frailty increased.ConclusionsDespite commonly held views that VE is poor in older adults, we found that TIV provided good protection against influenza hospitalization in older adults who were not frail, though VE diminished as frailty increased.Clinical Trials RegistrationNCT01517191.

### 15. New drug-strategies to tackle viral-host interactions for the treatment of influenza virus infections.

**Author(s):** van de Wakker, Simonides I; Fischer, Marcel J E; Oosting, Ronald S

**Source:** European journal of pharmacology; Aug 2017; vol. 809 ; p. 178-190

**Publication Type(s):** Journal Article Review

**Abstract:**The influenza virus (IV) is a highly contagious virus causing seasonal global outbreaks affecting annually up to 20% of the world's population and leading to 250,000-500,000 deaths worldwide. Current vaccines have variable effectiveness, and, in particular during a pandemic outbreak, they are probably not available in the amounts needed to protect the world population. Therefore we need effective small molecule drugs to combat an IV infection and that can be produced, in case of pandemic, rapidly and in large quantities. Unfortunately, natural occurring IV becomes more and more resistant to current anti-IV drugs. And thus, there is an urgent need for development of alternative agents with new mechanisms of action. This review provides an overview of the pharmacology and effectiveness of new anti-IV agents, focusing on inhibition mechanisms directed against virus-host interactions.

### 16. Benefits of flu vaccination for persons with diabetes mellitus: A review.

**Author(s):** Goeijenbier, M; van Sloten, T T; Slobbe, L; Mathieu, C; van Genderen, P; Beyer, Walter E P; Osterhaus, Albert D M E

**Source:** Vaccine; Aug 2017

**Publication Type(s):** Journal Article Review

Available at [Vaccine](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:**Diabetes mellitus imposes a significant and increasing burden on society, with major consequences for human health, welfare and the economy worldwide. Persons with diabetes mellitus are at increased risk of developing severe complications after influenza virus infection and guidelines advise vaccination. The present evidence for influenza vaccine effectiveness in persons with diabetes mellitus is mainly based on observational studies with clinical endpoints like hospitalization and death, indicating a beneficial reduction of morbidity and mortality. Further supportive evidence comes from serological studies, in which persons with diabetes mellitus usually develop similar antibody levels after vaccination as healthy people. Observational studies may be prone to selection bias, and serological studies may not completely mirror vaccine effectiveness in the field. Although more controlled trials in persons with diabetes mellitus with laboratory-confirmed, influenza-specific outcomes would be desirable to better estimate the effect of vaccination, the currently available data justify routine influenza vaccination in persons with diabetes mellitus. As in this risk group, the use of influenza vaccine is far below target worldwide, efforts should be made to increase vaccination coverage.

### 17. Urgent challenges in implementing live attenuated influenza vaccine.

**Author(s):** Singanayagam, Anika; Zambon, Maria; Lalvani, Ajit; Barclay, Wendy

**Source:** The Lancet. Infectious diseases; Aug 2017

**Publication Type(s):** Journal Article Review

**Abstract:**Conflicting reports have emerged about the effectiveness of the live attenuated influenza vaccine. The live attenuated influenza vaccine appears to protect particularly poorly against currently circulating H1N1 viruses that are derived from the 2009 pandemic H1N1 viruses. During the 2015-16 influenza season, when pandemic H1N1 was the predominant virus, studies from the



USA reported a complete lack of effectiveness of the live vaccine in children. This finding led to a crucial decision in the USA to recommend that the live vaccine not be used in 2016-17 and to switch to the inactivated influenza vaccine. Other countries, including the UK, Canada, and Finland, however, have continued to recommend the use of the live vaccine. This policy divergence and uncertainty has far reaching implications for the entire global community, given the importance of the production capabilities of the live attenuated influenza vaccine for pandemic preparedness. In this Personal View, we discuss possible explanations for the observed reduced effectiveness of the live attenuated influenza vaccine and highlight the underpinning scientific questions. Further research to understand the reasons for these observations is essential to enable informed public health policy and commercial decisions about vaccine production and development in coming years.

### **18. First Trimester Influenza Vaccination and Risks for Major Structural Birth Defects in Offspring.**

**Author(s):** Kharbanda, Elyse Olshen; Vazquez-Benitez, Gabriela; Romitti, Paul A; Naleway, Allison L; Cheetham, T Craig; Lipkind, Heather S; Klein, Nicola P; Lee, Grace; Jackson, Michael L; Hambidge, Simon J; McCarthy, Natalie; DeStefano, Frank; Nordin, James D; Vaccine Safety Datalink

**Source:** The Journal of pediatrics; Aug 2017; vol. 187 ; p. 234

**Publication Type(s):** Journal Article Observational Study

**Abstract:**OBJECTIVETo examine risks for major structural birth defects in infants after first trimester inactivated influenza vaccine (IIV) exposures.STUDY DESIGNIn this observational study, we used electronic health data from 7 Vaccine Safety Datalink sites to examine risks for selected major structural defects in infants after maternal IIV exposure. Vaccine exposures for women with continuous insurance enrollment through pregnancy who delivered singleton live births between 2004 and 2013 were identified from standardized files. Infants with continuous insurance enrollment were followed to 1 year of age. We excluded mother-infant pairs with other exposures that potentially increased their background risk for birth defects. Selected cardiac, orofacial or respiratory, neurologic, ophthalmologic or otologic, gastrointestinal, genitourinary and muscular or limb defects were identified from diagnostic codes in infant medical records using validated algorithms. Propensity score adjusted generalized estimating equations were used to estimate prevalence ratios (PRs).RESULTSWe identified 52 856 infants with maternal first trimester IIV exposure and 373 088 infants whose mothers were unexposed to IIV during first trimester. Prevalence (per 100 live births) for selected major structural birth defects was 1.6 among first trimester IIV exposed versus 1.5 among unexposed mothers. The adjusted PR was 1.02 (95% CI 0.94-1.10). Organ system-specific PRs were similar to the overall PR.CONCLUSIONFirst trimester maternal IIV exposure was not associated with an increased risk for selected major structural birth defects in this large cohort of singleton live births.

### **19. Influenza: A Global Perspective.**

**Author(s):** Rotrosen, Elizabeth T; Neuzil, Kathleen M

**Source:** Pediatric clinics of North America; Aug 2017; vol. 64 (no. 4); p. 911-936

**Publication Type(s):** Journal Article Review

**Abstract:**Influenza is a common respiratory illness in children and accounts for substantial morbidity and mortality on an annual basis. Inactivated and live influenza vaccines are approved for children and are safe and efficacious. The absolute effectiveness of vaccines varies by year and is influenced by several factors. The reason for recent reduced performance of live-attenuated influenza vaccines is poorly understood, and active research is ongoing. Vaccination programs are less common in tropical and subtropical countries, where unique logistical and feasibility challenges exist. Antiviral

medications for prevention and treatment of influenza in children are an important adjunct to vaccines.

## **20. Comparison of Efficacy of Intravenous Peramivir and Oral Oseltamivir for the Treatment of Influenza: Systematic Review and Meta-Analysis.**

**Author(s):** Lee, Jonghoo; Park, Ju Hee; Jwa, Hyeyoung; Kim, Yee Hyung

**Source:** Yonsei medical journal; Jul 2017; vol. 58 (no. 4); p. 778-785

**Publication Type(s):** Meta-analysis Comparative Study Journal Article Review

Available at [Yonsei medical journal](#) - from Europe PubMed Central - Open Access

Available at [Yonsei medical journal](#) - from EBSCO (MEDLINE Complete)

**Abstract:** PURPOSE Peramivir is the first intravenously administered neuramidase inhibitor for immediate delivery of an effective single-dose treatment in patients with influenza. However, limited data are available on intravenous (IV) peramivir treatment compared to oral oseltamivir for these patients. MATERIALS AND METHODS With a systematic review and meta-analysis, we compared the efficacy of IV peramivir with oral oseltamivir for treatment of patients with seasonal influenza. MEDLINE, EMBASE, and Cochrane Central Register were searched for relevant clinical trials. RESULTS A total of seven trials [two randomized controlled trials (RCTs) and five non-randomized observational trials] involving 1676 patients were finally analyzed. The total number of peramivir- and oseltamivir-treated patients was 956 and 720, respectively. Overall, the time to alleviation of fever was lower in the peramivir-treated group compared with the oseltamivir-treated group [mean difference (MD), -7.17 hours; 95% confidence interval (CI) -11.00 to -3.34]. Especially, pooled analysis of observational studies (n=4) and studies of outpatients (n=4) demonstrated the superiority of the peramivir-treated group (MD, -7.83 hours; 95% CI -11.81 to -3.84 and MD, -7.71 hours; 95% CI -11.61 to -3.80, respectively). Mortality, length of hospital stay, change in virus titer 48 hours after admission, and the incidence of adverse events in these patients were not significantly different between the two groups. CONCLUSION IV peramivir therapy might reduce the time to alleviation of fever in comparison with oral oseltamivir therapy in patients with influenza; however, we could not draw clear conclusions from a meta-analysis because of the few RCTs available and methodological limitations.

## **21. Pertussis and influenza immunisation during pregnancy: a landscape review.**

**Author(s):** Abu Raya, Bahaa; Edwards, Kathryn M; Scheifele, David W; Halperin, Scott A

**Source:** The Lancet. Infectious diseases; Jul 2017; vol. 17 (no. 7); p. e209

**Publication Type(s):** Journal Article Review

Available at [The Lancet. Infectious diseases](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:** Immunisation during pregnancy is a relatively new strategy, and is currently limited to tetanus, pertussis, and influenza vaccines. None of these vaccines were developed specifically for use in pregnancy, but they provide an effective method of protecting mothers and young infants. In response to increases in pertussis morbidity and mortality among young infants, several countries have recommended universal tetanus, diphtheria, and acellular pertussis immunisation during pregnancy. Similarly, many countries recommend influenza immunisation during pregnancy to reduce the risk of disease for mother and infant. Although scientific evidence to support maternal immunisation against pertussis and influenza is rapidly accumulating, important knowledge gaps remain that need to be addressed by future research, which we have highlighted in this Series paper.

## **22. Influenza detection and prediction algorithms: comparative accuracy trial in Östergötland county, Sweden, 2008-2012.**

**Author(s):** Spreco, A; Eriksson, O; Dahlström, Ö; Timpka, T

**Source:** *Epidemiology and infection*; Jul 2017; vol. 145 (no. 10); p. 2166-2175

**Publication Type(s):** Comparative Study Journal Article

Available at [Epidemiology and infection](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:** Methods for the detection of influenza epidemics and prediction of their progress have seldom been comparatively evaluated using prospective designs. This study aimed to perform a prospective comparative trial of algorithms for the detection and prediction of increased local influenza activity. Data on clinical influenza diagnoses recorded by physicians and syndromic data from a telenursing service were used. Five detection and three prediction algorithms previously evaluated in public health settings were calibrated and then evaluated over 3 years. When applied on diagnostic data, only detection using the Serfling regression method and prediction using the non-adaptive log-linear regression method showed acceptable performances during winter influenza seasons. For the syndromic data, none of the detection algorithms displayed a satisfactory performance, while non-adaptive log-linear regression was the best performing prediction method. We conclude that evidence was found for that available algorithms for influenza detection and prediction display satisfactory performance when applied on local diagnostic data during winter influenza seasons. When applied on local syndromic data, the evaluated algorithms did not display consistent performance. Further evaluations and research on combination of methods of these types in public health information infrastructures for 'nowcasting' (integrated detection and prediction) of influenza activity are warranted.

## **23. Design and rationale for the Influenza vaccination After Myocardial Infarction (IAMI) trial. A registry-based randomized clinical trial.**

**Author(s):** Fröbert, Ole; Götberg, Matthias; Angerås, Oskar; Jonasson, Lena; Erlinge, David; Engström, Thomas; Persson, Jonas; Jensen, Svend E; Omerovic, Elmir; James, Stefan K; Lagerqvist, Bo; Nilsson, Johan; Kåregren, Amra; Moer, Rasmus; Yang, Cao; Agus, David B; Erglis, Andrejs; Jensen, Lisette O; Jakobsen, Lars; Christiansen, Evald H; Pernow, John

**Source:** *American heart journal*; Jul 2017; vol. 189 ; p. 94-102

**Publication Type(s):** Randomized Controlled Trial Multicenter Study Journal Article

**Abstract:** BACKGROUND Registry studies and case-control studies have demonstrated that the risk of acute myocardial infarction (AMI) is increased following influenza infection. Small randomized trials, underpowered for clinical end points, indicate that future cardiovascular events can be reduced following influenza vaccination in patients with established cardiovascular disease. Influenza vaccination is recommended by international guidelines for patients with cardiovascular disease, but uptake is varying and vaccination is rarely prioritized during hospitalization for AMI. METHODS/DESIGN The Influenza vaccination After Myocardial Infarction (IAMI) trial is a double-blind, multicenter, prospective, registry-based, randomized, placebo-controlled, clinical trial. A total of 4,400 patients with ST-segment elevation myocardial infarction (STEMI) or non-STEMI undergoing coronary angiography will randomly be assigned either to in-hospital influenza vaccination or to placebo. Baseline information is collected from national heart disease registries, and follow-up will be performed using both registries and a structured telephone interview. The primary end point is a composite of time to all-cause death, a new AMI, or stent thrombosis at 1 year. IMPLICATIONS The

IAMI trial is the largest randomized trial to date to evaluate the effect of in-hospital influenza vaccination on death and cardiovascular outcomes in patients with STEMI or non-STEMI. The trial is expected to provide highly relevant clinical data on the efficacy of influenza vaccine as secondary prevention after AMI.

#### **24. Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-analysis.**

**Author(s):** Sarkanen, Tomi O; Alakuijala, Anniina P E; Dauvilliers, Yves A; Partinen, Markku M

**Source:** Sleep medicine reviews; Jun 2017

**Publication Type(s):** Journal Article Review

**Abstract:**An increased incidence of narcolepsy was seen in many countries after the pandemic H1N1 influenza vaccination campaign in 2009-2010. The H1N1 vaccine - narcolepsy connection is based on observational studies that are prone to various biases, e.g., confounding by H1N1 infection, and ascertainment, recall and selection biases. A direct pathogenic link has, however, remained elusive. We conducted a systematic review and meta-analysis to analyze the magnitude of H1N1 vaccination related risk and to examine if there was any association with H1N1 infection itself. We searched all articles from PubMed, Web of Science and Scopus, and other relevant sources reporting the incidence and risk of post-vaccine narcolepsy. In our paper, we show that the risk appears to be limited to only one vaccine (Pandemrix®). During the first year after vaccination, the relative risk of narcolepsy was increased 5 to 14-fold in children and adolescents and 2 to 7-fold in adults. The vaccine attributable risk in children and adolescents was around 1 per 18,400 vaccine doses. Studies from Finland and Sweden also appear to demonstrate an extended risk of narcolepsy into the second year following vaccination, but such conclusions should be interpreted with a word of caution due to possible biases. Benefits of immunization outweigh the risk of vaccination-associated narcolepsy, which remains a rare disease.

#### **25. Knowledge, attitudes, beliefs and practices of Occupational Physicians towards seasonal influenza vaccination: a cross-sectional study from North-Eastern Italy.**

**Author(s):** Riccò, M; Cattani, S; Casagrande, F; Gualerzi, G; Signorelli, C

**Source:** Journal of preventive medicine and hygiene; Jun 2017; vol. 58 (no. 2); p. E141

**Publication Type(s):** Journal Article Review

**Abstract:**INTRODUCTIONThe present study aims to characterize personal attitudes and knowledge of a sample of Italian Occupational Physicians (OPh) towards Seasonal Influenza Vaccine (SIV) in healthcare workers (HCWs).METHODSIn total, 92 OPh (42.4% males, 57.6% females, mean age of  $47.3 \pm 10.4$  years, 50 specialists in Occupational Medicine, 42 specialists in Hygiene and Public Health) were asked about their attitudes towards influenza vaccine, their general knowledge of vaccine practice, their propensity towards vaccines and, eventually, their risk perception about the influenza and influenza vaccine was investigated. A regression analysis was then performed in order to better characterize predictive factors for vaccine propensity.RESULTSInfluenza was recognized as a vaccination recommended for HCWs in 89/92 of the sampled OPh (96.7%). However, prevalence of misconceptions about vaccines was relatively high, with 26/92 (28.3%) and 24/92 (26.1%) referring vaccinations as eliciting allergic and autoimmune diseases, respectively and identifying lethargic encephalitis (18/92, 19.6%), autism (17/92, 18.5%), diabetes mellitus (15/92, 16.3%) and multiple sclerosis (13/92, 14.1%) as causatively vaccine-related. Propensity towards influenza vaccination found a significant predictor in the general knowledge (beta coefficient 0.213, p value = 0.043), risk perception (beta coefficient 0.252, p value = 0.018) and general propensity towards vaccinations (beta coefficient 0.384, p value = 0.002).DISCUSSIONIn spite of a diffuse propensity towards SIV,

adherence of OPh was still < 50% of the sample. Moreover, sharing of misbeliefs and misconceptions was significant. As knowledge and risk perceptions were identified as significant predictors of vaccine propensity, our results suggest that information and training programs for OPh should be appropriately designed.

## 26. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older.

**Author(s):** Dunkle, Lisa M; Izikson, Ruvim; Patriarca, Peter; Goldenthal, Karen L; Muse, Derek; Callahan, Janice; Cox, Manon M J; PSC12 Study Team

**Source:** The New England journal of medicine; Jun 2017; vol. 376 (no. 25); p. 2427-2436

**Publication Type(s):** Research Support, Non-u.s. Gov't Comparative Study Randomized Controlled Trial Clinical Trial, Phase Iv Multicenter Study Journal Article Clinical Trial, Phase Iii

**PubMedID:** 28636855

Available at [The New England journal of medicine](#) - from Ovid (Journals @ Ovid)

Available at [The New England journal of medicine](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:**BACKGROUND Improved influenza vaccines are needed to control seasonal epidemics. This trial compared the protective efficacy in older adults of a quadrivalent, recombinant influenza vaccine (RIV4) with a standard-dose, egg-grown, quadrivalent, inactivated influenza vaccine (IIV4) during the A/H3N2-predominant 2014-2015 influenza season, when antigenic mismatch between circulating and vaccine influenza strains resulted in the reduced effectiveness of many licensed vaccines. METHODS We conducted a randomized, double-blind, multicenter trial of RIV4 (45 µg of recombinant hemagglutinin [HA] per strain, 180 µg of protein per dose) versus standard-dose IIV4 (15 µg of HA per strain, 60 µg of protein per dose) to compare the relative vaccine efficacy against reverse-transcriptase polymerase-chain-reaction (RT-PCR)-confirmed, protocol-defined, influenza-like illness caused by any influenza strain starting 14 days or more after vaccination in adults who were 50 years of age or older. The diagnosis of influenza infection was confirmed by means of RT-PCR assay and culture of nasopharyngeal swabs obtained from participants with symptoms of an influenza-like illness. The primary end point was RT-PCR-confirmed, protocol defined, influenza-like illness between 14 days or more after vaccination and the end of the influenza season. RESULTS A total of 9003 participants were enrolled and underwent randomization; 8855 (98.4%) received a trial vaccine and underwent an efficacy follow-up (the modified intention-to-treat population), and 8604 (95.6%) completed the per-protocol follow-up (the modified per-protocol population). Among RIV4 recipients, the RT-PCR-confirmed influenza attack rate was 2.2% (96 cases among 4303 participants) in the modified per-protocol population and 2.2% (96 cases among 4427 participants) in the modified intention-to-treat population. Among IIV4 recipients, the attack rate was 3.2% (138 cases among 4301 participants) in the modified per-protocol population and 3.1% (138 cases among 4428 participants) in the modified intention-to-treat population. A total of 181 cases of influenza A/H3N2, 47 cases of influenza B, and 6 cases of nonsubtypeable influenza A were detected. The probability of influenza-like illness was 30% lower with RIV4 than with IIV4 (95% confidence interval, 10 to 47; P=0.006) and satisfied prespecified criteria for the primary noninferiority analysis and an exploratory superiority analysis of RIV4 over IIV4. The safety profiles of the vaccines were similar. CONCLUSIONS RIV4 provided better protection than standard-dose IIV4 against confirmed influenza-like illness among older adults. (Funded by Protein Sciences; ClinicalTrials.gov number, NCT02285998 ).

## **27. Value for Money in H1N1 Influenza: A Systematic Review of the Cost-Effectiveness of Pandemic Interventions.**

**Author(s):** Pasquini-Descomps, H el ene; Brender, Nathalie; Maradan, David

**Source:** Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research; Jun 2017; vol. 20 (no. 6); p. 819-827

**Publication Type(s):** Journal Article Review

**Abstract:**BACKGROUNDThe 2009 A/H1N1 influenza pandemic generated additional data and triggered new studies that opened debate over the optimal strategy for handling a pandemic. The lessons-learned documents from the World Health Organization show the need for a cost estimation of the pandemic response during the risk-assessment phase. Several years after the crisis, what conclusions can we draw from this field of research?OBJECTIVEThe main objective of this article was to provide an analysis of the studies that present cost-effectiveness or cost-benefit analyses for A/H1N1 pandemic interventions since 2009 and to identify which measures seem most cost-effective.METHODSWe reviewed 18 academic articles that provide cost-effectiveness or cost-benefit analyses for A/H1N1 pandemic interventions since 2009. Our review converts the studies' results into a cost-utility measure (cost per disability-adjusted life-year or quality-adjusted life-year) and presents the contexts of severity and fatality.RESULTSThe existing studies suggest that hospital quarantine, vaccination, and usage of the antiviral stockpile are highly cost-effective, even for mild pandemics. However, school closures, antiviral treatments, and social distancing may not qualify as efficient measures, for a virus like 2009's H1N1 and a willingness-to-pay threshold of \$45,000 per disability-adjusted life-year. Such interventions may become cost-effective for severe crises.CONCLUSIONSThis study helps to shed light on the cost-utility of various interventions, and may support decision making, among other criteria, for future pandemics. Nonetheless, one should consider these results carefully, considering these may not apply to a specific crisis or country, and a dedicated cost-effectiveness assessment should be conducted at the time.

## **28. A systematic review of the health economic consequences of quadrivalent influenza vaccination.**

**Author(s):** de Boer, Pieter T; van Maanen, Britt M; Damm, Oliver; Ultsch, Bernhard; Dolk, Franklin C K; Cr epey, Pascal; Pitman, Richard; Wilschut, Jan C; Postma, Maarten J

**Source:** Expert review of pharmacoeconomics & outcomes research; Jun 2017; vol. 17 (no. 3); p. 249-265

**Publication Type(s):** Journal Article Review

**Abstract:**BACKGROUNDQuadrivalent influenza vaccines (QIVs) contain antigens derived from an additional influenza type B virus as compared with currently used trivalent influenza vaccines (TIVs). This should overcome a potential reduced vaccine protection due to mismatches between TIV and circulating B viruses. In this study, we systematically reviewed the available literature on health economic evaluations of switching from TIV to QIV. Areas covered: The databases of Medline and Embase were searched systematically to identify health economic evaluations of QIV versus TIV published before September 2016. A total of sixteen studies were included, thirteen cost-effectiveness analyses and three cost-comparisons. Expert commentary: Published evidence on the cost-effectiveness of QIV suggests that switching from TIV to QIV would be a valuable intervention from both the public health and economic viewpoint. However, more research seems mandatory. Our main recommendations for future research include: 1) more extensive use of dynamic models in order to estimate the full impact of QIV on influenza transmission including indirect effects, 2) improved availability of data on disease outcomes and costs related to influenza type B viruses, and 3) more research on immunogenicity of natural influenza infection and vaccination, with emphasis on cross-reactivity between different influenza B viruses and duration of protection.

### **29. A systematic review and meta-analysis of cross-reactivity of antibodies induced by oil-in-water emulsion adjuvanted influenza H5N1 virus monovalent vaccines.**

**Author(s):** Chada, Kinnera E; Forshee, Richard; Golding, Hana; Anderson, Steven; Yang, Hong

**Source:** Vaccine; May 2017; vol. 35 (no. 24); p. 3162-3170

**Publication Type(s):** Journal Article Review

Available at [Vaccine](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:**BACKGROUND Cross-clade immunogenic stockpiled H5N1 vaccines may decrease the morbidity and transmission of infection during the initial phase of influenza pandemic. Meta-analysis of cross-reactive antibodies induced by oil-in-water emulsion adjuvanted (OWEA) influenza H5N1 virus monovalent vaccines with circulating heterologous H5N1 virus strains, isolated from human infections was performed. METHODS Literature search of MEDLINE, EMBASE, Web of Knowledge, The Cochrane Library, ClinicalTrials.gov, and International Standard Randomised Controlled Trial Number registry was conducted up through December 1, 2015. Methodologically qualified studies were included for (1) use of two doses of licensed OWEA (AS03 or MF59) egg-derived, inactivated influenza H5N1 virus monovalent vaccine, (2) participant age between 18 and 64 years, and (3) evaluation of immunogenicity outcome for one or more subclade. Meta-analysis assessed the cross-reactivity of antibodies elicited by clade 1 adjuvanted vaccine strain against clade 2.1 virus strain (A/Vietnam/1194/2004 vs. A/Indonesia/05/2005); and separately against clade 2.2 virus strain (A/Vietnam/1194/2004 vs. A/turkey/Turkey/1/05); and clade 2.1 adjuvanted vaccine strain against clade 1 virus strain (A/Indonesia/05/2005 vs. A/Vietnam/1194/2004). Quantitative publication bias and influence analysis was conducted to evaluate potential impact of unpublished or new studies on the robustness of meta-analysis. RESULTS Of 960 articles, 53 qualified for quality assessment and 15 studies met the inclusion criteria. All assessed clade pairs elicited cross-reactive antibodies (clade 1 against clade 2.1 and 2.2; clade 2.1 against clade 1, 2.2, and 2.3). Heterologous strains of same subclade are likely to elicit higher cross-reactive antibodies. CONCLUSIONS OWEA influenza H5N1 virus monovalent vaccines exhibit broad cross-clade immunogenicity, a desired feature for vaccine stockpiling not yet demonstrated by unadjuvanted vaccines. In case of an impending H5N1 virus pandemic, stockpiled OWEA influenza H5N1 virus monovalent vaccines may allow population priming that could slow down the course of pandemic and could offer additional time needed for development of an effective strain specific vaccine supply.

### **30. Efficacy and safety of high-dose influenza vaccine in elderly adults: A systematic review and meta-analysis.**

**Author(s):** Wilkinson, Krista; Wei, Yichun; Szwajcer, Andrea; Rabbani, Rasheda; Zarychanski, Ryan; Abou-Setta, Ahmed M; Mahmud, Salaheddin M

**Source:** Vaccine; May 2017; vol. 35 (no. 21); p. 2775-2780

**Publication Type(s):** Journal Article Review

Available at [Vaccine](#) - from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract:**INTRODUCTION Older adults are prioritized for influenza vaccination but also have lowered antibody responses to the vaccine. Higher-doses of influenza antigen may increase immune response and thus be more effective. Our objectives were to compare the efficacy and safety of the high-dose influenza vaccine to the standard-dose influenza vaccine in the elderly (age > 65). METHODS Data sources: Randomized trials (RCTs) from Medline (Ovid), EMBASE (Ovid), Cochrane Library (Wiley), ClinicalTrials.gov, reference lists of relevant articles, and gray literature. STUDY SELECTION Two reviewers independently identified RCTs comparing high-dose

influenza vaccine (60µg of hemagglutinin per strain) to standard-dose influenza vaccine (15µg of hemagglutinin per strain) in adults over the age of 65years. DATA EXTRACTION Two reviewers independently extracted trial-level data including population characteristics, interventions, outcomes, and funding sources. Risk of bias was assessed using the Cochrane Risk of Bias tool. RESULTS We included seven eligible trials; all were categorized as having a low (n=3) or unclear (n=4) risk of bias. Patients receiving the high-dose vaccine had significantly less risk of developing laboratory-confirmed influenza infections (Relative Risk 0.76, 95%CI 0.65 to 0.90; I<sup>2</sup> 0%, 2 trials, 41,141 patients). Post-vaccination geometric mean titres and seroprotection rates were also higher in high-dose vaccine recipients. There were no protocol-defined serious adverse events in the included trials in either group. CONCLUSIONS In elderly adults, the high-dose influenza vaccine was well-tolerated, more immunogenic, and more efficacious in preventing influenza infections than the standard-dose vaccine. Further pragmatic trials are needed to determine if the higher efficacy translates into higher vaccine effectiveness in adults over the age of 65.

### **31. The use of saliva specimens for detection of influenza A and B viruses by rapid influenza diagnostic tests.**

**Author(s):** Yoon, Jung; Yun, Seung Gyu; Nam, Jeonghun; Choi, Sung-Hyuk; Lim, Chae Seung

**Source:** Journal of virological methods; May 2017; vol. 243 ; p. 15-19

**Publication Type(s):** Comparative Study Journal Article Evaluation Studies

**Abstract:** BACKGROUND AND OBJECTIVES Diagnostic tests for influenza infection commonly use nasopharyngeal swabs (NPS) even though these are invasive to obtain. As an alternative specimen, we evaluated the diagnostic usefulness of saliva samples with rapid influenza diagnostic tests (RIDTs). STUDY DESIGN Both NPS and saliva samples were collected from 385 influenza suspected patients and analyzed using Sofia Influenza A+B Fluorescence Immunoassay (Quidel Corporation, San Diego, CA, USA), ichroma TRIAS Influenza A+B (Boditech, Chuncheon, Korea), SD Bioline Influenza Ag (Standard Diagnostic, Yonggin, Korea), BinaxNOW Influenza A/B antigen kit (Alere Inc., Waltham, MA, USA), and real-time reverse transcriptase PCR (RT-PCR). RESULTS Of the 385 patients, 31.2% (120/385) were positive for influenza A, and 7.5% (29/385) were positive for influenza B virus with saliva or NPS by RT-PCR. The diagnostic sensitivity was slightly higher in NPS than in saliva samples for both influenza A and B by all of the four RIDTs. The diagnostic sensitivities of Sofia and ichroma TRIAS were significantly superior to those of the other conventional influenza RIDTs with both types of sample. The sensitivities of Sofia and ichroma TRIAS with saliva specimens were comparable to the sensitivities of the other two conventional RIDTs with NPS specimens. The simultaneous use of saliva and NPS samples exhibited improved sensitivity from 10.0% to 13.3% for influenza A and from 10.3% to 17.2% for influenza B compared to using NPS alone. CONCLUSION This study demonstrates that saliva is a useful specimen for influenza detection, and that the combination of saliva and NPS could improve the sensitivities of influenza RIDTs.

### **32. Workshop report: Immunoassay standardisation for "universal" influenza vaccines.**

**Author(s):** Pavlova, Sophia; D'Alessio, Flavia; Houard, Sophie; Remarque, Edmond J; Stockhofe, Norbert; Engelhardt, Othmar G

**Source:** Influenza and other respiratory viruses; May 2017; vol. 11 (no. 3); p. 194-201

**Publication Type(s):** Journal Article Review

Available at [Influenza and other respiratory viruses](#) - from Wiley Online Library Free Content - NHS

Available at [Influenza and other respiratory viruses](#) - from Europe PubMed Central - Open Access

Available at [Influenza and other respiratory viruses](#) - from EBSCO (MEDLINE Complete)



**Abstract:**The development of broadly reactive influenza vaccines raises the need to identify the most appropriate immunoassays that can be used for the evaluation of so-called universal influenza vaccines and to explore a path towards the standardisation of such assays. More than fifty experts from the global influenza vaccine research and development field met to initiate such discussion at a workshop co-organised by the EDUFLUVAC consortium, a European Union funded project coordinated by the European Vaccine Initiative, and the National Institutes of Health/National Institute of Allergy and Infectious Diseases, USA. The workshop audience agreed that it was not possible to establish a single immunoassay for "universal" influenza vaccines because the current approaches differ in the vaccines' nature and immunogenicity properties. Therefore, different scientific rationales for the immunoassay selection are required. To avoid dilution of efforts, the choice of the primary evaluation criteria (eg serological assays or T-cell assays) should drive the effort of harmonisation. However, at an early phase of clinical development, more efforts on exploratory assessments should be undertaken to better define the immune profile in response to immunisation with new vaccines. The workshop concluded that each laboratory should aim towards validation of the appropriate immunoassays used during the entire process of vaccine development from antigen discovery up to establishment of correlates of protection, including the different steps of quality control (eg potency assays), animal studies and human clinical development. Standardisation of the immunoassays is the ultimate goal, and there is a long way to go.

### **33. Efficacy of Clarithromycin-Naproxen-Oseltamivir Combination in the Treatment of Patients Hospitalized for Influenza A(H3N2) Infection: An Open-label Randomized, Controlled, Phase IIb/III Trial.**

**Author(s):** Hung, Ivan F N; To, Kelvin K W; Chan, Jasper F W; Cheng, Vincent C C; Liu, Kevin S H; Tam, Anthony; Chan, Tuen-Ching; Zhang, Anna Jinxia; Li, Patrick; Wong, Tin-Lun; Zhang, Ricky; Cheung, Michael K S; Leung, William; Lau, Johnson Y N; Fok, Manson; Chen, Honglin; Chan, Kwok-Hung; Yuen, Kwok-Yung

**Source:** Chest; May 2017; vol. 151 (no. 5); p. 1069-1080

**Publication Type(s):** Randomized Controlled Trial Clinical Trial, Phase II Journal Article Clinical Trial, Phase III

**Abstract:**BACKGROUND Influenza causes excessive hospitalizations and deaths. The study assessed the efficacy and safety of a clarithromycin-naproxen-oseltamivir combination for treatment of serious influenza. METHODS From February to April 2015, we conducted a prospective open-label, randomized, controlled trial. Adult patients hospitalized for A(H3N2) influenza were randomly assigned to a 2-day combination of clarithromycin 500 mg, naproxen 200 mg, and oseltamivir 75 mg twice daily, followed by 3 days of oseltamivir or to oseltamivir 75 mg twice daily without placebo for 5 days as a control method (1:1). The primary end point was 30-day mortality. The secondary end points were 90-day mortality, serial nasopharyngeal aspirate (NPA) virus titer, percentage of neuraminidase-inhibitor-resistant A(H3N2) virus (NIRV) quasispecies, pneumonia severity index (PSI), and duration of hospital stay. RESULTS Among the 217 patients with influenza A(H3N2) enrolled, 107 were randomly assigned to the combination treatment. The median age was 80 years, and 53.5% were men. Adverse events were uncommon. Ten patients died during the 30-day follow-up. The combination treatment was associated with lower 30-day mortality ( $P = .01$ ), less frequent high dependency unit admission ( $P = .009$ ), and shorter hospital stay ( $P < .0001$ ). The virus titer and PSI (days 1-3;  $P < .01$ ) and the NPA specimens with NIRV quasispecies  $\geq 5\%$  (days 1-2;  $P < .01$ ) were significantly lower in the combination treatment group. Multivariate analysis showed that combination treatment was the only independent factor associated with lower 30-day mortality (OR, 0.06; 95% CI, 0.004-0.94;  $P = .04$ ). CONCLUSIONS Combination treatment reduced both 30- and 90-day mortality and length of hospital stay. Further study of the antiviral and immunomodulatory effects of this combination treatment of severe influenza is warranted. TRIAL REGISTRY BioMed

Central; No.: ISRCTN11273879 DOI 10.1186/ISRCTN11273879; URL: [www.isrctn.com/ISRCTN11273879](http://www.isrctn.com/ISRCTN11273879).

## Norovirus

### 1. Norovirus Infection in Older Adults: Epidemiology, Risk Factors, and Opportunities for Prevention and Control.

**Author(s):** Cardemil, Cristina V; Parashar, Umesh D; Hall, Aron J

**Source:** Infectious disease clinics of North America; Dec 2017; vol. 31 (no. 4); p. 839-870

**Publication Type(s):** Journal Article Review

**Abstract:** Norovirus is the leading cause of acute gastroenteritis. In older adults, it is responsible for an estimated 3.7 million illnesses; 320,000 outpatient visits; 69,000 emergency department visits; 39,000 hospitalizations; and 960 deaths annually in the United States. Older adults are particularly at risk for severe outcomes, including prolonged symptoms and death. Long-term care facilities and hospitals are the most common settings for norovirus outbreaks in developed countries. Diagnostic platforms are expanding. Several norovirus vaccines in clinical trials have the potential to reap benefits. This review summarizes current knowledge on norovirus infection in older adults.

### 2. Community-based surveillance of norovirus disease: a systematic review.

**Author(s):** Inns, Thomas; Harris, John; Vivancos, Roberto; Iturriza-Gomara, Miren; O'Brien, Sarah

**Source:** BMC infectious diseases; Sep 2017; vol. 17 (no. 1); p. 657

**Publication Type(s):** Journal Article

Available at [BMC infectious diseases](#) - from BioMed Central

Available at [BMC infectious diseases](#) - from Europe PubMed Central - Open Access

Available at [BMC infectious diseases](#) - from EBSCO (MEDLINE Complete)

**Abstract:** BACKGROUND Norovirus is a common cause of infectious gastrointestinal disease. Despite the increased ability to detect norovirus in affected people, the number of reported cases and outbreaks in the community is still substantially underestimated. We undertook a systematic review to determine the nature, scope and scale of community-based surveillance systems which capture information on norovirus disease. METHODS We searched MEDLINE, EMBASE and Scopus for studies published between 01 January 1995 and 31 December 2015, using terms relating to norovirus and surveillance. Publications were screened independently by two reviewers using exclusion criteria. Data extraction from included papers was performed using a standardized data extraction form. Outcomes were descriptions of the methods reported in included papers, and any estimates of incidence rate of norovirus disease in each community, stratified by age. RESULTS After exclusions, we reviewed 45 papers of which 23 described surveillance studies and 19 included estimates of incidence. The estimates of incidence varied by outcome measure, type of laboratory test and study population. There were two estimates of norovirus hospitalisation; 0.72 and 1.04 per 1000 person-years. Estimates of norovirus disease ranged between 0.024 cases per 1000 person-years and 60 cases per 1000 person-years and estimates of all gastroenteritis varied between 49 and 1100 cases per 1000 person-years. CONCLUSIONS Our systematic review found few papers describing community-based surveillance for norovirus disease. Standardised age-specific estimates of norovirus incidence would be valuable for calculating the true global burden of norovirus disease; robust community surveillance systems would be able to produce this information. TRIAL REGISTRATION PROSPERO 2016: CRD42016048659 .

### 3. Super-infections and relapses occur in chronic norovirus infections.

**Author(s):** Brown, Julianne R; Roy, Sunando; Tutill, Helena; Williams, Rachel; Breuer, Judith

**Source:** Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology; Sep 2017; vol. 96 ; p. 44-48

**Publication Type(s):** Journal Article

**Abstract:**BACKGROUND Norovirus causes chronic infections in immunocompromised patients with considerable associated morbidity. It is not known whether chronic infections involve super- or re-infections or relapses. OBJECTIVES To retrospectively investigate whether longitudinal sampling in chronically infected patients demonstrates persistent infection with the same virus, or super- or re-infection. STUDY DESIGN Norovirus full genomes were generated from 86 longitudinal samples from 25 paediatric patients. Consensus sequences were used for phylogenetic analysis and genotyping. RESULTS Super-infections occurred in 17% of chronically infected patients who were continuously PCR positive; including two with mixed norovirus infections. The median duration of infection was 107 days longer in those with super-infections; however this was not statistically significant. A third of patients with interrupted norovirus shedding continued to be infected with the same virus despite up to 2 months of PCR negative stools, classified as a relapse. The majority (67%) of patients with interrupted shedding were re-infected with a different genotype. CONCLUSIONS Chronically infected patients who are continuously PCR positive are most likely to remain infected with the same virus; however super-infections do occur leading to mixed infection. Patients with interrupted shedding are likely to represent re-infection with a different genotype, however relapsing infections also occur. Our findings have implications for infection control as immunosuppressed patients remain susceptible to new norovirus infections despite current or recent infection and may continue to be infectious after norovirus is undetectable in stool. The relevance to children without co-morbidities remains to be determined.

### 4. Norovirus and Clostridium difficile outbreaks: squelching the wildfire.

**Author(s):** Fisher, Ann; Dembry, Louise M

**Source:** Current opinion in infectious diseases; Aug 2017; vol. 30 (no. 4); p. 440-447

**Publication Type(s):** Journal Article

**Abstract:**PURPOSE OF REVIEW Gastrointestinal outbreaks in the healthcare setting cause increased morbidity and mortality in an already vulnerable population. Optimization of infection prevention measures can be a challenge in healthcare settings. This review describes new literature that may change the traditional infection prevention approach to such outbreaks. RECENT FINDINGS Asymptomatic carriers of both norovirus and Clostridium difficile can pose risk of transmission to others and the environment. Rapid recognition and diagnosis can decrease the extent of an outbreak. No-touch technologies for environmental disinfection are new and effective tools. Infection prevention consultant services and systems redesign can augment efforts to control baseline infection rates and outbreaks. Antimicrobial stewardship continues to be essential to prevent C. difficile infection. SUMMARY New approaches are needed to stem the tide of norovirus and C. difficile clusters and outbreaks in healthcare settings. Accurate recognition, testing, and implementation of infection prevention measures can be supported with rapid testing modalities, access to updated guidelines and no-touch disinfection systems. The work-environment culture should be carefully assessed and restructured using human engineering models to promote effective infection prevention practices. Antimicrobial stewardship initiatives are needed at the bedside and at national levels.

### **5. Estimating the burden of medically-attended norovirus gastroenteritis: modelling linked primary care and hospitalization datasets.**

**Author(s):** Verstraeten, Thomas; Cattaert, Tom; Harris, John; Lopman, Ben; Tam, Clarence C; Ferreira, Germano

**Source:** The Journal of infectious diseases; Aug 2017

**Publication Type(s):** Journal Article

**Abstract:**BackgroundNorovirus is the leading cause of community-acquired and nosocomial acute gastroenteritis. Routine testing for norovirus is seldom undertaken and diagnosis is mainly based on presenting symptoms. This makes understanding the burden of medically-attended norovirus-attributable gastroenteritis (MA-NGE) and targeting care and prevention strategies challenging.MethodsWe used linked population-based health care datasets (Clinical Practice Research Datalink General Practice OnLine Database linked with Hospital Episode Statistics Admitted Patient Care) to model the incidence of MA-NGE associated with primary care consultations or hospitalisations according to age groups in England in the period July 2007 - June 2013.ResultsMean annual incidence rates of MA-NGE were 4.9/1,000 person-years and 0.7/1,000 person-years for episodes involving primary care or hospitalisations, respectively. Incidence rates were highest in children younger than 5 years of age: 34.0 consultations/1,000 person-years and 3.3 hospitalisations/1,000 person-years. MA-NGE hospitalisation rates were second highest in adults aged 65 years and older (1.7/1,000 person-years).ConclusionsIn this particular study, the burden of MA-NGE estimated from healthcare datasets was higher than previously estimated in small cohort studies in England. Routinely collected primary care and hospitalisation datasets are useful resources to estimate and monitor the burden of MA-NGE in a population over time.

### **6. Norovirus vaccines under development.**

**Author(s):** Lucero, Yalda; Vidal, Roberto; O'Ryan G, Miguel

**Source:** Vaccine; Jun 2017

**Publication Type(s):** Journal Article

**Abstract:**Noroviruses (NoVs) are one of the leading causes of acute gastroenteritis, including both outbreaks and endemic infections. The development of preventive strategies, including vaccines, for the most susceptible groups (children <5years of age, the elderly and individuals suffering crowding, such as military personnel and travelers) is desirable. However, NoV vaccine development has faced many difficulties, including genetic/antigenic diversity, limited knowledge on NoV immunology and viral cycle, lack of a permissive cell line for cultivation and lack of a widely available and successful animal model. Vaccine candidates rely on inoculation of virus-like particles (VLPs) formed by the main capsid protein VP1, subviral particles made from the protruding domain of VP1 (P-particles) or viral vectors with a NoV capsid gene insert produced by bioengineering technologies. Polivalent vaccines including multiple NoV genotypes and/or other viruses acquired by the enteric route have been developed. A VLP vaccine candidate has reached phase II clinical trials and several others are in pre-clinical stages of development. In this article we discuss the main challenges facing the development of a NoV vaccine and the current status of prevailing candidates.

### **7. Rapid diagnosis of acute norovirus-associated gastroenteritis: evaluation of the Xpert Norovirus assay and its implementation as a 24/7 service in three hospitals in Jönköping County, Sweden.**

**Author(s):** Henningsson, A J; Nilsson Bowers, A; Nordgren, J; Quttineh, M; Matussek, A; Haglund, S

**Source:** European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology; May 2017

**Publication Type(s):** Journal Article

**Abstract:** Noroviruses are a leading cause of epidemic and sporadic cases of acute gastroenteritis worldwide. The rapid diagnosis of norovirus infection is important for prompt infection control measures and may reduce the need for additional diagnostic testing. Here we evaluated the performance of the rapid Xpert Norovirus assay, and assessed the turn-around time (TAT) before and after the implementation of the analysis as a 24/7 service at all the three hospitals in Jönköping County, Sweden. We describe the implementation process which was performed in two steps during 2014. A total number of 276 clinical samples (stool and vomitus) from patients with symptoms of acute gastroenteritis were included in 2014-2015. The samples were analysed with the Xpert Norovirus assay and the already existing routine method: an in-house reverse transcription real-time PCR. Samples showing discrepant results with the two assays were further analysed by a third PCR method. The Xpert Norovirus assay performed well with a sensitivity of 100% and a specificity of 93% compared to the gold standard (defined as the result obtained by at least two of the three PCR methods). The median TAT decreased from 22 hours in 2013 to 2.4 hours in 2015 ( $p < 0.001$ ). We conclude that the performance of the Xpert Norovirus assay was excellent, and that the implementation of the analysis as a 24/7 service at all three hospitals in the county has greatly reduced the time to diagnosis which is beneficial for both patients and healthcare providers.

**8. Evaluation of Various Real-Time Reverse Transcription Quantitative PCR Assays for Norovirus Detection.**

**Author(s):** Yoo, Ju Eun; Lee, Cheonghoon; Park, SungJun; Ko, GwangPyo

**Source:** Journal of microbiology and biotechnology; Apr 2017; vol. 27 (no. 4); p. 816-824

**Publication Type(s):** Journal Article

**Abstract:** Human noroviruses are widespread and contagious viruses causing nonbacterial gastroenteritis. Real-time reverse transcription quantitative PCR (real-time RT-qPCR) is currently the gold standard for the sensitive and accurate detection of these pathogens and serves as a critical tool in outbreak prevention and control. Different surveillance teams, however, may use different assays, and variability in specimen conditions may lead to disagreement in results. Furthermore, the norovirus genome is highly variable and continuously evolving. These issues necessitate the re-examination of the real-time RT-qPCR's robustness in the context of accurate detection as well as the investigation of practical strategies to enhance assay performance. Four widely referenced real-time RT-qPCR assays (Assays A-D) were simultaneously performed to evaluate characteristics such as PCR efficiency, detection limit, and sensitivity and specificity with RT-PCR, and to assess the most accurate method for detecting norovirus genogroups I and II. Overall, Assay D was evaluated to be the most precise and accurate assay in this study. A ZEN internal quencher, which decreases nonspecific fluorescence during the PCR, was added to Assay D's probe, which further improved the assay performance. This study compared several detection assays for noroviruses, and an improvement strategy based on such comparisons provided useful characterizations of a highly optimized real-time RT-qPCR assay for norovirus detection.



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