Dự phòng toàn diện trên đối tượng bệnh thận mạn tính - giá trị của vắc xin phế cầu cộng hợp

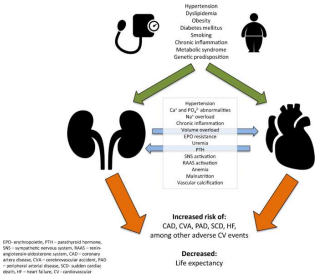
PGS.TS.BS Phạm Văn Bùi

Content

Impact of CKD on multi-organ dysfunction and increased risk of infections

CKD triggers **systemic inflammation**, **endothelial dysfunction**, and **metabolic disturbances**, impacting the kidneys and cardiovascular system, amongst others

Shared risk factors and mechanisms result in **complex interplay that affects the immune function**, amplifying susceptibility to infection and **fostering a spectrum of dysfunctions at an early stage due to prevalent comorbidities**, such as atherosclerosis and vascular calcification



EPO- erythropoietin, PTH – parathyroid hormone, SNS – sympathetic nervous system, RAAS – renin-angiotensin-aldosterone system, CAD – coronary artery disease, CVA – cerebrovascular accident, PAD – peripheral arterial disease, SCD– sudden cardiac death, HF – heart failure, CV - cardiovascular

- CKD, chronic kidney disease.
- Laffin LJ, et al. *Curr Cardiol Reports* 2021; 23(117).

Understanding immune dysfunction in CKD

CKD predisposes patients to an elevated risk of infections due to compromised immune function driven by factors such as PBURS accumulation, altered intestinal microbiota, and metabolic dysregulation[1]

CKD results in a **decrease in** innate and adaptive immune responses[2]

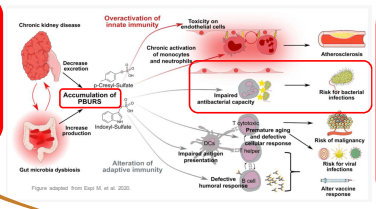


Figure adapted from Espi M, et al. 2020.

Disturbances of innate immunity result in **inadequate monocyte and neutrophil function** and **persistent low-grade inflammation**[2]

•CKD, chronic kidney disease; PBURS, protein-bound uremic retention solutes.

•1.Espi M, et al. *Toxins* 2020;12(5):300; 2. Vandecasteele SJ, et al. *Clin Kidney J* 2015;8(3):318–24.

Many vaccinations, including pneumococcal vaccination, are recommended for adults with CKD[1]

	Chronic kidney disease (pre-dialysis)	Maintenance dialysis	Kidney transplant recipient
Cholera	Usual[a]	Usual	Contraindicated
Hepatitis A	Usual	Usual	Usual
Hepatitis B	Recommended[b]	Recommended	Usual
Hib	Usual	Usual	Usual
HPV	Usual	Usual	Usual
JEV	Usual	Usual	Usual
Influenza	Recommended	Recommended	Recommended/Contraindicated[c]
Meningococcal	Usual	Usual	Usual
MMR	Usual	Usual	Contraindicated
Pneumococcal	Recommended	Recommended	Recommended
Rabies	Usual	Usual	Usual
Tdap	Usual	Usual	Usual
Typhoid fever	Usual	Usual	Usual
Yellow fever	Usual	Usual	Contraindicated
VZV	Usual	Usual	Recommended/ Contraindicated[c]

Adapted from KDIGO CKD guideline[2], Kim et al[3] and Janus et al[4].
[a]The recommendation is the same as that for the general population. [b]Details elaborated in text and Table 2. [c]Live-attenuated vaccine formulation is contraindicated in kidney transplant recipients.

In >1,300 adult at-risk patients in Belgium, coverage rates were relatively **low** for **all recommended vaccines**[*,5]

23% (32/138) of patients with CKD received pneumococcal vaccination (95% CI, 16.6–31.3)

[*]Monocentric cross-sectional survey of 1,331 adult at-risk patients at the university hospitals of Leuven, the largest tertiary hospital in Belgium.
CKD, chronic kidney disease; Hib, haemophilus influenzae; HPV, human papilloma virus; JEV, Japanese Encephalitis Virus; MMR, measles, mumps, rubella; Tdap, tetanus, diphtheria, acellular pertussis; VZV, varicella-zoster virus.
1. Ma BM, et al. *Nephrology (Carlton)* 2021;26(1):5–11. 2. Kidney Disease: Improving global outcomes (KDIGO) CKD workgroup. *Kidney Int Suppl* 2013;1:1–150. 3. Kim DK, et al. *Ann Intern Med* 2019;170(3):182–92.
4. Janus N, et al. *Nephrol Dial Transplant* 2007;22(3):803–7. 5. Bovy L, et al. *Hum Vaccin Immunother* 2020;16(9):2159–63.

Content

1. Impact of CKD and risk of infections
2. **Clinical stages of CKD, including changes in immune status and risk of infection**
3. Risk and burden of pneumococcal infection by clinical stage of CKD
4. Vaccination recommendations for patients with CKD
5. Differences between pneumococcal vaccines

Stages of CKD according to KDIGO 2024

Albuminuria and GFR grid reflects the risk of progression by intensity of coloring (green, yellow, orange, red, and deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Reproduced from de Boer IH, et al. *Kidney Int* 2022;102:974–989.

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat 3	Treat 3
	G4	Severely decreased	15–29	Treat* 3	Treat* 3	Treat 4+
	G5	Kidney failure	<15	Treat 4+	Treat 4+	Treat 4+

Low risk (if no other markers of kidney disease, no CKD) · Moderately increased risk · High risk · Very high risk

CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.
KDIGO CKD Work Group. *Kidney Int* 2024;105(4S):S117-S314.

Among **patients aged ≤50 years old, those with CKD stage 3 had significantly higher risks of infection-related hospitalization and mortality** compared with stage 1 patients

An Asian prospective cohort study of 119,871 patients with CKD stages 1–3

Crude HR for infection-related hospitalization

- **1.61x** higher in **stage 2 patients** compared with stage 1 patients (HR, 1.61; 95% CI, 1.54–1.67)
- **4.84x** higher in **stage 3 patients** compared with stage 1 patients (HR, 4.84; 95% CI, 4.58–5.11)

Adjusted HR for infection-related hospitalization

- **2.58x** higher in **younger* stage 3 patients** compared with stage 1 patients (HR, 2.58; 95% CI, 1.84–3.61)

Adjusted HR for infection-related mortality

- **1.39x** higher in **younger* stage 2 patients** compared with stage 1 patients (HR, 1.39; 95% CI, 0.94–2.06)
- **2.03x** higher in **younger* stage 3 patients** compared with stage 1 patients (HR, 2.03; 95% CI, 1.82–3.12)

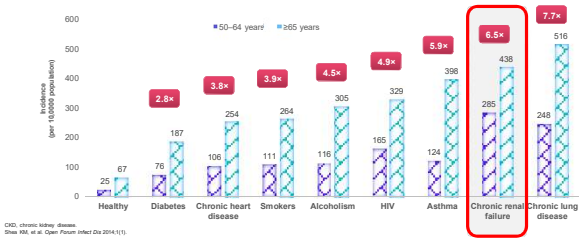
*Younger patients are those aged <50 years old.
Patients were from the New Taipei City Community Health Screening Program between 2005 and 2008. Median follow-up of 8.14 years
CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; HR, hazard ratio
Yang WS, et al. *Sci Rep* 2020;10(1):4475.

Content

1. Impact of CKD and risk of infections
2. Clinical stages of CKD, including changes in immune status and risk of infection
3. **Risk and burden of pneumococcal infection by clinical stage of CKD**
4. Vaccination recommendations for patients with CKD
5. Differences between pneumococcal vaccines

Older patients with CKD are at an up to 6.5× times higher risk of pneumococcal pneumonia than healthy individuals

Rates of pneumococcal pneumonia among healthy, at-risk, and high-risk adults



CKD, chronic kidney disease.
Shea KM, et al. *Open Forum Infect Dis* 2014;1(1).

Association of infection with patient outcomes

In a study involving 20,566 patients with advanced CKD, pulmonary infection emerged as the second most common type of infection[1]

Incidence of infections

- Urinary tract infection (41.9%)
- **Pulmonary infection (41.5%)**
- Septicaemia (23.5%)

Two studies suggested a notable prevalence of *Streptococcus pneumoniae* in patients with CKD and pneumonia[2,3]

Cross-sectional study in a tertiary care centre nephrology department in Nepal[2]:

n=407 patients with CKD

19.1% (78/407) of patients had **pneumonia**

Streptococcus pneumoniae was identified as one of the most commonly isolated organisms, accounting for **8 (10.2%) cases of pneumonia among patients with CKD**[2]

In a single-centre study in India[3]:

32.6% (15/46) of patients had **streptococcal infections progressing to kidney diseases**[3]

CKD, chronic kidney disease.
1. Cheng CH, et al. *Sci Rep* 2020;10:2938; 2. Pant A, et al. *Journal of the Nepal Medical Assoc* 2021;59(242):1000–3; 3. Vincent S. & Jaryal A. *Kidney Int Rep* 2022;7(9), 5482–3.

Improved clinical outcomes in patients with CKD after **Pneumococcal Vaccination**

Reduced mortality

Retrospective cohort studies have reported **mortality reductions ranging from 6% to 16% among vaccinated patients with CKD**[1]

Protection against pneumococcal infection

Studies confirm that pneumococcal vaccination (both PCV13 and PPSV23) **increases antibody levels** in patients with CKD, including dialysis patients [2,3]

This indicates that vaccines potentially offer **protection against pneumococcal infections**

Recommendations by health organisations

Major health organisations such as the CDC and the ACIP **strongly recommend pneumococcal vaccination for all adults with CKD and dialysis patients**[3]

ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; CKD, chronic kidney disease; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine.
1. Vandecasteele SJ, et al. *Clin Kidney J* 2015;8(3):318–24; 2. Costo FG, et al. *Kidney Int* 1981; 20(2), 254–8. 3. Ma BM, et al. *Nephrology (Carlton)* 2021;26(1):5–11.

Content

1. Impact of CKD and risk of infections
2. Clinical stages of CKD, including changes in immune status and risk of infection
3. Risk and burden of pneumococcal infection by clinical stage of CKD
4. **Vaccination recommendations for patients with CKD**
5. Differences between pneumococcal vaccines

US CDC guidelines for vaccination in patients with CKD

List of Vaccines and their use for Dialysis or CKD Patients

Vaccine	Recommended for Dialysis or CKD Patients	Recommended for All Adults	May Use if Otherwise Indicated*	Contraindicated
Anthrax			X	
DTaP/TdapTd		X	X	
Hib			X	
Hepatitis A			X	
Hepatitis B	X			
Human papillomavirus			X	
Influenza (TIV)		X		
Influenza (LAIV)				X
Japanese Encephalitis			X	
MMR		X	X	
Meningococcal			X	
Pneumococcal	X			
Polio (IPV)			X	
Rabies			X	
Rotavirus			X	
Smallpox			X	
Typhoid			X	
Varicella		X	X	
Yellow Fever			X	
Zoster			X	

- Recommendations generated by the ACIP.
- *No specific ACIP recommendation for this vaccine exists for dialysis patients or patients with chronic kidney disease.
- ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; CKD, chronic kidney disease; DTaP/Tdap, tetanus, diphtheria, acellular pertussis; Hib, haemophilus influenzae; IPV, inactivated polio vaccine; LAIV, live attenuated influenza vaccine; MMR, measles mumps rubella; TIV, trivalent inactivated influenza vaccine.

"As secondary antibody responses are less affected by immune compromise than primary antibody responses, **immunisation strategies should be formulated early in the course of progressive renal disease** to maximise likelihood of vaccine-induced immunity"

Vaccination recommendations for adults with CKD[1]

	Chronic kidney disease (pre-dialysis)	Maintenance dialysis	Kidney transplant recipient
Cholera	Usual[a]	Usual	Contraindicated
Hepatitis A	Usual	Usual	Usual
Hepatitis B	Recommended[b]	Recommended	Usual
Hib	Usual	Usual	Usual
HPV	Usual	Usual	Usual
JEV	Usual	Usual	Usual
Influenza	Recommended	Recommended	Recommended/Contraindicated[c]
Meningococcal	Usual	Usual	Usual
MMR	Usual	Usual	Contraindicated
Pneumococcal	Recommended	Recommended	Recommended
Rabies	Usual	Usual	Usual
Tdap	Usual	Usual	Usual
Typhoid fever	Usual	Usual	Usual
Yellow fever	Usual	Usual	Contraindicated
VZV	Usual	Usual	Recommended/ Contraindicated[d]

Adapted from KDIGO CKD guidelines[2], Kim et al[3] and Jarus et al[4].
[a]The recommendation is the same as that for the general population. [b]Details elaborated in text and Table 2. [c]Live-attenuated vaccine formulation is contraindicated in kidney transplant recipients.

CKD, chronic kidney disease; Hib, haemophilus influenzae; HPV, human papilloma virus; JEV, Japanese Encephalitis Virus; MMR, measles, mumps, rubella; Tdap, tetanus, diphtheria, acellular pertussis; VZV, varicella-zoster virus.
1. Ma BM, et al. *Nephrology (Carlton)* 2021;26(1):5-11. 2. Kidney Disease. Improving global outcomes (KDIGO). CKD workgroup. *Kidney Int Suppl* 2013;1:1-150. 3. Kim DK, et al. *Ann Intern Med* 2019;170(3):182-92.
4. Jarus N, et al. *Nephrol Dial Transplant* 2007;23(3):800-7.

Pneumococcal vaccine in CKD patients ?

1. **Older patients with CKD are at an up to 6.5× times higher risk** of pneumococcal pneumonia than otherwise healthy individuals[1]
2. Among etiology-confirmed **bacterial pneumonia in dialysis patients, more than 50% is reported to be due to *Streptococcus pneumoniae*[2]**
3. In a study involving 20,566 patients with **"advanced CKD", 41.5% had history of pulmonary infection,** which emerged as the second most common type of infection after UTI[3]
4. Studies suggest that there is a 14- to 16-fold greater pneumonia-related mortality rate in CKD as compared to the general population[4]

CKD, chronic kidney disease; UTI, urinary tract infection.
1. Shea KM, et al. *Open Forum Infect Dis* 2014;1(1):ofu024. 2. Inara H, et al. *J Clin Exp Nephrol* 2020; 4(3):77. 3. Chang CH, et al. *Sci Rep* 2020;10(1):2308. 4. Pant A, et al. *JIMA J Nepal Med Assoc* 2021;59(242):1000–3.

Pneumococcal vaccine in CKD patients ?

1 Patients with CKD are at an up to 6.5× times higher risk of pneumococcal pneumonia than otherwise healthy individuals[1]

2 Among etiology-confirmed bacterial pneumonia in dialysis patients, more than 50% is reported to be due to *streptococcus pneumoniae*[2]

3 In a study involving 20,566 patients with "advanced CKD", 41.5% had history of pulmonary infection, which emerged as the second most common type of infection after UTI[3]

4 Studies suggest that there is a **14- to 16-fold greater pneumonia-related mortality rate in CKD** as compared to the general population[4]

CKD, chronic kidney disease.
1. Shea KM, et al. *Open Forum Infect Dis* 2014;1(1)ofu024; 2 Ihara H, et al. *J Clin Exp Nephrol* 2020; 4(3):77; 3. Chang CH, et al. *Sci Rep* 2020;10(1):2938; 4. Pant A, et al. *JNMA J Nepal Med Assoc* 2021;59(242):1000–3.

Pneumococcal vaccine in CKD patients ?

5 **PCV13 vaccination in individuals with Stage 3 CKD** (reduced eGFR; 30-59 mL/min/1.73m²) was **associated with a reduced risk of *S. pneumoniae* hospitalization**[1]

6 Studies have suggested that there could be a **benefit to immunization before the onset of dialysis or transplantation** because patients with early stage CKD generally have higher rates of seroconversion[2]

7 **Immunisation strategies should be formulated early in the course of progressive renal disease to maximise likelihood of vaccine-induced immunity**[3]

8 Pneumococcal vaccination is recommended for CKD patients by both CDC and KDIGO[3–5]

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PCV, pneumococcal conjugate vaccine.
1. Le D, et al. *Clin Kidney J* 2024;17(6):sfae145; 2. Krueger KM, et al. *Am J Kidney Dis* 2020;75(3):417-25; 3. Chi C, et al. Guidelines for vaccinating dialysis patients and patients with chronic kidney disease; summarized from recommendations of the ACIP (2012). Available from: https://stacks.cdc.gov/view/cdc/13599 [Accessed July 2024]; 4. Kidney Disease. Improving global outcomes (KDIGO) CKD workgroup. *Kidney Int Suppl* 2013;1:1-150;
5. Ma BM, et al. *Nephrology* (Carlton) 2021;26(1):5-11

Pneumococcal vaccine in CKD patients

5 PCV13 vaccination in individuals with Stage 3 CKD (reduced eGFR; 30 – 59 mL/min/1.73m²) was associated with a reduced risk of *S. pneumoniae* hospitalization[1]

6 Studies have suggested that there could be a benefit to immunization before the onset of dialysis or transplantation because patients with early stage CKD generally have higher rates of seroconversion[2]

7 Immunisation strategies should be formulated early in the course of progressive renal disease to maximise likelihood of vaccine-induced immunity[3]

8 **Pneumococcal vaccination is recommended for CKD patients by both CDC and KDIGO[3–5]**

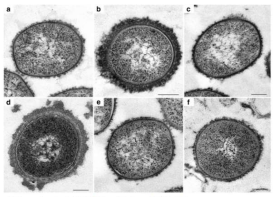
CDC, Centers for Disease Control and Prevention; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PCV, pneumococcal conjugate vaccine; KDIGO, Kidney Disease: Improving global outcomes.
1. Le D, et al. *Clin Kidney J* 2024;17(6):sfae145; 2. Krueger KM, et al. *Am J Kidney Dis* 2020;75(3):417-25; 3. Chi C, et al. Guidelines for vaccinating dialysis patients and patients with chronic kidney disease; summarized from recommendations of the ACIP (2012). Available from: https://stacks.cdc.gov/view/cdc/13599 [Accessed July 2024]; 4. Kidney Disease. Improving global outcomes (KDIGO) CKD workgroup. *Kidney Int Suppl* 2013;1:1-150;
5. Ma BM, et al. *Nephrology* (Carlton) 2021;26(1):5-11

Content

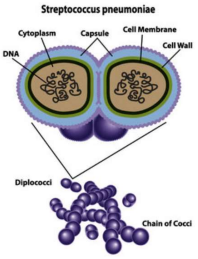
1. Impact of CKD and risk of infections
2. Clinical stages of CKD, including changes in immune status and risk of infection
3. Risk and burden of pneumococcal infection by clinical stage of CKD
4. Vaccination recommendations for patients with CKD
5. **Differences between pneumococcal vaccines**

PHẾ CẦU VÀ VẮC-XIN PHẾ CẦU

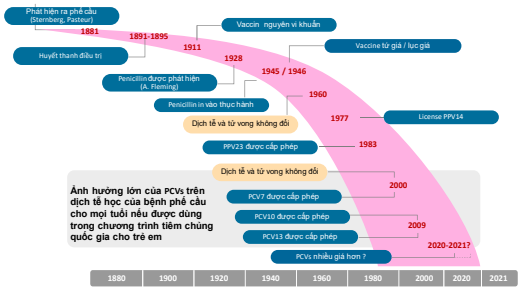
Liên cầu khuẩn gram dương
Có lớp nang (capsule) là polysaccharide, giúp phế cầu trốn được hệ MD, từ đó xâm lấn dễ dàng hơn



Ndlangsia, et al. BMC Microbiology 2016; 126



Lịch sử vaccin phế cầu



Durando et al. PCVs for prevention in children and adults
Clinical Microbiology and Infection, Volume 19 Supplement 1, October 2013

Vắc xin liên hợp đạt được phản ứng miễn dịch mạnh mẽ hơn so với vắc xin polysaccharide bằng cách kích hoạt tế bào B, tế bào T và tế bào B nhớ

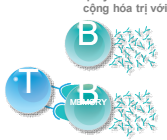
Vắc xin Polysaccharide [1,2]

Kháng nguyên Polysaccharide[2]

- **Kích hoạt tế bào B** và sản xuất kháng thể[3]
- Phản ứng miễn dịch ngắn hạn **không phụ thuộc tế bào T**, hoặc sự tăng ngắn hạn của kháng thể trong huyết thanh sau tiêm chủng, hoặc không tạo ra trí nhớ miễn dịch[2,4]
- **Có thể làm cạn kiệt tế bào B nhớ**[4]

Vắc xin liên hợp [1-3]

Các kháng nguyên polysaccharide được liên kết cộng hóa trị với protein mang[2]



- **Kích hoạt tế bào B** và sản xuất kháng thể[3]
- Phản ứng miễn dịch **phụ thuộc tế bào T** với hiệu ứng tăng cường khi tiêm nhắc lại[2–4]
- **Kích hoạt tế bào B nhớ**[2–4]

1. de Roux A, et al. *Clin Infect Dis* 2008;46:1015–1023; 2 Clutterbuck EA, et al. *Immunology* 2008;119:328–337; 3. Pollard AJ, et al. *Nat Rev Immunol* 2009;9:213–220; 4. Clutterbuck EA, et al. *J Infect Dis* 2012;205:1408–1416.

Tìm hiểu các điểm khác biệt của các vắc xin phế cầu khuẩn

	PCV13	PPSV23
Loại vắc xin	Polysaccharid vỏ, mỗi huyết thanh được liên kết riêng lẻ với một protein mang	Các kháng nguyên polysaccharid vỏ không liên kết
Kháng nguyên	13 serotypes thông thường	23 serotypes thông thường
Đáp ứng miễn dịch	Phụ thuộc tế bào T (thời gian hiệu lực lâu hơn và có hiệu ứng tăng cường khi tiêm nhắc lại).	Không phụ thuộc tế bào T (kháng thể IgM được sản xuất, phản ứng suy giảm trong 3–5 năm, không có phản ứng ghi nhớ khi tiêm nhắc lại).
Hiệu quả	• Hiệu quả tiềm năng giúp giảm mang vi khuẩn qua đường mũi • Giảm tác động của việc tiêm chủng trong tương lai ở người lớn/người cao tuổi	• Không hiệu quả giảm tỷ lệ mang vi khuẩn ở hầu họng • Chưa được chứng minh có tác động trong việc giảm gánh nặng bệnh tật tổng thể.

IgM, immunoglobulin M.
Koul PA *et al. Lung India* 2019;36:216–225.

Vaccine Safety

Pneumococcal Vaccine Side Effects

Pneumococcal vaccines are very safe and effective at preventing pneumococcal disease. Vaccines, like any medicine, can have side effects. The most common side effects from pneumococcal vaccines are mild and last for 1 or 2 days.

Common Side Effects of Pneumococcal Vaccine

- Feeling drowsy
- Loss of appetite
- Sore or swollen arm from the shot
- Fever
- Headache

Very rarely, severe (anaphylactic) allergic reactions may occur after vaccination.

Safety Information for Pneumococcal Vaccines | CDC

Kết luận

- **Nhiễm phế cầu:** vẫn là **gánh nặng cho cộng đồng**, đặc biệt trên bệnh nhân có **bệnh lý thận mạn**
- **Dự phòng bằng vắc xin phế cầu: mang lại nhiều lợi ích** – nhìn về lâm sàng và tiên lượng bệnh nền
- **Bệnh nhân có bệnh lý thận mạch mạn tính được khuyến cáo dự phòng vắc xin phế cầu để giảm các biến chứng liên quan đến nhiễm phế cầu và các biến cố thận mạn**