BC KIDNEY DAYS

Hosted by BC Transplant and the BC Renal Agency

2015

Getting shot: Vaccinations in SOT

Alissa Jade Wright, MD FRCPC MSc

October 1, 2015

Disclosures

- Educational grant money
  - UBC-Pfizer
  - UBC-Sunovion
- Advisory Board
  - Merck

Objectives

- Identify the appropriate vaccinations for patients in the pretransplant setting

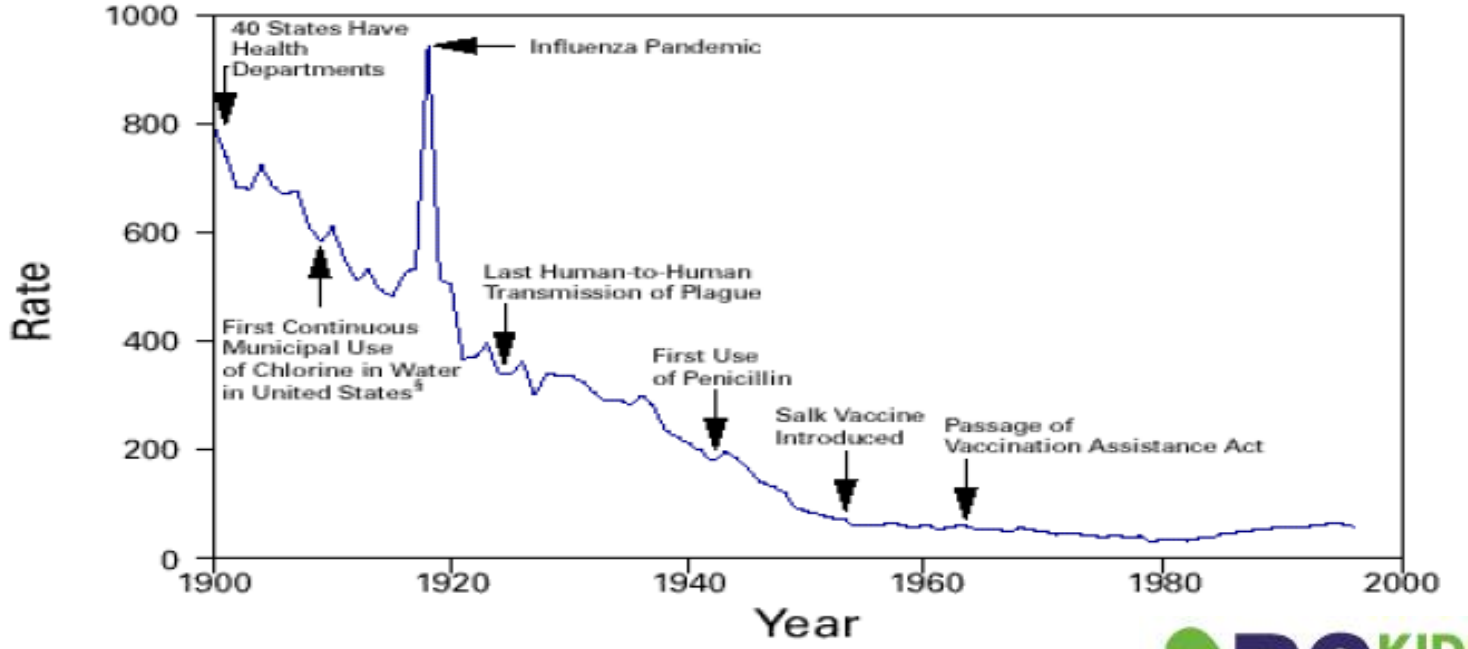
- Discuss the challenges and limitations with vaccination in the post-transplant setting

Case

- 37M (DOB: 1978)
- Received 1 MMR as child
  - May, 2013 – Measles serology <150 (negative)
  - No additional MMR given
  - Renal transplant Oct, 2013
- Feb, 2015 – Wants to visit Disneyland
  - Now what?

History of Infectious Disease

FIGURE 1. Crude death rate* for infectious diseases — United States, 1900–1996†



*Per 100,000 population per year.

MMWR. July 30, 1999 / 48(29);621-629

BC KIDNEY DAYS 2015
Hosted by BC Transplant and the BC Renal Agency

SOT

- Vaccine preventable diseases cause major morbidity and mortality in SOT
  - IS suppresses T/B cell immunity
  - More infections, more severe infections
- Updating vaccine status is a critical part of pre- and post-transplant care

Which vaccines?

- Serology can be done for:
  - HAV & HBV
  - MMR
  - VZV
  - Rarely others (e.g. tetanus)
- Other routine vaccines:
  - Pneumococcus
  - Influenza
  - Tdap

Influenza

- Seasonal viral infection
  - Two main human subtypes A >>> B
- Causes severe disease in SOT
  - ICU (16%)
  - Death (6%)
  - Extra-pulmonary complications
  - Prolonged shedding
  - Increased risk of graft rejection

BC KIDNEY DAYS 2015
Hosted by BC Transplant and the BC Renal Agency

Chow & Golan. Clin Infect Dis. (2009) 49 (10):1550-1556. Perez-Romaro. Clin Microbiol Infect. 2012 Dec;18(12):E533-40.

Influenza

- Two vaccines – IIV & LAIV
- IIV more common
  - Usually trivalent +/- adjuvants
  - 2 strains influenza A, 1 strain influenza B
- LAIV
  - Administered intranasally
  - Only replicates at lower nasal temperature

Influenza

- LAIV has not been studied in SOT
  - Contraindicated at present
- In BC, only for children 2-17 y.o.
- Not free for other age groups
  - IIV provides better protection
- Pre-transplant: Either
- Post-transplant: IIV

Influenza Vaccination Is Efficacious and Safe in Renal Transplant Recipients

American Journal of Transplantation 2008; 8: 332–337

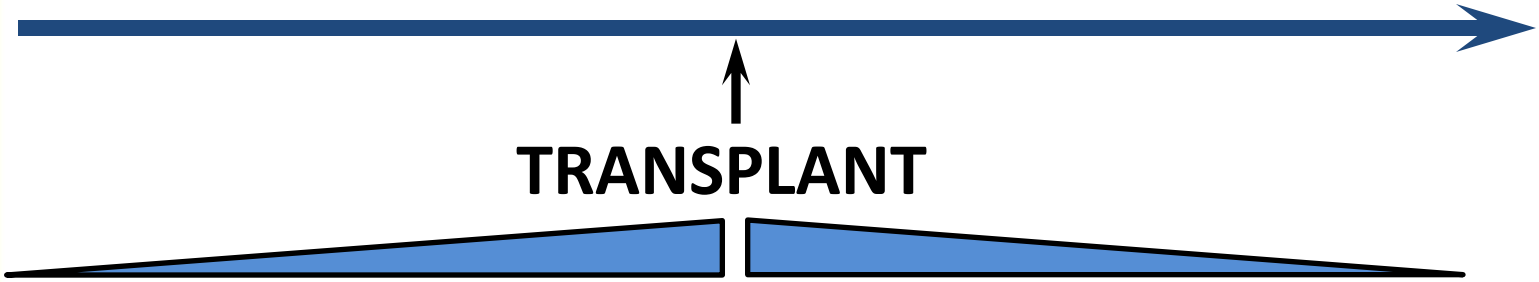
- 165 renal tx recipients
  - SP rates high (79-93%)
  - Inversely related to MMF use (2.6-5x lower response)
  - No benefit to booster dose
  - No rejection noted
- SP in other studies: 15-93%
  - Likely 2^{o} to timing/IS

Influenza Vaccine

- Concerns re: graft rejection
  - Not found in studies
- Has been elevated anti-HLA Ab detected post-immunization
  - 5-17% of RTR
  - May depend on vaccine (& adjuvant)
  - Uncertain clinical significance
  - Transient

Katerinis et al. Am J Transplant. 2011 Aug;11(8):1727-33

When to vaccinate?



- Both run risk of altered immune response

When to vaccinate?

- Generally pre-transplant has best immune responses in studies
  - Healthy > Dialysis > Post-transplant
- Pre-transplant Ab predict post-transplant Ab
- Abs do wane over time in SOT
  - Can be accelerated
  - Test & boost if appropriate

L'Huillier et al. Pediatr Transplant. 2012 Feb;16(1):50-7.

Resuming Vaccination

- Timing post-tx varies by guideline
- Influenza example:
  - AST 3-6 mo.
  - IDSA 2-6 mo. unless outbreak
  - KDIGO 1 mo.
- No harm to early
- Less immunogenic → trade-off between response vs. risk

Pneumococcus

- IPD more common in SOT
  - Incidence 146 infections/100,000 person-year
  - Risk 12.8x general population
  - 29% mortality
- If non-sterile sites included
  - Incidence 419 infections /100,000 person-years

Kumar et al. Am J Transplant. 2007 May;7(5):1209-14.

Pneumococcus

- Two vaccines
  - Polysaccharide (PPV-23)
  - Conjugate (PCV-13)
- Polysaccharide = sugar
  - B cells produce Ab without T-cell help
- Conjugate = add diphtheria protein
  - T-cells stimulated
  - Get B memory cell response

Pneumococcus

- Improved efficacy in HIV
- Improved immunogenicity in HSCT
- Minimal data in SOT
  - Similar SP rates
  - 80% in PCV-13 vs. 83% in PPV-23 in one study
  - Similar duration of response
- NACI grades evidence “fair”

NACI. CCDR. 2013. Volume 29:5.

Pneumococcus

- Most guidelines have recommended both for any IC individual
  - IDSA/AICP
- In BC, PCV-13 only covered for HSCT & HIV
  - Requested update on this → stay tuned

Pneumococcus

- If given:
  - PCV-13 followed by PPV-23 at 8 weeks
  - PPV-23 followed by PCV-13 at 1 year
- Reflects hyporesponsiveness polysaccharide antigens
- Booster dose at 5 years with PPV-23

O'Brien. Lancet ID. 2007 Sep;7(9):597-606.

Varicella

- Higher incidence than general population
  - 27-55 cases/1000 patient-years vs. 1.5-3
- High morbidity and mortality
  - Multidermatomal zoster
  - 40% risk dissemination
  - 4%–34% mortality
  - Graft rejection

Netchiporouk. Transplant Proc. 2013 Mar;45(2):701-4.

BC KIDNEY DAYS 2015
Hosted by BC Transplant and the BC Renal Agency

Varicella Vaccine

- LAV with Oka strain
  - Available since 1990
- In BC, 2 doses for seronegative pts. if not IC
  - Separate by 6 weeks if ≥13 y.o.
- Pre-transplant
  - Acceptable if minimal IS
  - 4 week hold for Tx

Varicella Vaccine

- Post-transplant
  - Generally contraindicated
- Select pediatric SOT patients have undergone immunization
  - Seroconversion rates 65-87%
  - Few side-effects under study conditions
  - Not ready for prime time

L'Huillier & Kumar. Hum Vaccin Immunother. 2015 Aug 20:0

Non-Immune Patients

- Post-exposure prophylaxis available
  - VarIg within 96h of exposure
  - +/- (val)acyclovir
- May not be fully protective
  - 8 pediatric patients with 1^{o} disease
  - 2 deaths including 1 pt who received VarIg

Lynfield et al. Pediatrics. 1992 Aug;90(2 Pt 1):216-20.

Vaccine Efficacy

- Best measure = clinical outcome
  - Not always feasible
- Ab levels are cheap & easy
  - May not be protective or functional Ab
- VZV is good example
  - CMI is what predicts zoster protection

Oxman. Clin Infect Dis. (2010) 51 (2):197-213.

Varicella Zoster Vaccine

- Zostavax contains 14x PFU of Oka strain
- Licensed for healthy individuals ≥ 50 y.o.
  - In BC, recommended but not provided
  - Cost ~$175
- Pre-transplant
  - Acceptable if minimal IS
  - 4 week hold for Tx

Varicella Zoster Vaccine

- Post-transplant
  - Generally contraindicated
- New vaccines likely more promising

Safety and Immunogenicity of an Adjuvanted Herpes Zoster Subunit Candidate Vaccine in HIV-Infected Adults: A Phase 1/2a Randomized, Placebo-Controlled Study

The Journal of Infectious Diseases® 2015;211:1279–87

LAV & Household Contacts

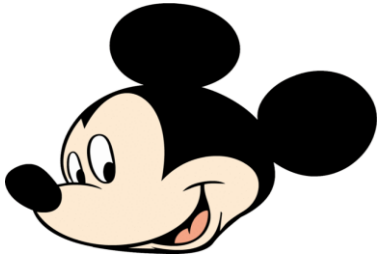
- Contacts should receive routine vaccines
  - Oral polio vaccine is only exception
- Shedding may be inverse to age
  - 80% if 8-36 mo. vs. 30% if 5-49 y.o. for LAIV
- Max shedding w/i 2 days of vaccination
  - Up to 4 weeks for rotavirus

Rubin et al. Clin Infect Dis. 2014 Feb;58(3):309-18.

LAV & Household Contacts

- Actually transmission events rare outside polio
  - Typically no sequela given attenuated virus
- Tips:
  - Mothers of tx recipients: avoid nursing
  - Rotavirus: avoid diapers
  - VZV: cover rash

Measles



- 20 million cases/year world-wide
- Local outbreaks – Vancouver (2010), Fraser Valley (2014)…
- High morbidity and mortality in all pts
  - Pneumonia (1/20), encephalitis (1/1,000), SSPE (4-11/1,000,000), death (1-2/1,000)
  - Rejection in transplant pts.

BC KIDNEY DAYS 2015
Hosted by BC Transplant and the BC Renal Agency

CDC. November, 2014.

Measles

- No specific treatment available
  - Supportive care + Vitamin A
  - Ribavirin (off-label)
- PEP
  - MMR vaccine within 72 hrs
  - IVIG if MMR contraindicated
- Best protection is immunization

Gans & Maldonado. UTD, 2015.

Measles

- LAV with Edmonston B strain
  - Available since 1960s (MMR)
- Measles immunity (routine)
  - Born <1970, or
  - Lab confirmed infection or immunity, or
  - Documentation of two vaccines if 2-17 y.o., or
  - Documentation of one vaccine if ≥ 18 y.o. and born >1970
- If high risk → need 2 vaccines OR lab-confirmed immunity

BC KIDNEY DAYS 2015
Hosted by BC Transplant and the BC Renal Agency

NACI. Canadian Immunization Guide.

Measles

- In BC, 2 doses if not IC
  - Prior to mid-1990s, only 1 dose was given → patients may need second dose
  - Separate by 4 weeks
- Pre-transplant
  - Acceptable if on minimal IS
  - 4 week hold for Tx

Measles

- Post-transplant
  - Generally contraindicated
- Four studies of pediatric SOT patients have undergone immunization
  - Seroconversion rates 40-100%
  - Not ready for prime time

L'Huillier & Kumar. Hum Vaccin Immunother. 2015 Aug 20:0.

Other Routine Vaccines

- Pertussis (inactivated)
  - Multiple outbreaks
  - Update Tdap pre-tx + booster q10 years
- HBV (inactivated)
  - Give to all patients (HBcAb+ donor/blood products)
  - Seroconversion varies 20-70% pre/post
  - Antibody waning frequent → booster doses post-Tx

L'Huillier & Kumar. Hum Vaccin Immunother. 2015 Aug 20:0.

Other Routine Vaccines

- HAV (inactivated)
  - Recommended for high-risk patients pre-transplant (e.g. MSM, liver disease)
  - Accelerated waning in SOT recipients
  - May need (booster) post-transplant
  - Seroconversion rates post-Tx ~25%
  - IM Ig if urgent, high-risk travel

L'Huillier & Kumar. Hum Vaccin Immunother. 2015 Aug 20:0.

HPV

- Many subtypes
  - HPV 16/18 (cancer) vs. 6/11 (90% warts)
- Causes significant morbidity
  - Tx patients have 14-100x risk CIN/AIN
  - Increased skin cancer risk
  - Increased risk of warts
- Two vaccines – bivalent & quadrivalent
  - Inactivated

Kumar et al. Am J Transplant. 2013 Sep;13(9):2411-7.

HPV

- In BC, available to women born ≥ 1994
  - 2 dose schedule in BC
  - Sept 1, 2015 → high-risk males also covered
- Other eligible populations can receive it
  - Not free
  - Women ≤ 45 y.o., males 9-26 y.o., MSM ≥ 27 y.o.

HPV

- Pretransplant:
  - If candidate → give series
- Post-transplant:
  - Can be given if still eligible
  - Immunogenicity rates lower than non-IC group
  - Seropositivity in 53-68% for different subtypes

Kumar et al. Am J Transplant. 2013 Sep;13(9):2411-7.

Travel Vaccines

- Most have not been specifically tested in SOT
  - Protection may be uncertain
  - If inactivated product, okay to give
- Live products to avoid
  - YF, oral polio vaccine, oral typhoid vaccine, BCG

Travel Vaccines

- Acceptable vaccines
  - Rabies vaccine
  - Inactivated polio vaccine
  - Inactivated typhoid vaccine
  - Cholera/enterotoxigenic *E. coli*. (Dukoral™)
  - Meningococcal vaccine
  - Japanese encephalitis vaccine

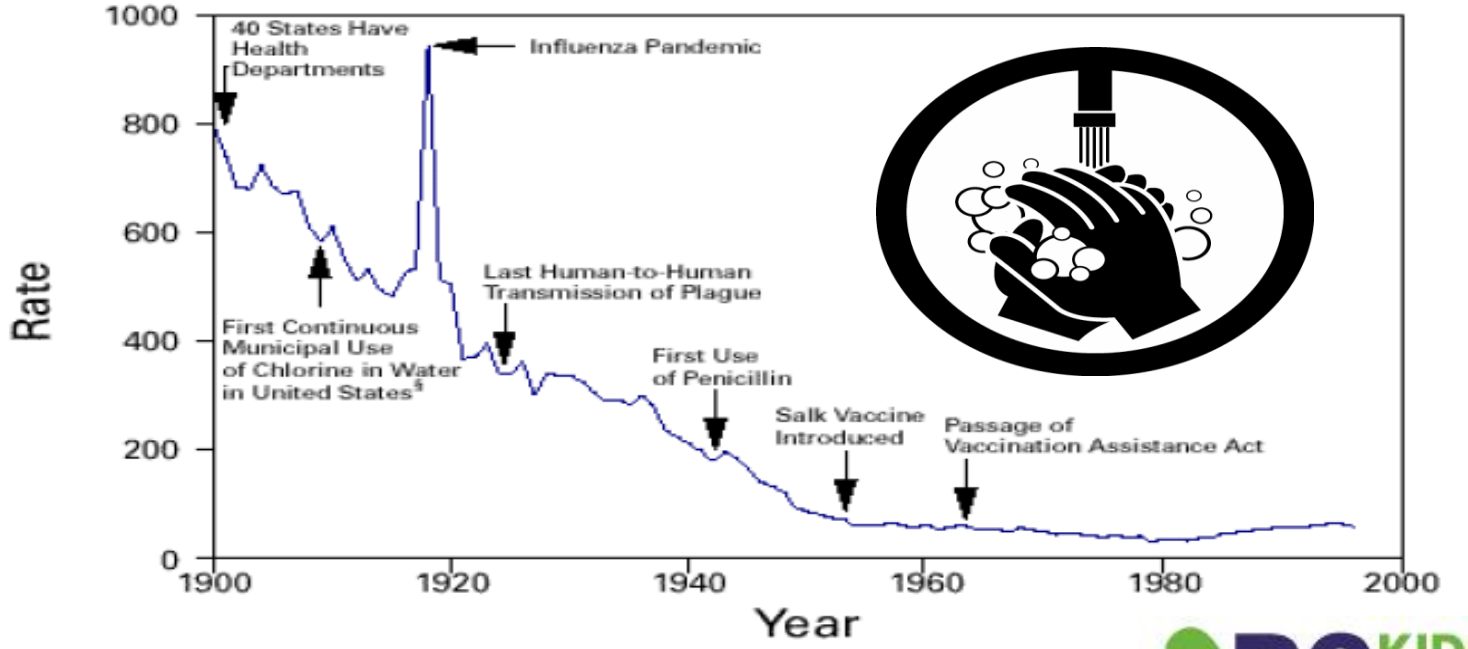
Vaccine	Pre?	Post?
HAV	✓	✓
HBV	✓	✓
Tdap	✓	✓
Pneumococcal	✓	✓
VZV/Zoster	✓	✗
MMR	✓	✗
HPV	✓	✓
Dukoral	✓	✓
YF	✓	✗
Rabies	✓	✓
IM Typhoid	✓	✓

Final Tips

- Think about vaccination
  - Check serology
  - Encourage updates
- Vaccinate as early as possible
  - Prefer pre > post-Tx
- Repeat serology & boost as needed

History of Infectious Disease

FIGURE 1. Crude death rate* for infectious diseases — United States, 1900–1996†



*Per 100,000 population per year.

MMWR. July 30, 1999 / 48(29);621-629

BC KIDNEY DAYS 2015
Hosted by BC Transplant and the BC Renal Agency

Objectives

- Identify the appropriate vaccinations for patients in the pretransplant setting

- Discuss the challenges and limitations with vaccination in the post-transplant setting

BC KIDNEY DAYS

Hosted by BC Transplant and the BC Renal Agency

2015

Questions?

References

•BCCDC. Immunization Manual. Available at: http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap2.htm

•Berkowitz EM, Moyle G, Stellbrink HJ, Schürmann D, Kegg S, Stoll M, El Idrissi M, Oostvogels L, Heineman TC; Zoster-015 HZ/su Study Group. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. J Infect Dis. 2015 Apr 15;211(8):1279-87.

•CDC. Achievements in Public Health, 1900-1999: Control of Infectious Diseases. MMWR. July 30, 1999 / 48(29);621-629.

•CDC. Complications of Measles. November 3, 2014. Available at: http://www.cdc.gov/measles/about/complications.html.

•Chow J, Golan Y. Vaccination of solid-organ transplantation candidates. Clin Infect Dis. 2009 Nov 15;49(10):1550-6.

•Cohn J, Blumberg EA. Immunizations for renal transplant candidates and recipients. Nat Clin Pract Nephrol. 2009 Jan;5(1):46-53.

•Danziger-Isakov L, Kumar D; AST Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. Am J Transplant. 2013 Mar;13 Suppl 4:311-7.

•Katerinis I, Hadaya K, Duquesnoy R, Ferrari-Lacraz S, Meier S, van Delden C, Martin PY, Siegrist CA, Villard J. De novo anti-HLA antibody after pandemic H1N1 and seasonal influenza immunization in kidney transplant recipients. Am J Transplant. 2011 Aug;11(8):1727-33.

•Kumar D, Humar A, Plevneshi A, Green K, Prasad GV, Siegal D; Toronto Invasive Bacterial Diseases Network, McGeer A. Invasive pneumococcal disease in solid organ transplant recipients--10-year prospective population surveillance. Am J Transplant. 2007 May;7(5):1209-14.

•Kumar D, Unger ER, Panicker G, Medvedev P, Wilson L, Humar A. Immunogenicity of quadrivalent human papillomavirus vaccine in organ transplant recipients. Am J Transplant. 2013 Sep;13(9):2411-7.

References

•L'Huillier AG, Kumar D. Immunizations in solid organ and hematopoeitic stem cell transplant patients: A comprehensive review. Hum Vaccin Immunother. 2015 Aug 20:0.

•NACI. Statement on the Use of Conjugate Pneumococcal Vaccine – 13 Valent in Adults (Pneu-C-13) . CCDR. Volume 39. October, 2013.

•NACI. Canadian Immunization Guide. Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php.

•Netchiporouk E1, Tchervenkov J, Paraskevas S, Sasseville D, Billick R. Evaluation of varicella zoster virus infection morbidity and mortality in pancreas and kidney-pancreas transplant recipients. Transplant Proc. 2013 Mar;45(2):701-4.

•O'Brien KL, Hochman M, Goldblatt D. Combined schedules of pneumococcal conjugate and polysaccharide vaccines: is hyporesponsiveness an issue? Lancet Infect Dis. 2007 Sep;7(9):597-606.

•Oxman MN. Zoster vaccine: current status and future prospects. Clin Infect Dis. 2010 Jul 15;51(2):197-213.

•Perez-Romero P, Aydillo TA, Perez-Ordoñez A, Muñoz P, Moreno A, López-Medrano F, Bodro M, Montejo M, Gavaldà J, Fariñas MC, Pachon J, Cordero E. Reduced incidence of pneumonia in influenza-vaccinated solid organ transplant recipients with influenza disease. Clin Microbiol Infect. 2012 Dec;18(12):E533-40.

•Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I, Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014 Feb;58(3):309-18.

•Scharpé J, Evenepoel P, Maes B, Bammens B, Claes K, Osterhaus AD, Vanrenterghem Y, Peetermans WE. Influenza vaccination is efficacious and safe in renal transplant recipients. Am J Transplant. 2008 Feb;8(2):332-7.