Influenza and pneumococcal vaccination in kidney transplant candidates and recipients

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Introduction

- Infection is among the leading causes of morbidity and mortality in patients with underlying CKD, including those with kidney failure treated by dialysis or transplantation.
- CKD results in a state of immunosuppression that is likely multifactorial due to a combination of innate and adaptive immune system dysfunction, chronic inflammation, endothelial cell dysfunction, and uremia.
- The incidence of infection and infection-related hospitalizations has been shown to increase as kidney function declines
- Risk for infection in transplant recipients is compounded by the need for immunosuppressive agents

Points of vaccination
Transplant candidates and recipients are at increased risk of infectious complications of vaccine-preventable diseases
Vaccination status should be reviewed at the first transplant clinic visit
Vaccination status and implementation strategy should be reviewed once again at the time the patient is listed for transplantation
Since the response to many vaccines is diminished in organ failure, transplant candidates should be immunized early in the course of their disease.
Every effort should be made to ensure that transplant candidates and their household members have completed the full complement of recommended vaccinations prior to transplantation.
Vaccination during active treatment for rejection should be avoided
Recommendations made by national immunization advisory committees (for example, the Advisory Committee on Immunization Practices [ACIP] in the United States) for the general population should be followed.

CLINICAL GUIDELINE

Annals of Internal Medicine

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Recommended Adult Immunization Schedule, United States, 2019*

David K. Kim, MD, MA, and Paul Hunter, MD; on behalf of the Advisory Committee on Immunization Practices†

Recommended Adult Immunization Schedule
for ages 19 years or older

UNITED STATES 2019

How to use the adult immunization schedule

1 Determine recommended vaccinations by age (Table 1)

2 Assess need for additional recommended vaccinations by medical condition and other indications (Table 2)

3 Review vaccine types, frequencies, and intervals and considerations for special situations (Notes)

Recommended by the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/acip) and approved by the Centers for Disease Control and Prevention (www.cdc.gov), American College of Physicians (www.acponline.org), American Academy of Family Physicians (www.aafp.org), American College of Obstetricians and Gynecologists (www.acog.org), and American College of Nurse-Midwives (www.midwife.org).

Vaccines in the Adult Immunization Schedule*

Vaccines	Abbreviations	Trade names
Haemophilus influenzae type b vaccine	Hib	ActHIB Hiberix
Hepatitis A vaccine	HepA	Havrix Vaqta
Hepatitis A and hepatitis B vaccine	HepA-HepB	Twinrix
Hepatitis B vaccine	HepB	Engerix-B Recombivax HB Heplisav-B
Human papillomavirus vaccine	HPV vaccine	Gardasil 9
Influenza vaccine, inactivated	IIV	Many brands
Influenza vaccine, live attenuated	LAIV	FluMist Quadrivalent
Influenza vaccine, recombinant	RIV	Flublok Quadrivalent
Measles, mumps, and rubella vaccine	MMR	M-M-R II
Meningococcal serogroups A, C, W, Y vaccine	MenACWY	Menactra Menveo
Meningococcal serogroup B vaccine	MenB-4C MenB-FHbp	Bexsero Trumenba
Pneumococcal 13-valent conjugate vaccine	PCV13	Prevnar 13
Pneumococcal 23-valent polysaccharide vaccine	PPSV23	Pneumovax
Tetanus and diphtheria toxoids	Td	Tenivac Td vaccine
Tetanus and diphtheria toxoids and acellular pertussis vaccine	Tdap	Adacel Boostrix
Varicella vaccine	VAR	Varivax
Zoster vaccine, recombinant	RZV	Shingrix
Zoster vaccine live	ZVL	Zostavax

*Administer recommended vaccines if vaccination history is incomplete or unknown. Do not restart or add doses to vaccine series for extended intervals between doses. The use of trade names is for identification purposes only and does not imply endorsement by the ACIP or CDC.

Report

- Suspected cases of reportable vaccine-preventable diseases or outbreaks to the local or state health department
- Clinically significant post-vaccination reactions to the Vaccine Adverse Event Reporting System at www.vaers.hhs.gov or 800-822-7967

Injury claims

All vaccines included in the adult immunization schedule except pneumococcal 23-valent polysaccharide and zoster vaccines are covered by the Vaccine Injury Compensation Program. Information on how to file a vaccine injury claim is available at www.hrsa.gov/vaccinecompensation or 800-338-2382.

Questions or comments

Contact CDC at www.cdc.gov/cdc-info or 800-CDC-INFO (800-232-4636), in English or Spanish, 8 a.m.–8 p.m. ET, Monday through Friday, excluding holidays.

Download the CDC Vaccine Schedules App for providers at www.cdc.gov/vaccines/schedules/hcp/schedule-app.html

Helpful information

- Complete ACIP recommendations: www.cdc.gov/vaccines/hcp/acip-recs/index.html
- General Best Practice Guidelines for Immunization: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html
- Vaccine Information Statements: www.cdc.gov/vaccines/hcp/vis/index.html
- Manual for the Surveillance of Vaccine-Preventable Diseases (including case identification and outbreak response): www.cdc.gov/vaccines/pubs/surv-manual
- Travel vaccine recommendations: www.cdc.gov/travel
- Recommended Child and Adolescent Immunization Schedule, United States, 2019: www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Table 1 Recommended Adult Immunization Schedule by Age Group United States, 2019

Vaccine	19–21 years	22–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or Influenza recombinant (RIV)	1 dose annually				
or Influenza live attenuated (LAIV)	1 dose annually				
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap, then Td booster every 10 yrs				
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)				
Varicella (VAR)	2 doses (if born in 1980 or later)				
Zoster recombinant (RZV) (*preferred*)				2 doses	
or Zoster live (ZVL)					1 dose
Human papillomavirus (HPV) Female	2 or 3 doses depending on age at initial vaccination				
Human papillomavirus (HPV) Male	2 or 3 doses depending on age at initial vaccination				
Pneumococcal conjugate (PCV13)	1 dose				
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses depending on indication				1 dose
Hepatitis A (HepA)	2 or 3 doses depending on vaccine				
Hepatitis B (HepB)	2 or 3 doses depending on vaccine				
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains				
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication				
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication				

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

No recommendation

Table 2 Recommended Adult Immunization Schedule by Medical Condition and Other Indications United States, 2019

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 count		Asplenia, complement deficiencies	End-stage renal disease, on hemodialysis	Heart or lung disease, alcoholism[1]	Chronic liver disease	Diabetes	Health care personnel[2]	Men who have sex with men
			<200	≥200							
IIV or RIV or LAIV	1 dose annually									or 1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td booster every 10 yrs									
MMR	CONTRAINDICATED	1 or 2 doses depending on indication									
VAR	CONTRAINDICATED	2 doses									
RZV (*preferred*) or ZVL	DELAY / CONTRAINDICATED	2 doses at age ≥50 yrs or 1 dose at age ≥60 yrs									
HPV Female	DELAY	3 doses through age 26 yrs			2 or 3 doses through age 26 yrs						
HPV Male		3 doses through age 26 yrs			2 or 3 doses through age 21 yrs						2 or 3 doses through age 26 yrs
PCV13		1 dose									
PPSV23		1, 2, or 3 doses depending on age and indication									
HepA		2 or 3 doses depending on vaccine									
HepB		2 or 3 doses depending on vaccine									
MenACWY		1 or 2 doses depending on indication, then booster every 5 yrs if risk remains									
MenB	PRECAUTION	2 or 3 doses depending on vaccine and indication									
Hib		3 doses HSCT[3] recipients only			1 dose						

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction

Delay vaccination until after pregnancy if vaccine is indicated

Contraindicated—vaccine should not be administered because of risk for serious adverse reaction

No recommendation

1. Precaution for LAIV does not apply to alcoholism. 2. See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. 3. Hematopoietic stem cell transplant.

Influenza vaccination

Routine vaccination

- **Persons aged 6 months or older:** 1 dose IIV, RIV, or LAIV appropriate for age and health status annually
- For additional guidance, see www.cdc.gov/flu/professionals/index.htm

Special situations

- **Egg allergy, hives only:** 1 dose IIV, RIV, or LAIV appropriate for age and health status annually
- **Egg allergy more severe than hives** (e.g., angioedema, respiratory distress): 1 dose IIV, RIV, or LAIV appropriate for age and health status annually in medical setting under supervision of health care provider who can recognize and manage severe allergic conditions
- **Immunocompromising conditions (including HIV infection), anatomical or functional asplenia, pregnant women, close contacts and caregivers of severely immunocompromised persons in protected environment, use of influenza antiviral medications in previous 48 hours, cerebrospinal fluid leak or cochlear implant:** 1 dose IIV or RIV annually (LAIV not recommended)
- **History of Guillain-Barré syndrome within 6 weeks of previous dose of influenza vaccine:** Generally should not be vaccinated

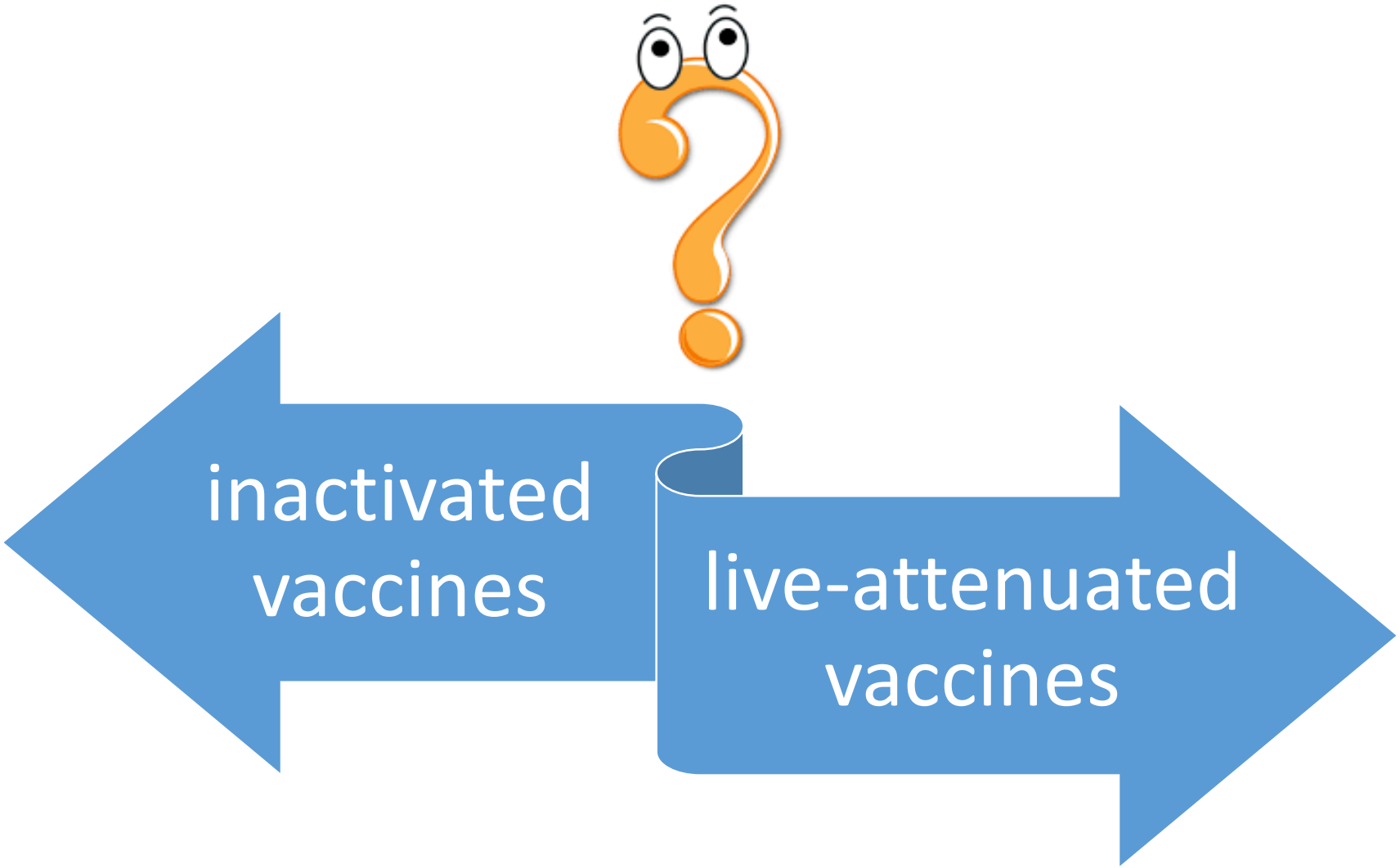
Pneumococcal vaccination

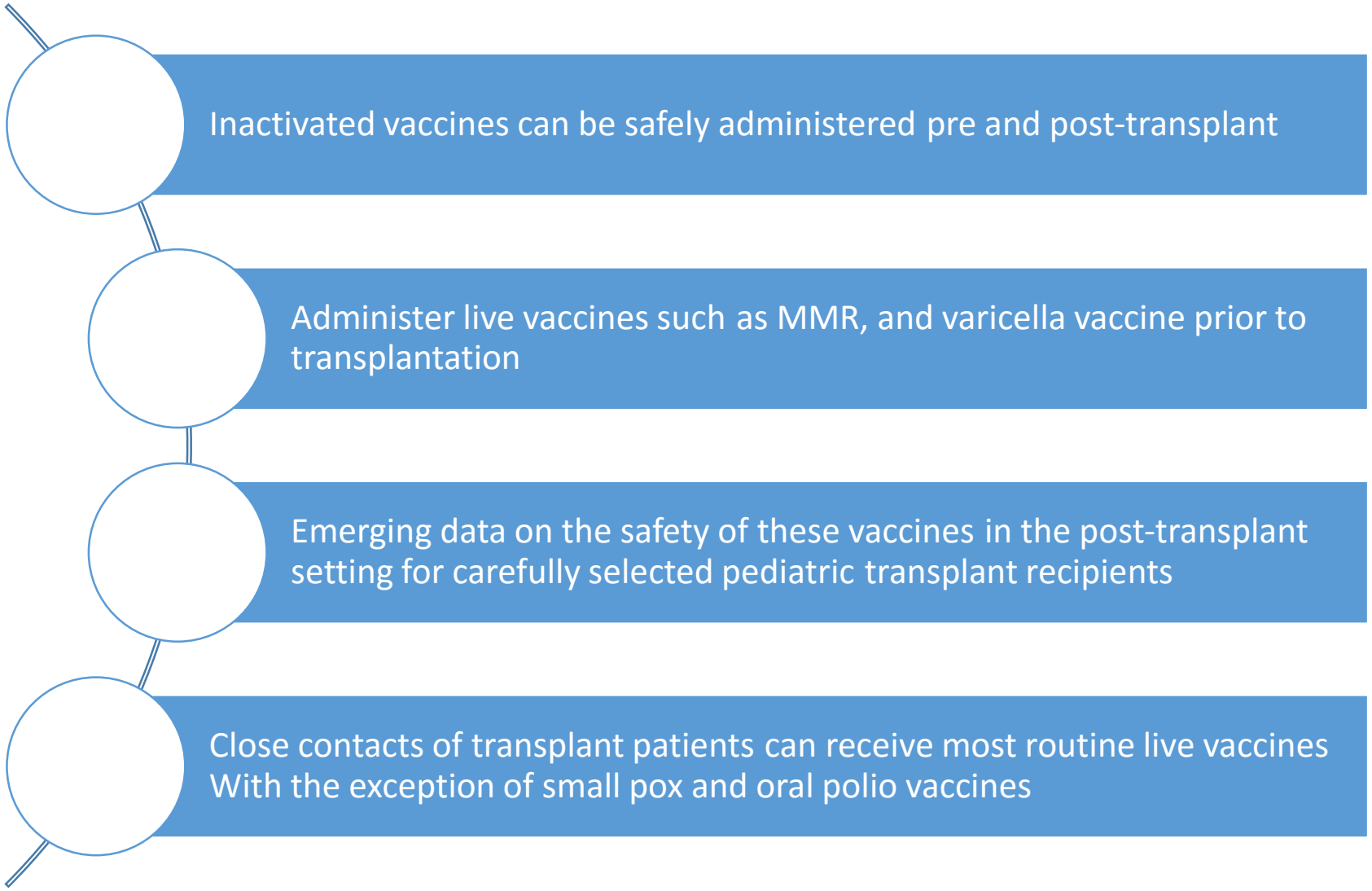
Routine vaccination

- **Age 65 years or older** (immunocompetent): 1 dose PCV13 if previously did not receive PCV13, followed by 1 dose PPSV23 at least 1 year after PCV13 and at least 5 years after last dose PPSV23
  - Previously received PPSV23 but not PCV13 at age 65 years or older: 1 dose PCV13 at least 1 year after PPSV23
  - When both PCV13 and PPSV23 are indicated, administer PCV13 first (PCV13 and PPSV23 should not be administered during same visit)

Special situations

- **Age 19 through 64 years with chronic medical conditions (chronic heart [excluding hypertension], lung, or liver disease; diabetes), alcoholism, or cigarette smoking:** 1 dose PPSV23
- **Age 19 years or older with immunocompromising conditions (congenital or acquired immunodeficiency [including B- and T-lymphocyte deficiency, complement deficiencies, and phagocytic disorders, HIV infection], chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression [e.g., drug or radiation therapy], solid organ transplant, multiple myeloma) or anatomical or functional asplenia (including sickle cell disease and other hemoglobinopathies):** 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later, then another dose PPSV23 at least 5 years after previous PPSV23; at age 65 years or older, administer 1 dose PPSV23 at least 5 years after most recent PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)
- **Age 19 years or older with cerebrospinal fluid leak or cochlear implant:** 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later; at age 65 years or older, administer another dose PPSV23 at least 5 years after PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)


inactivated vaccines
live-attenuated vaccines



If a live-attenuated vaccine was to be administered inadvertently to a transplant recipient, antiviral therapy and subsequent revaccination with an inactivated influenza vaccine can be considered

Timing of vaccination

Pre transplant vaccination

Ideally, vaccination for inactivated and live viral vaccination should be completed by 2 weeks and 4 weeks prior to transplantation, respectively, if possible

Post transplant vaccination

Most centers restart vaccination at approximately 3-6 months after transplantation when baseline immunosuppression levels are attained

Post transplant influenza vaccine

Data suggest vaccination can be given as early as one month post-transplant

ORIGINAL ARTICLE VIROLOGY

Influenza vaccination during the first 6 months after solid organ transplantation is efficacious and safe

P. Pérez-Romero[1], A. Bulnes-Ramos[1], J. Torre-Cisneros[2], J. Gavaldá[3], T. A. Aydillo[1], A. Moreno[4], M. Montejo[5], M. C. Fariñas[6], J. Carratalá[7], P. Muñoz[8], M. Blanes[9], J. Fortún[10], A. Suárez-Benjumea[11], F. López-Medrano[12], J. L. Barranco[2], M. Peghin[3], C. Roca[1], R. Lara[2] and E. Cordero[1], for the Influenza Vaccine in Solid Organ Transplant Recipient Study Group, Spanish Network of Research in Infectious Diseases (REIPI-GESITRA)

1) Instituto de Biomedicina de Sevilla (IBIS), University Hospital Virgen del Rocío/CSIC/University of Sevilla, Seville, 2) Reina Sofía University Hospital-Maimonides Institute for Biomedical Research (IMIBIC), University of Cordoba (UCO), Cordoba, 3) Vall d'Hebron University Hospital-VHIR, 4) University Clinic Hospital, Barcelona, 5) University Hospital Cruces, Bilbao, 6) University Hospital Marqués de Valdecilla, Santander, 7) University Hospital Belltvitge-IDIBELL, University of Barcelona, Barcelona, 8) General University Hospital Gregorio Marañón, Madrid, 9) University Hospital La Fe, Valencia, 10) University Hospital Ramón y Cajal, Madrid, 11) University Hospital Virgen Macarena, Sevilla and 12) University Hospital 12 de Octubre, Madrid, Spain

After adjusting for confounding factors, time since transplantation was not associated with response to vaccination. No cases of rejection or severe adverse events were detected in patients vaccinated within the first 6 months after transplantation.

In conclusion, influenza vaccination within the first 6 months after transplantation is as safe and immunogenic as vaccination thereafter. Thus, administration of the influenza vaccine can be recommended as soon as 1 month after transplantation

Clin Microbiol Infect 2015; 21: 1040.e11–1040.e18

Influenza vaccine

Influenza vaccines
standard dose (15 µg per strain) vs high-dose (60 µg per strain) trivalent vaccine
quadrivalent formulations, which contain two A and two B strains
MF59-adjuvanted
Live-attenuated

Most immunogenicity and safety data available are with the standard-dose trivalent vaccine which has a wide variability of antibody responses that range 15%-90%, but are all generally lower than responses in healthy controls

- The ability to mount an immune response will be impacted by the type and amount of immunosuppression after organ transplantation.
- Seroconversion should be documented by serologic assays where available.
- A minimum of 4 weeks should elapse between vaccine administration
- Serology may not be an accurate measure of immunity in the post transplant period, assays for cellular immunity
- Waning titers in the post-transplant period are well documented

- Infection with influenza virus is associated with significantly high morbidity and mortality in solid organ transplant (SOT) recipients.
- Patients receiving dialysis who develop influenza are at increased risk for complications, including hospital admission and death.

Observational Study > Clin Infect Dis. 2018 Oct 15;67(9):1322-1329. doi: 10.1093/cid/ciy294.

A 5-Year Prospective Multicenter Evaluation of Influenza Infection in Transplant Recipients

Deepali Kumar [1], Victor H Ferreira [1], Emily Blumberg [2], Fernanda Silveira [3], Elisa Cordero [4], Pilar Perez-Romero [4], Teresa Aydillo [4], Lara Danziger-Isakov [5], Ajit P Limaye [6], Jordi Carratala [7], Patricia Munoz [8], Miguel Montejo [9], Francisco Lopez-Medrano [10], Maria Carmen Farinas [11], Joan Gavalda [12], Asuncion Moreno [13], Marilyn Levi [14], Jesus Fortun [15], Julian Torre-Cisneros [16], Janet A Englund [17], Yoichiro Natori [1], Shahid Husain [1], Gail Reid [18], Tanvi S Sharma [19], Atul Humar [1]

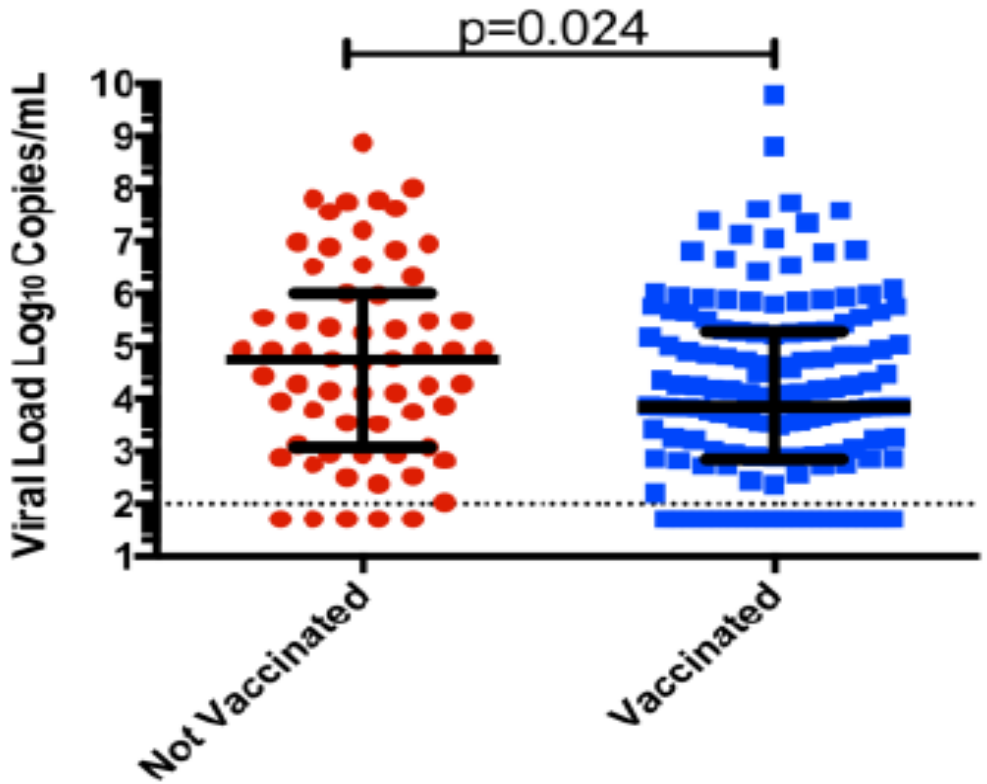
Abstract

Background: Seasonal influenza infection may cause significant morbidity and mortality in transplant recipients. The purpose of this study was to assess the epidemiology of symptomatic influenza infection posttransplant and determine risk factors for severe disease.

Methods: Twenty centers in the United States, Canada, and Spain prospectively enrolled solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) recipients with microbiologically confirmed influenza over 5 consecutive years (2010-2015). Demographics, microbiology data, and outcomes were collected. Serial nasopharyngeal swabs were collected at diagnosis and upto 28 days, and quantitative polymerase chain reaction for influenza A was performed.

Results: We enrolled 616 patients with confirmed influenza (477 SOT; 139 HSCT). Pneumonia at presentation was in 134 of 606 (22.1%) patients. Antiviral therapy was given to 94.1% for a median of 5 days (range, 1-42 days); 66.5% patients were hospitalized and 11.0% required intensive care unit (ICU) care. The receipt of vaccine in the same influenza season was associated with a decrease in disease severity as determined by the presence of pneumonia (odds ratio [OR], 0.34 [95% confidence interval {CI}, .21-.55], P < .001) and ICU admission (OR, 0.49 [95% CI, .26-.90], P = .023). Similarly, early antiviral treatment (within 48 hours) was associated with improved outcomes. In patients with influenza A, pneumonia, ICU admission, and not being immunized were also associated with higher viral loads at presentation (P = .018, P = .008, and P = .024, respectively).

Conclusions: Annual influenza vaccination and early antiviral therapy are associated with a significant reduction in influenza-associated morbidity, and should be emphasized as strategies to improve outcomes of transplant recipients.



Viral loads were significantly higher at presentation in patients who did not receive influenza vaccine in the same season as infection

- Importantly, no specific adverse events due to the influenza vaccine have been reported in patients with CKD.
- Vaccination may be associated with the development of de novo anti-HLA antibodies.
- Typically these are not donor specific and are generally not associated with adverse outcomes

Drug Saf (2017) 40:693–702
DOI 10.1007/s40264-017-0532-3

ORIGINAL RESEARCH ARTICLE

Adjuvanted (AS03) A/H1N1 2009 Pandemic Influenza Vaccines and Solid Organ Transplant Rejection: Systematic Signal Evaluation and Lessons Learnt

Gaël Dos Santos[1,2] · Harry A. Seifert[3] · Vincent Bauchau[4] · Vivek Shinde[4,5] · Dominique M. Barbeau[6] · Catherine Cohet[4]

Published online: 17 April 2017

Key Points

A stepwise multi-disciplinary investigation assessed a safety signal of solid organ transplant (SOT) rejection after immunisation with adjuvanted (AS03) A/H1N1 2009 pandemic vaccines.

Based on the overall findings supporting an acceptable safety profile in transplanted patients, the European Medicines Agency (EMA) closed the regulatory commitment to investigate in 2014, and SOT rejection as a potential risk was removed from the Risk Management Plan of adjuvanted (AS03) A/H1N1 pandemic influenza vaccines.

BMJ Open

Effect of the adjuvanted (AS03) A/H1N1 2009 pandemic influenza vaccine on the risk of rejection in solid organ transplant recipients in England: a self-controlled case series

Catherine Cohet,[1] François Haguinet,[1] Gaël Dos Santos,[2] Dave Webb,[3] John Logie,[3] Germano LC Ferreira,[1] Dominique Rosillon,[1] Vivek Shinde[1]

Participants: Of the 184 transplant recipients having experienced at least one SOT rejection (liver, kidney, lung, heart or pancreas) during the study period from 1 October 2009 to 31 October 2010, 91 participants were included in the main analysis, of which 71 had been exposed to *Pandemrix*.

Main outcome measures: Occurrence of SOT rejection during risk (30 and 60 days after any *Pandemrix* dose) and control periods. Covariates in the CPRD included time since transplantation, seasonal influenza vaccination, bacterial and viral infections, previous SOT rejections and malignancies.

Results: The relative incidence (RI) of rejection of any one of the five transplanted organs, adjusted for time since transplantation, was 1.05 (95% CI 0.52 to 2.14) and 0.80 (95% CI 0.42 to 1.50) within 30 and 60 days after vaccination, respectively. Similar estimates were observed for rejection of a kidney only, the most commonly transplanted organ (RI within 30 days after vaccination: 0.85 (95% CI 0.38 to 1.90)). Across various models and sensitivity analyses, RI estimates remained stable and within a consistent range around 1.0.

Conclusions: These results suggest a reassuring safety profile for *Pandemrix* with regard to the risk of rejection in SOT recipients in England and contribute to inform the benefit–risk of AS03-adjuvanted pandemic influenza vaccines in transplanted patients in the event of future pandemics.

Cohet C, et al. BMJ Open 2016;6:e009264.

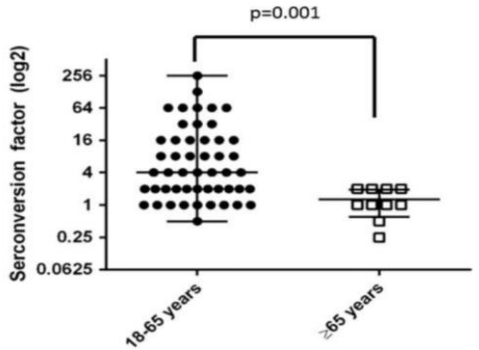
adjuvant vaccinations, higher doses of antigen, or boosters

Randomized Controlled Trial of Adjuvanted Versus Nonadjuvanted Influenza Vaccine in Kidney Transplant Recipients

Deepali Kumar, MD,[1] Patricia Campbell, MBChB,[2] Katja Hoschler, PhD,[3] Luis Hidalgo, PhD,[4] Mona Al-Dabbagh, MD,[1,5] Leticia Wilson, MSc,[6] and Atul Humar, MD[1]

Background. Influenza vaccine containing an oil-in-water emulsion adjuvant (MF-59) may lead to greater immunogenicity in organ transplant recipients. However, alloimmunization may be a concern with adjuvanted vaccines. **Methods.** We conducted a randomized trial comparing the safety and immunogenicity of adjuvanted versus nonadjuvanted influenza vaccine in adult kidney transplant patients. Patients were randomized 1:1 to receive 2012 to 2013 influenza vaccine with or without MF59 adjuvant. Preimmunization and postimmunization sera underwent strain-specific hemagglutination inhibition assay. HLA alloantibody was determined by Luminex single-antigen bead assay. **Results.** We randomized 68 patients and 60 (29 nonadjuvanted; 31 adjuvanted) had complete samples available at follow-up. Seroconversion to at least 1 of 3 influenza antigens was present in 71.0% versus 55.2% in adjuvanted versus nonadjuvanted vaccine respectively (P = 0.21). Geometric mean titers and seroprotection rates were similar between groups. Seroconversion rates were especially low in those on MMF of 2 g or greater daily (44.4% vs 71.4%; P = 0.047). In the subgroup of patients 18 to 64 years old, seroconversion was significantly greater with adjuvanted vaccine (odds ratio, 6.10; 95% confidence interval, 1.25-28.6). There were no increases in HLA alloantibodies in patients who received adjuvanted vaccine. **Conclusions.** Adjuvanted vaccine was safe and had similar immunogenicity to standard vaccine in the overall transplant cohort but did show a potential immunogenicity benefit for the 18 to 64 years age group.

(*Transplantation* 2016;100: 662–669)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

Carlos A. DiazGranados, M.D., Andrew J. Dunning, Ph.D., Murray Kimmel, D.O., Daniel Kirby, B.Sc., John Treanor, M.D., Avi Collins, B.Sc.N., Richard Pollak, D.P.M., Janet Christoff, R.N., John Earl, M.D., Victoria Landolfi, M.Sc., M.B.A., Earl Martin, D.O., Sanjay Gurunathan, M.D., Richard Nathan, D.O., David P. Greenberg, M.D., Nadia G. Tornieporth, M.D., Michael D. Decker, M.D., M.P.H., and H. Keipp Talbot, M.D., M.P.H.

RESULTS

A total of 31,989 participants were enrolled from 126 research centers in the United States and Canada (15,991 were randomly assigned to receive IIV3-HD, and 15,998 to receive IIV3-SD). In the intention-to-treat analysis, 228 participants in the IIV3-HD group (1.4%) and 301 participants in the IIV3-SD group (1.9%) had laboratory-confirmed influenza caused by any viral type or subtype associated with a protocol-defined influenza-like illness (relative efficacy, 24.2%; 95% confidence interval [CI], 9.7 to 36.5). At least one serious adverse event during the safety surveillance period was reported by 1323 (8.3%) of the participants in the IIV3-HD group, as compared with 1442 (9.0%) of the participants in the IIV3-SD group (relative risk, 0.92; 95% CI, 0.85 to 0.99). After vaccination, HAI titers and seroprotection rates (the percentage of participants with HAI titers ≥1:40) were significantly higher in the IIV3-HD group.

CONCLUSIONS

Among persons 65 years of age or older, IIV3-HD induced significantly higher antibody responses and provided better protection against laboratory-confirmed influenza illness than did IIV3-SD. (Funded by Sanofi Pasteur; ClinicalTrials.gov number, NCT01427309.)

N Engl J Med 2014;371:635-45.

Randomized Controlled Trial > Clin Infect Dis. 2018 May 17;66(11):1698-1704.
doi: 10.1093/cid/cix1082.

A Double-Blind, Randomized Trial of High-Dose vs Standard-Dose Influenza Vaccine in Adult Solid-Organ Transplant Recipients

Yoichiro Natori [1], Mika Shiotsuka [1], Jaclyn Slomovic [1], Katja Hoschler [2], Victor Ferreira [1], Peter Ashton [1], Coleman Rotstein [1], Les Lilly [1], Jeffrey Schiff [1], Lianne Singer [1], Atul Humar [1], Deepali Kumar [1]

Abstract

Background: The annual standard-dose (SD) influenza vaccine has suboptimal immunogenicity in solid organ transplant recipients (SOTRs). Influenza vaccine that contains higher doses of antigens may lead to greater immunogenicity in this population.

Methods: We conducted a randomized, double-blind trial to compare the safety and immunogenicity of the 2016-2017 high-dose (HD; FluzoneHD, Sanofi) vs SD (Fluviral, GSK) influenza vaccine in adult SOTRs. Preimmunization and 4-week postimmunization sera underwent strain-specific hemagglutination inhibition assay.

Results: We enrolled 172 patients who received study vaccine, and 161 (84 HD; 77 SD) were eligible for analysis. Seroconversion to at least 1 of 3 vaccine antigens was present in 78.6% vs 55.8% in HD vs SD vaccine groups (P < .001), respectively. Seroconversions to A/ H1N1, A/H3N2, and B strains were 40.5% vs 20.5%, 57.1% vs 32.5%, and 58.3% vs 41.6% in HD vs SD vaccine groups (P = .006, P = .002, P = .028, respectively). Post-immunization geometric mean titers of A/H1N1, A/H3N2, and B strains were significantly higher in the HD group (P = .007, P = .002, P = .033). Independent factors associated with seroconversion to at least 1 vaccine strain were the use of HD vaccine (odds ratio [OR], 3.23; 95% confidence interval [CI], 1.56-6.67) and use of mycophenolate doses <2 g daily (OR, 2.76; 95% CI, 1.12-6.76).

Conclusions: HD vaccine demonstrated significantly better immunogenicity than SD vaccine in adult transplant recipients and may be the preferred influenza vaccine for this population.

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

High-dose influenza vaccine use among patients receiving hemodialysis in the United States, 2010–2013

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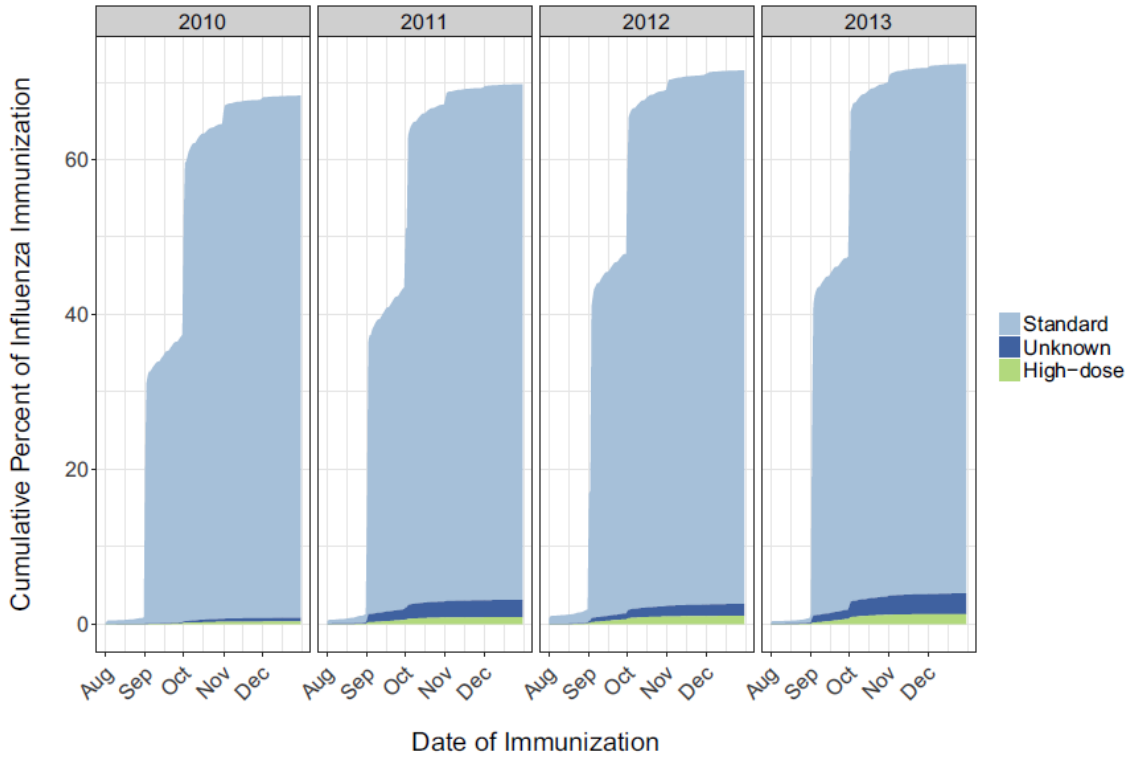
ABSTRACT

Background: Standard influenza vaccines may be of limited benefit to patients with end-stage renal disease (ESRD). These patients may benefit from high-dose influenza vaccine, currently indicated for patients aged ≥65 years. Studies in other populations have demonstrated that high-dose vaccine elicits a stronger immunological response. We compared vaccine uptake in the United States and predictors of receipt for high-dose and standard influenza vaccines.

Methods: Using data from the United States Renal Data System (2010–2013), we conducted a cohort study of 421,482 adult patients on hemodialysis. We examined temporal trends in uptake of high-dose or standard trivalent influenza vaccine each influenza season, and used multivariate logistic regression to assess the association between individual-level variables (e.g., demographics, comorbidities) and facility-level variables (e.g., facility size and type) with vaccine receipt.

Results: The proportion of patients with ESRD who were vaccinated with any influenza vaccine increased from 68.3% in 2010 to 72.4% in 2013. High-dose vaccines were administered to 0.9% of patients during the study period, and 16.7% of high-dose vaccines were administered to patients <65 years of age. Among patients aged ≥65 years, older patients (>79 vs. 65–69 years: OR, 1.29; 95% CI, 1.19–1.41) and patients at hospital-based versus free-standing dialysis facilities (OR, 2.31; 95% CI, 2.13–2.45) were more likely to receive high-dose vaccine, while blacks (vs. whites [OR, 0.66; 95% CI, 0.61–0.71]) and patients with longer duration of ESRD (>9 vs. 0 years: OR, 0.66; 95% CI, 0.55–0.78) were less likely to receive the high-dose vaccine.

Conclusions: While the overall influenza vaccination rate has increased, use of high-dose vaccine among patients with ESRD was very low. Being an older patient, living in the Midwest, and receiving care at hospital-based facilities were the strongest predictors of receiving high-dose vaccine.



Cumulative percent of adult (18 years) patients with end-stage renal disease receiving dialysis immunized with influenza vaccine, by year

- Repeat vaccination, typically 4 to 8 weeks after the initial vaccine, is another approach to improve responses to standard-dose vaccines in transplant recipients and is commonly used in individuals needing vaccination shortly after transplantation
- This approach is associated with a consistent but modest improvement in seroconversion and seroprotective humoral responses (10%-12% increase in seroprotection with the second vaccine).

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Changes of immunogenic profiles between a single dose and one booster influenza vaccination in hemodialysis patients – an 18-week, open-label trial

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Annual influenza vaccination is recommended, but its efficacy in dialysis population is still controversial. Here we aimed to compare the dynamic changes of immune response between various influenza vaccination protocols in hemodialysis patients. A 18-week open label, non-randomized, controlled trial was conducted during 2011–2012. The efficacy between unvaccinated, one- and two-dose regimens were evaluated in 175 hemodialysis patients. Immunogenic profiles were assessed by hemagglutination-inhibition assays. At 3–9 weeks post-vaccination, antibody responses were similar between the one- and two-dose regimens, while the seroprotection rates (antibody titer $\geq$1:40) for influenza A were 55.6–82.5% in the adult (18–60 years) and 33.3–66.7% in the elderly (>60 years). Meanwhile, the seroprotection rates for influenza B were low (4.0–25.0%). By 18 weeks post-vaccination, the seroprotection rates for influenza A and B declined (0.0–33.3%) in both the adult and elderly receiving one- or two-dose regimens. Of dialysis patients, at most 2.4% developed moderate to severe adverse effects(myalgia and headache) after vaccination. In conclusion, the two-dose regimen could not improve immune responses than the one-dose regimen in hemodialysis patients; meanwhile the induced protective antibodies of both regimens could not be maintained for more than 4 months. Modification of current influenza vaccination strategy in dialysis population should be re-considered.

Clinical Infectious Diseases

MAJOR ARTICLE

Two Doses of Inactivated Influenza Vaccine Improve Immune Response in Solid Organ Transplant Recipients: Results of TRANSGRIPE 1–2, a Randomized Controlled Clinical Trial

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Background. Influenza vaccine effectiveness is not optimal in solid organ transplant recipients (SOTR). We hypothesized that a booster dose might increase it.

Methods. TRANSGRIPE 1–2 is a phase 3, randomized, controlled, multicenter, open-label clinical trial. Patients were randomly assigned (1:1 stratified by study site, type of organ, and time since transplantation) to receive 1 dose (control group) or 2 doses (booster group) of the influenza vaccine 5 weeks apart.

Results. A total of 499 SOTR were enrolled. Although seroconversion at 10 weeks did not meet significance in the modified intention-to-treat population, seroconversion rates were significantly higher in the booster arm for the per-protocol population (53.8% vs 37.6% for influenza A(H1N1)pdm; 48.1% vs 32.3% for influenza A(H3N2); and 90.7% vs 75% for influenza B; $P < .05$). Furthermore, seroprotection at 10 weeks was higher in the booster group: 54% vs 43.2% for A(H1N1)pdm; 56.9% vs 45.5% for A(H3N2); and 83.4% vs 71.8% for influenza B ($P < .05$). The number needed to treat to seroprotect 1 patient was <10. The clinical efficacy (99.2% vs 98.8%) and serious adverse events (6.4% vs 7.5%) were similar for both groups.

Conclusions. In SOTR, a booster strategy 5 weeks after standard influenza vaccination is safe and effective and induces an increased antibody response compared with standard influenza vaccination consisting of a single dose.

Clinical Trials Registration. EudraCT (2011-003243-21).

Keywords. influenza vaccine; immune response; solid organ transplantation; booster dose.

Where possible, the use of either a booster strategy or high-dose IIV may provide greater immunogenicity benefit over a single standard-dose IIV in this highly immunosuppressed population

Pneumococcal vaccine

23-valent polysaccharide vaccine (PPSV23)	• T-cell independent response
13-valent protein-conjugated vaccine (PCV13)	• induce a T-cell dependent response and may produce antibodies of higher avidity and also lead to formation of memory B cells

- Pneumonia is the second most common infection in the ESKD population after bloodstream infections and is associated with increased mortality and overall poor long term prognosis.
- Streptococcus pneumoniae remains the most common bacterial pathogen isolated
- Recent data suggest the incidence of IPD in the SOT population is up to 45-fold that of the general population with higher case fatality rates

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Blackwell Munksgaard

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Invasive Pneumococcal Disease in Solid Organ Transplant Recipients—10-Year Prospective Population Surveillance

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Received 26 September 2006, revised 21 November 2006 and accepted for publication 4 December 2006

In this study, in which 52.4% of patients with IPD were KTRs, it was found that 85% of infections were attributable to a pneumococcal serotype included in the 23-valent pneumococcal polysaccharide vaccine (PPSV-23). The data revealed that only 23.8% of SOT recipients who developed IPD had been vaccinated with PPSV-23 in the last 5 years.

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Invasive Pneumococcal Disease Among Immunocompromised Persons: Implications for Vaccination Programs

Altynay Shigayeva [1], Wallis Rudnick [2], Karen Green [1], Danny K Chen [3], Walter Demczuk [4], Wayne L Gold [5], Jennie Johnstone [6], Ian Kitai [7], Sigmund Krajden [8], Reena Lovinsky [9], Matthew Muller [10], Jeff Powis [11], Neil Rau [12], Sharon Walmsley [5], Gregory Tyrrell [13], Ari Bitnun [14], Allison McGeer [2], Toronto Invasive Bacterial Diseases Network

Abstract

Background: In 2012/2013, a single dose of 13-valent pneumococcal conjugate vaccine (PCV13) was recommended for immunocompromised adults in the United States and Canada. To assess the potential benefits of this recommendation, we assessed the serotype-specific burden of invasive pneumococcal disease (IPD) among immunocompromised individuals.

Methods: From 1995 to 2012, population-based surveillance for IPD was conducted in Metropolitan Toronto and Peel Region, Canada. Disease incidence and case fatality were measured in immunocompromised populations over time, and the contribution of different serotypes determined.

Results: Overall, 2115/7604 (28%) episodes of IPD occurred in immunocompromised persons. IPD incidence was 12-fold higher (95% confidence interval [CI], 8.7-15) in immunocompromised compared to immunocompetent persons; the case fatality rate was elevated in both younger (odds ratio [OR] 1.8) and older (OR 1.3) adults. Use of immunosuppressive medications was associated with a 2.1-2.7 fold increase in the risk of IPD. Five years after PPV23 program implementation, IPD incidence had declined significantly in immunocompromised adults (IRR 0.57, 95% CI, .40-.82). Ten years after pediatric PCV7 authorization, IPD due to PCV7 serotypes had decreased by 90% (95% CI, 77%-96%) in immunocompromised persons of all ages. In 2011/2012, 37% of isolates causing IPD in immunocompromised persons were PCV13 serotypes and 27% were PPV23/not PCV13 serotypes.

Conclusions: Immunocompromised individuals comprised 28% of IPD. Both PPV23 and herd immunity from pediatric PCV7 were associated with reductions in IPD in immunocompromised populations. PCV13 vaccination of immunocompromised adults may substantially reduce the residual burden until herd immunity from pediatric PCV13 is fully established.

Randomized, Double-Blind, Controlled Trial of Pneumococcal Vaccination in Renal Transplant Recipients

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Renal transplant recipients are at increased risk for developing invasive pneumococcal disease but may have a poor response to pneumococcal polysaccharide vaccine (PPV23). For them, pneumococcal conjugate vaccine (PCV7) may be more immunogenic. Patients were given a single dose of PPV23 or PCV7 in our randomized, controlled, double-blind trial. Immunogenicity was assessed 8 weeks after vaccination by serotype-specific enzyme-linked immunosorbent assay (ELISA) and opsonophagocytic assay (OPA). Baseline demographics, renal function, time since transplantation, and immunosuppression were comparable. In the PCV7 group, the vaccine response rate was improved for serotypes 23F ($P = .046$) and 6B ($P = .067$), and mean fold increases in antibody titer were higher for serotypes 23F ($P = .046$) and 9V ($P = .09$). The response rate and mean fold increase in OPA titers were not significantly different between groups. There was a trend toward enhanced immunogenicity for PCV7 by ELISA. However, functional antibody responses were not different.

Dosing Schedule for Pneumococcal Immunizations in Adult Patients With Kidney Disease

Table 3. Dosing Schedule for Pneumococcal Immunizations in Adult Patients With Kidney Disease

Initial Vaccine	Subsequent Vaccination Needs
PCV13	8+ wk later give PPSV23, then 5 y later give a second dose of PPSV23
PPSV23[a]	1 y later give PCV13 and 5 y after initial PPSV23 vaccine give second dose of PPSV23
Either	All patients should get an additional PPSV23 vaccine at age 65 y if initial vaccine series started before age 65

Note: Based on information in Kim et al.[9] PCV13 is the preferred initial vaccine. Subsequent PPSV23 vaccines should be given a minimum of 5 years after the prior dose.
Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal capsular polysaccharide vaccine.
[a]Either previously vaccinated with PPSV23 or first dose given is PPSV23.

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Immunogenicity of 13-Valent Conjugate Pneumococcal Vaccine in Patients 50 Years and Older with End-Stage Renal Disease and on Dialysis

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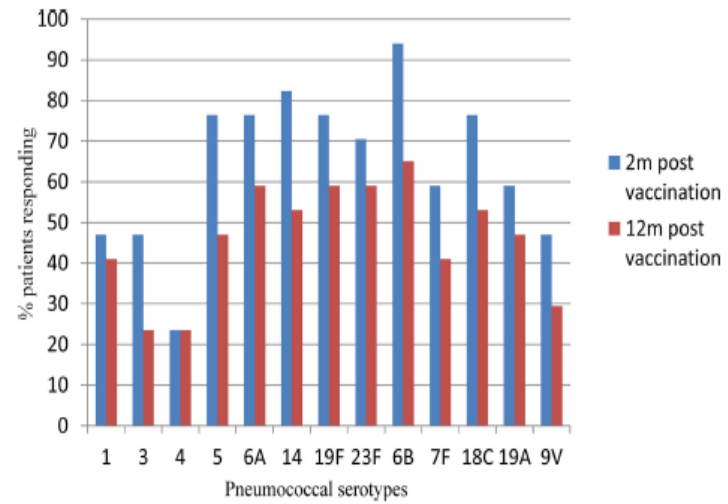
Patients with end-stage renal disease (ESRD) and on dialysis are at increased risk of pneumococcal disease. We evaluated the immunogenicity of the 13-valent pneumococcal conjugate vaccine (PCV13) in this population. Eligible patients with ESRD and on dialysis were given a single dose of PCV13. The concentrations of serum antibodies against 13 pneumococcal capsular polysaccharides were measured at the baseline and at 2 and 12 months postvaccination. A response to the vaccine was defined as a ≥2-fold increase in antibody concentration from that at the baseline and an absolute postvaccination value of at least 1 μg/ml. Seventeen patients completed the study. Increases in the concentrations of antibodies to the vaccine serotype were demonstrated 2 months after vaccination. The geometric mean antibody concentrations at 12 months postvaccination declined by 38% to 72% compared to those measured at 2 months postvaccination. A response to at least 1 serotype in the vaccine was seen in all patients at both 2 and 12 months postvaccination. The overall rate of the response to each individual vaccine serotype varied between 23.5% and 94.1% at 2 months postvaccination and 23.5% and 65% at 12 months postvaccination. Pain at the injection site was the most common local reaction. Vaccination with PCV13 induces antibody responses to vaccine serotypes in patients with ESRD and on dialysis at 2 months postvaccination. However, the decline in antibody concentrations at 12 months postvaccination with a conjugate pneumococcal vaccine requires further study. (This study has been registered at ClinicalTrials.gov under registration no. NCT01974817.)



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Original article

Immunogenicity and safety of the 13-valent Pneumococcal Conjugate vaccine in 23-valent pneumococcal polysaccharide vaccine-naive and pre-immunized patients under treatment with chronic haemodialysis: a longitudinal quasi-experimental phase IV study

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ABSTRACT

Objective: To benchmark the immunogenicity of pneumococcal conjugated vaccine (PCV-13) versus pneumococcal polysaccharide vaccine (PPV-23) in haemodialysis patients pre-vaccinated or not with PPV-23.
Methods: The study is a longitudinal quasi-experimental phase IV study in chronic haemodialysis patients aged ≥50 years. Total (ELISA) and functional (opsonophagocytic assay) antibodies after pneumococcal vaccination were quantified at baseline, and after 28 and 365 days. Of 201 eligible patients, 155 were included. Patients were divided in four groups. PPV-23 naive patients were randomized to PPV-23 (40) or PCV-13 (40) vaccination. PPV-23-pre-vaccinated patients were categorized as being vaccinated more (40) or less (35) than 4 years before the study and all received PCV-13.
Results: Patients among the four groups had a significant ELISA antibody response for most serotypes that remained significant up to day 365 versus baseline. In PPV-23-naive patients, ELISA antibody titres were significantly higher among PCV-13 versus PPV-23 recipients for six serotypes (1.85–2.34-fold) after 28 days, and remained significantly higher for one serotype (6A, 1.57-fold) after 365 days. Following PCV-13 vaccination, increase in ELISA antibody titres was significantly higher among PPV-23-naive versus PPV-23-pre-vaccinated patients for 12 serotypes after 28 days (1.68–7.74-fold) and remained significantly higher in ten serotypes (1.44–3.29-fold) after 365 days.
Conclusion: Immune response after PPV-23 and PCV-13 remains significant for at least 1 year in non-PPV-23-pre-vaccinated patients. Among vaccine-naive haemodialysis patients PCV-13 seems more immunogenic than PPV-23. Immune response to PCV-13 is weaker in PPV-23-pre-vaccinated compared with vaccine-naive patients. **S.J. Vandecasteele, Clin Microbiol Infect 2018;24:65**

Transpl Infect Dis. 2018 Apr;20(2):e12866. doi: 10.1111/tid.12866. Epub 2018 Apr 1.

Seroresponses and safety of 13-valent pneumococcal conjugate vaccination in kidney transplant recipients

Claire Dendle [1], Rhonda L Stuart [1], Kevan R Polkinghorne [2 3 4], Anne Balloch [5], John Kanellis [2 3], Johnathan Ling [3], Megan Kummrow [6], Chelsea Moore [6], Karin Thursky [7 8], Jim Buttery [4 9], Kim Mulholland [5], Poh-Yi Gan [2], Stephen Holdsworth [2 3], William R Mulley [2 3]

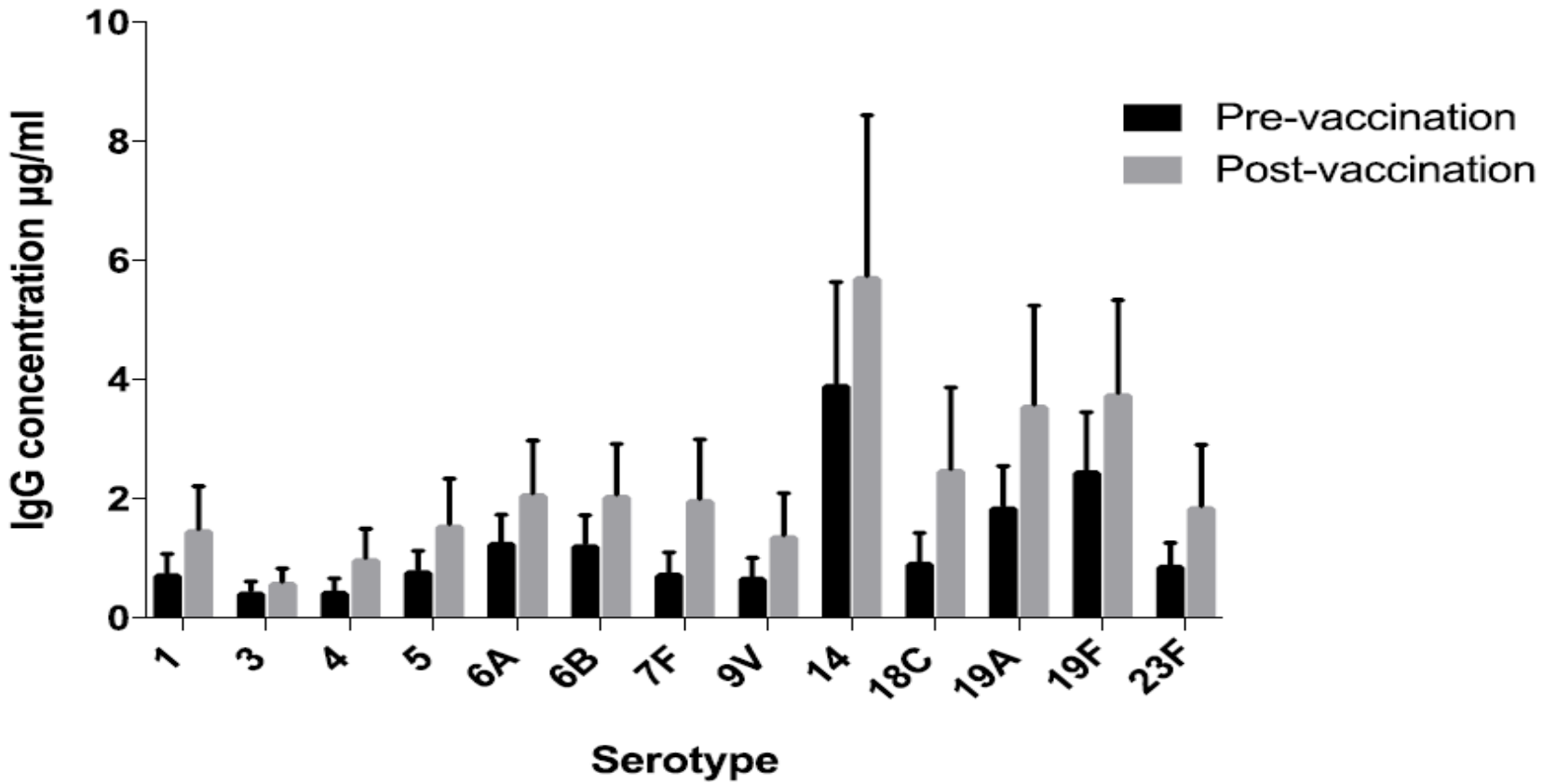
Abstract

Background: Conjugated pneumococcal vaccine is recommended for kidney transplant recipients, however, their immunogenicity and potential to trigger allograft rejection though generation of de novo anti-human leukocyte antigen antibodies has not been well studied.

Methods: Clinically stable kidney transplant recipients participated in a prospective cohort study and received a single dose of 13-valent conjugate pneumococcal vaccine. Anti-pneumococcal IgG was measured for the 13 vaccine serotypes pre and post vaccination and functional anti-pneumococcal IgG for 4 serotypes post vaccination. Anti-human leukocyte antigen antibodies antibodies were measured before and after vaccination. Kidney transplant recipients were followed clinically for 12 months for episodes of allograft rejection or invasive pneumococcal disease.

Results: Forty-five kidney transplant recipients participated. Median days between pre and post vaccination serology was 27 (range 21-59). Post vaccination, there was a median 1.1 to 1.7-fold increase in anti-pneumococcal IgG antibody concentrations for all 13 serotypes. Kidney transplant recipients displayed a functional antibody titer ≥1:8 for a median of 3 of the 4 serotypes. Post vaccination, there were no de novo anti-human leukocyte antigen antibodies, no episodes of biopsy proven rejection or invasive pneumococcal disease.

Conclusion: A single dose of 13-valent conjugate pneumococcal vaccine elicits increased titers and breadth of functional anti-pneumococcal antibodies in kidney transplant recipients without stimulating rejection or donor-specific antibodies.



Pneumococcal antibody concentrations in 45 kidneys transplant recipients pre- and four weeks post-vaccination with 13-valent conjugate pneumococcal vaccine. Median and interquartile range are given separately for 13 serotypes of capsular polysaccharides. All 13 pre and post pairs $p>0.001$.

Immunization Recommendations for Adult Patients with Kidney Disease

	Non–KRT-Dependent CKD	Maintenance Dialysis	Kidney Transplant Recipients	Safe in Contacts of Kidney Transplant Recipients
Cholera	Usual recommendation	Usual recommendation	Contraindicated[a]	Precaution[a]
Hepatitis A	Usual recommendation	Usual recommendation	Usual recommendation	Yes
Hepatitis B[b]	Recommended[c]	Recommended	Usual recommendation	Yes
Hib	Usual recommendation	Usual recommendation	Usual recommendation	Yes
HPV[d]	Usual recommendation	Usual recommendation	Usual recommendation	Yes
JEV	Usual recommendation	Usual recommendation	Usual recommendation	Yes
Influenza				
IIV/RIV	Recommended	Recommended	Recommended	Yes
High dose	Recommended ≥65 y	Recommended ≥65 y	Recommended ≥65 y	Yes
LAIV	Precaution	Precaution	Contraindicated	Yes[e]
Meningococcal	Usual recommendation	Usual recommendation	Usual recommendation	Yes
MMR	Usual recommendation	Usual recommendation	Contraindicated	Yes
Pneumococcal[f]	Recommended	Recommended	Recommended	Yes
Rabies	Usual recommendation	Usual recommendation	Usual recommendation	Yes
Tdap/Td[g]	Usual recommendation	Usual recommendation	Usual recommendation	Yes
Typhoid	Usual recommendation	Usual recommendation	Usual recommendation[h]	Yes[h]
Yellow fever	Usual recommendation	Usual recommendation	Contraindicated	Yes
VZV				
RZV	Usual recommendation	Usual recommendation	Usual recommendation[i]	Yes
LZV	Usual recommendation	Usual recommendation	Contraindicated	Yes[j]
Varicella	Usual recommendation	Usual recommendation	Contraindicated	Yes[j]

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