Associations of Chronic Kidney Disease with Infectious Disease

Bertrand L. Jaber, M.D.

Tufts University School of Medicine, Boston, MA

KDIGO Controversies Conference, Amsterdam, The Netherlands
October 12-14, 2006

Objectives

- **What is known?**
  - ⇨ **Review the evidence**
- **What can be done with what is known?**
  - ⇨**Provide clinical practice recommendations**
- **What needs to be known?**
  - ⇨**Provide clinical research recommendations**

Review of the Evidence

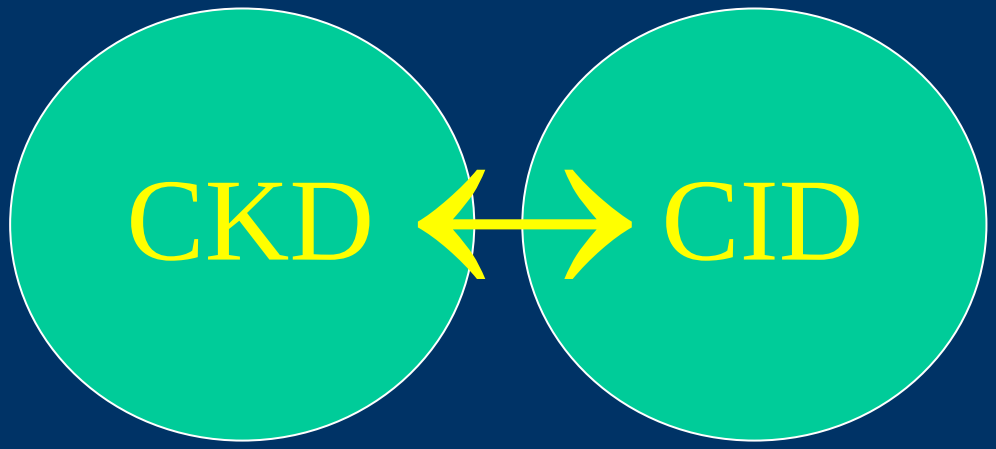
Main Topics

- CKD and 5 chronic infectious diseases (CID) of global importance
- Vaccination strategies in CKD
- Potential pitfalls of GFR estimates in infectious disease

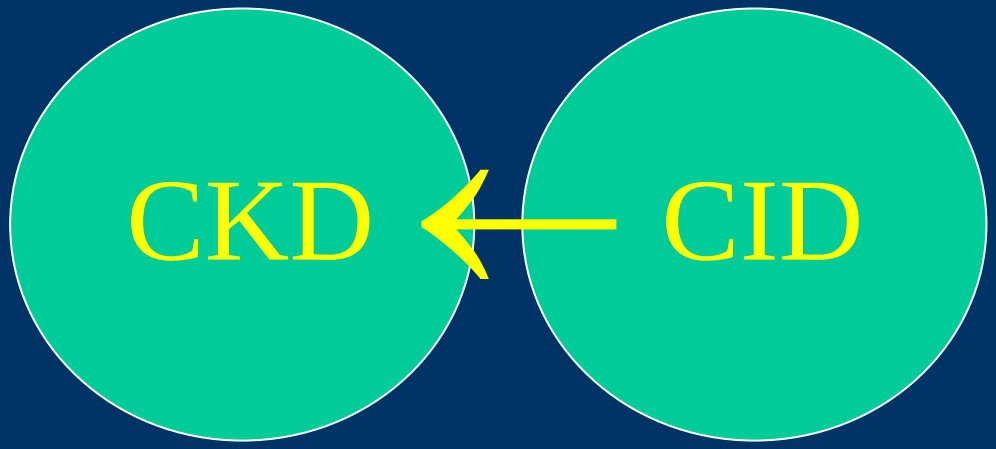
Other Topics

- CKD and acute infectious diseases
  - Pneumonia
  - Sepsis
- CKD-T (transplant) and infectious disease
- CKD and infectious disease in children

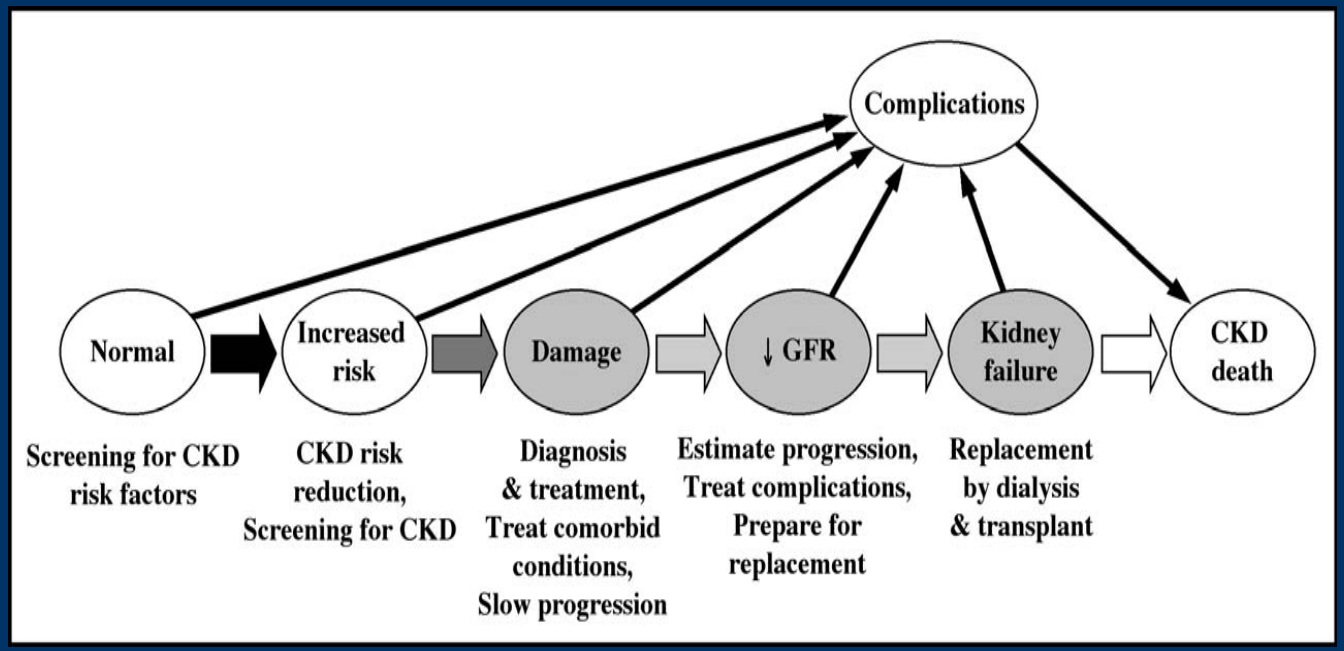
The CKD-CID Complex



The CKD-CID Complex



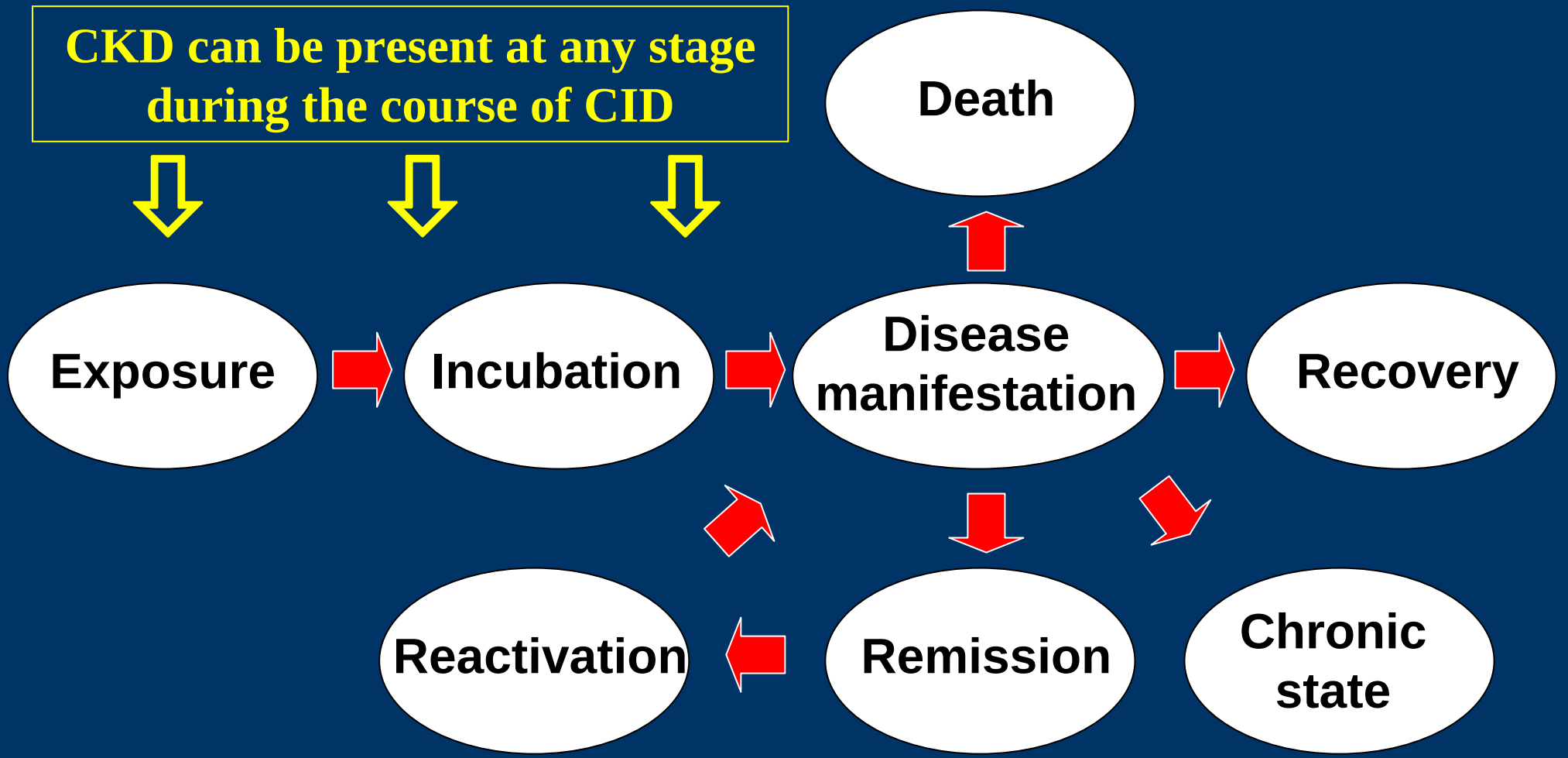
Original CKD Conceptual Framework: CID ⇨ CKD



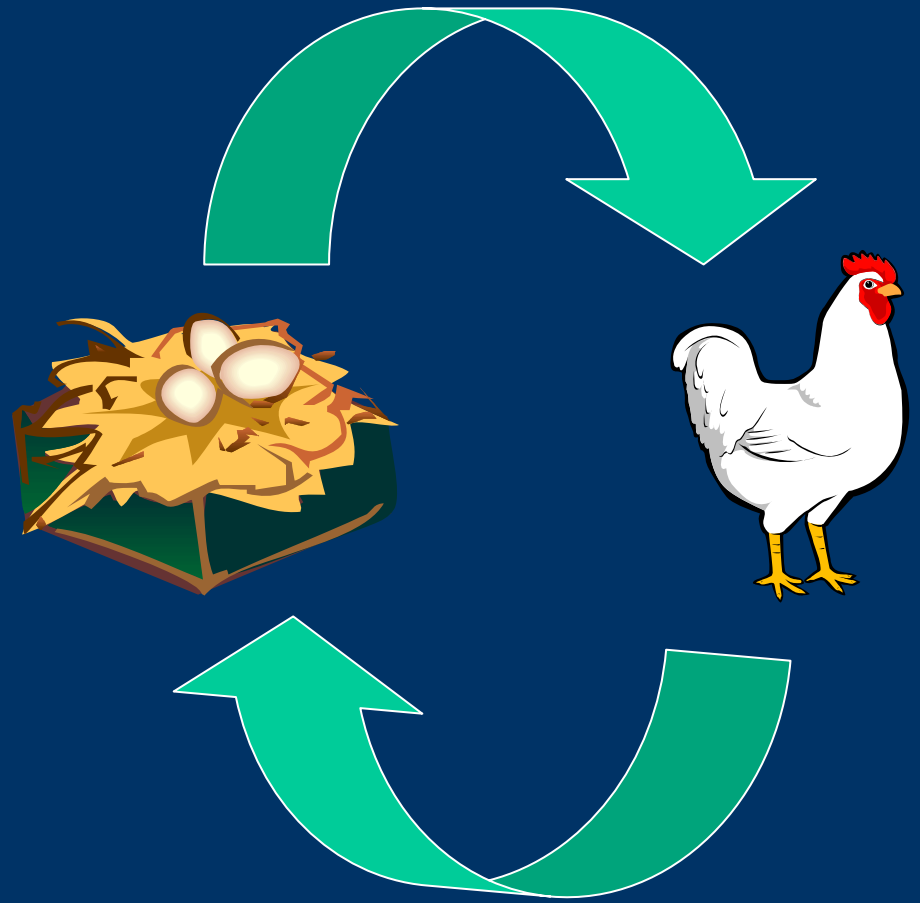
Susceptibility factor ⇨ Initiation factor ⇨ Progression factor ⇨ End-stage factor

HIV, HCV, HBV

Conceptual Framework: CKD in the Natural Course of CID



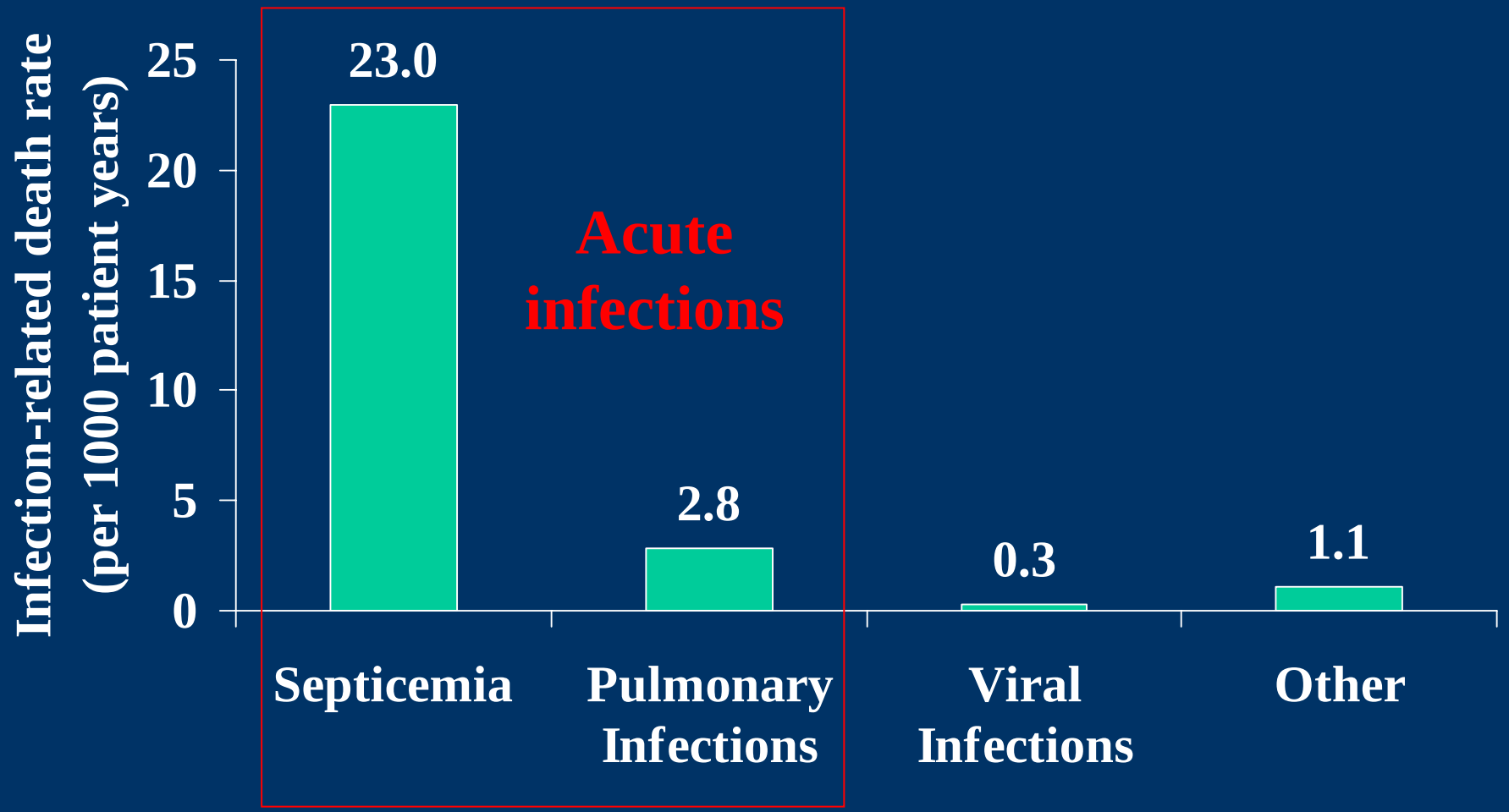
Is CKD a Risk Multiplier for CID?



Stage-5 CKD-D and Infectious Disease: What Have We Learned?

The Analogy with CVD!

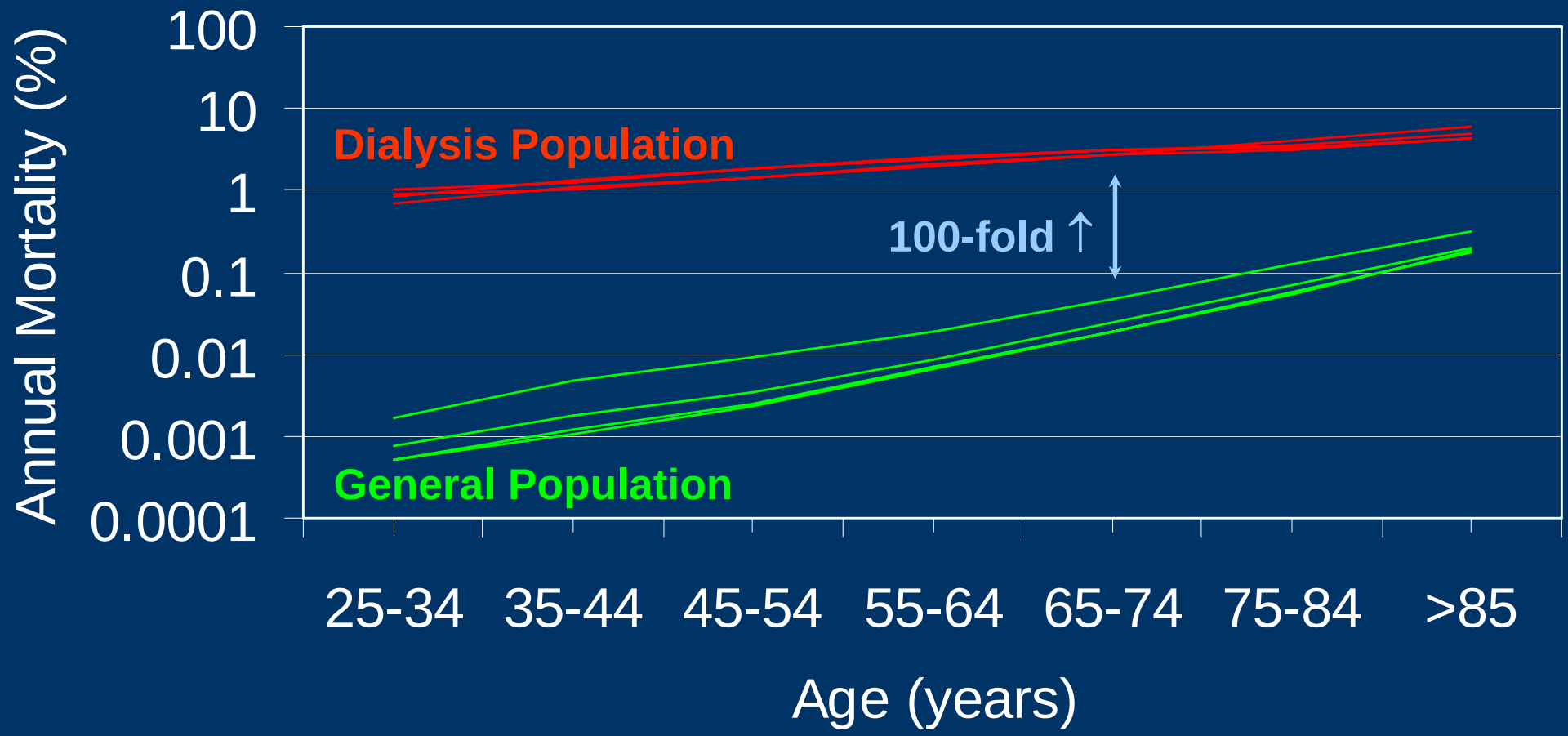
Infection 2nd Leading Cause of Death (15%) in Dialysis Patients Following CVD



Total Death Rate = 176 deaths per 1000 patient years

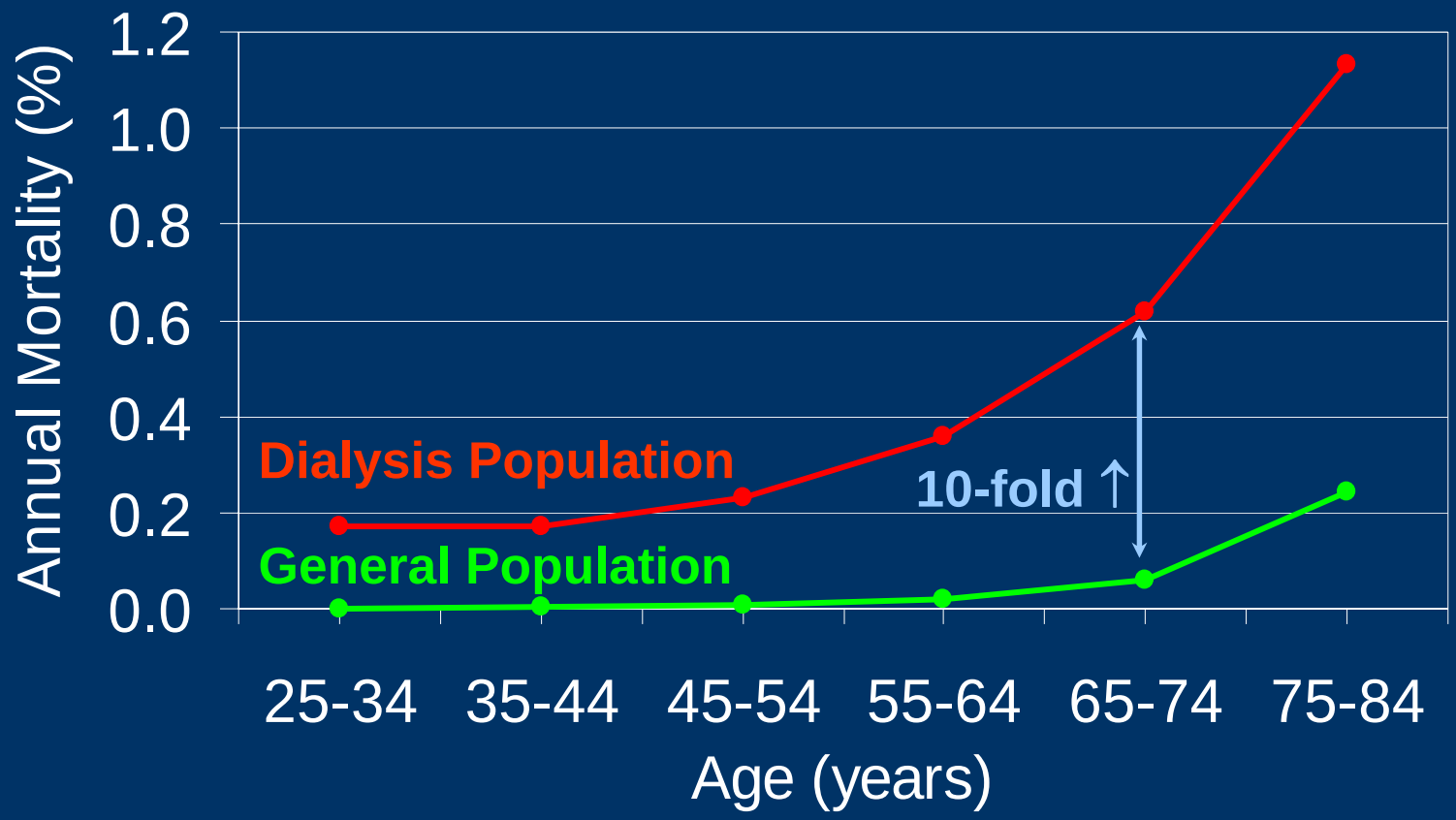
USRDS 2003 Annual Report

Sepsis-Related Mortality of Dialysis Patients Compared with the General Population



Sarnak & Jaber: *Kidney Int* 58:1758–1764, 2000

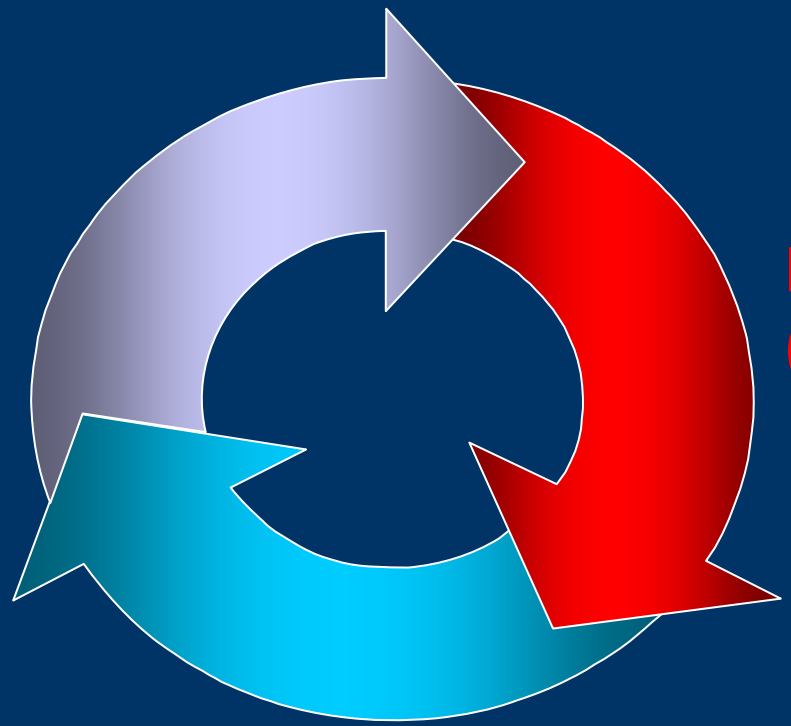
Pulmonary Infectious Mortality of Dialysis Patients Compared with the General Population



Sarnak & Jaber: *Chest* 120:1883-1887, 2001

Susceptibility of Patients with CKD to Infections

Virulence of microorganisms



Dialysis-related Factors (for CKD-5-D)

Impaired Host Immunity

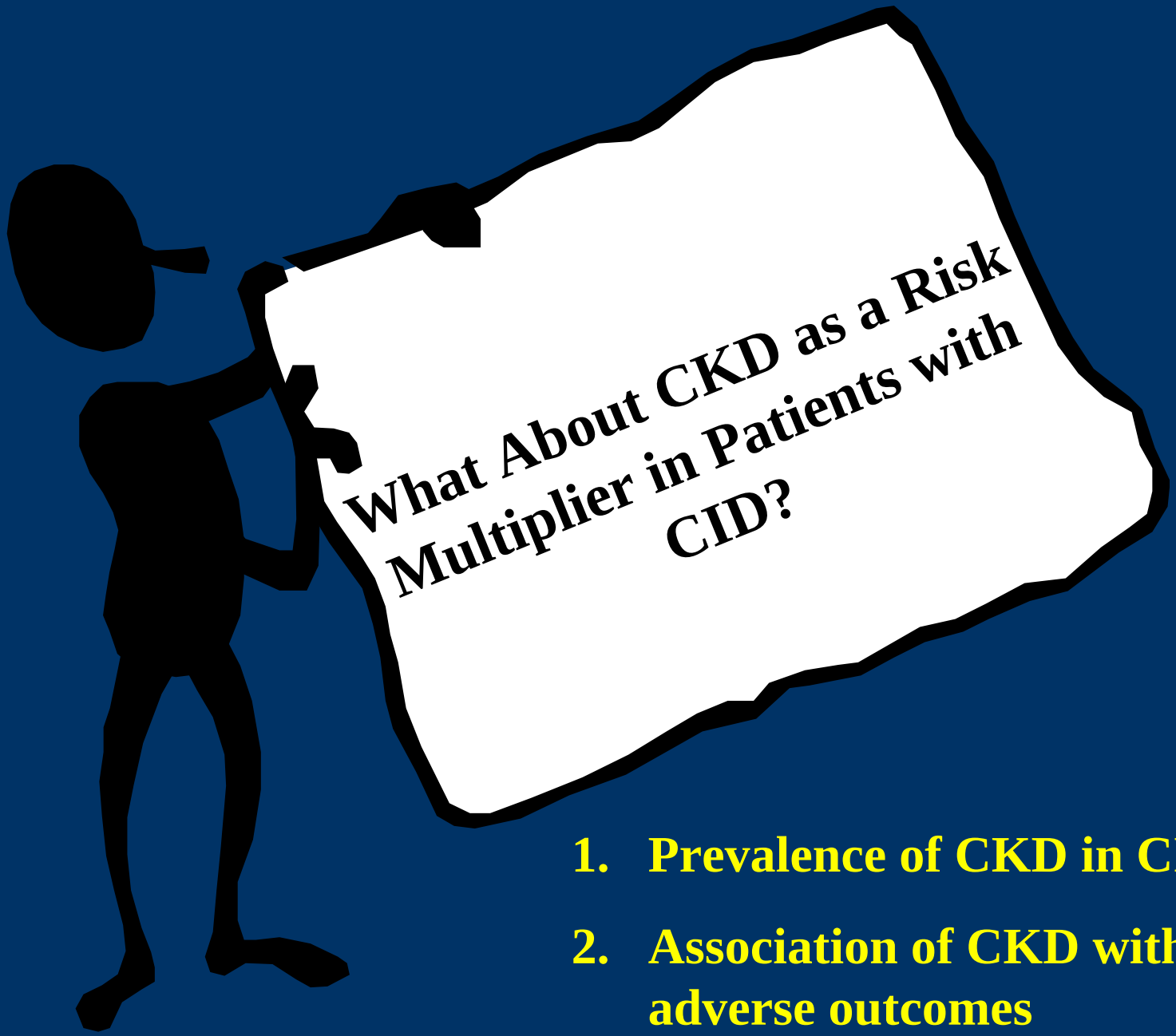
Pathogenesis of Infections in CKD

Virulence of microorganisms

Dialysis-related Factors (for CKD-5-D)

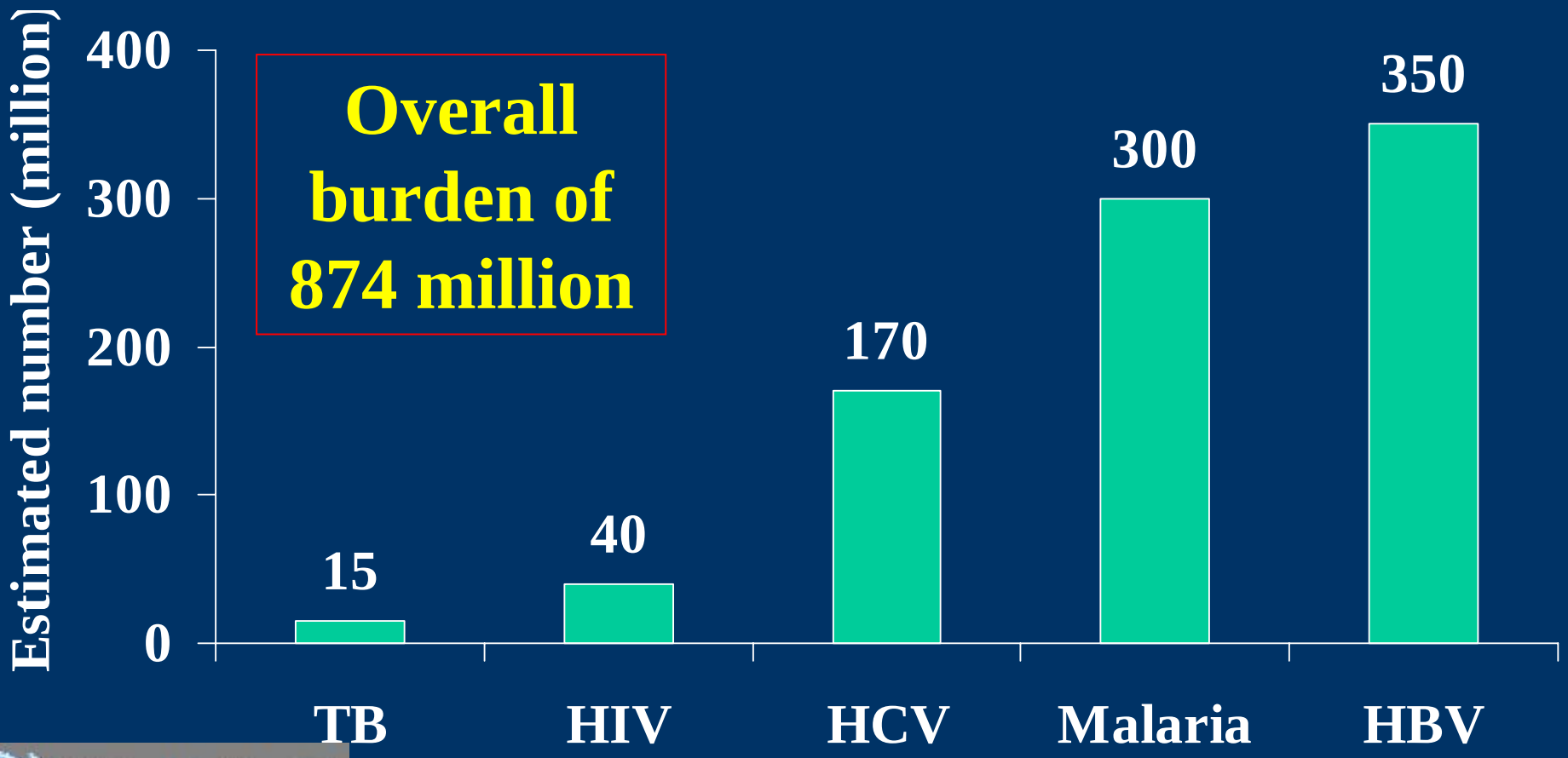
- Neutrophil dysfunction
- Monocyte dysfunction
- Impaired T-cell activation
- Impaired humoral responses

→ Impaired Host Immunity



1. **Prevalence of CKD in CID**
2. **Association of CKD with CID-associated adverse outcomes**

Infections of Global Importance



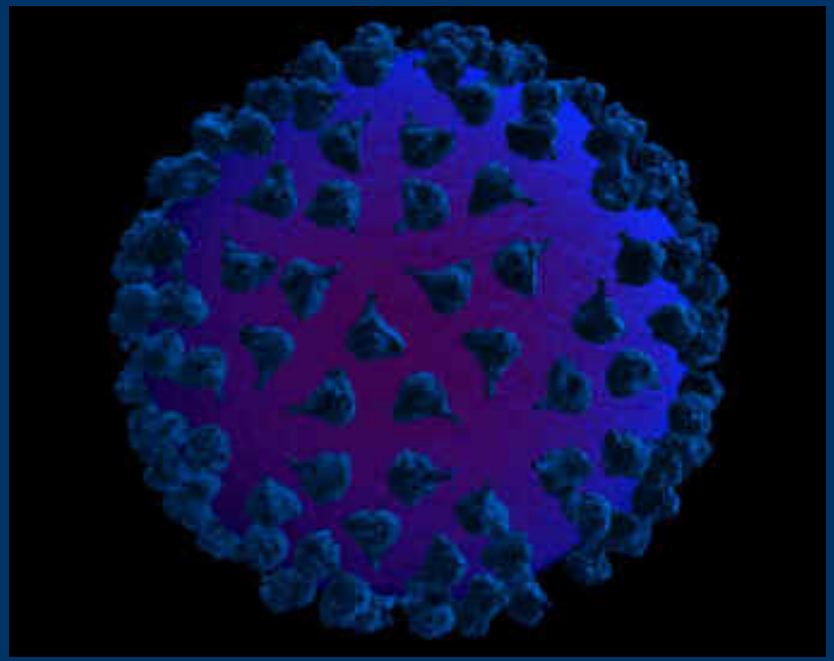
World Health Organization

www.who.int

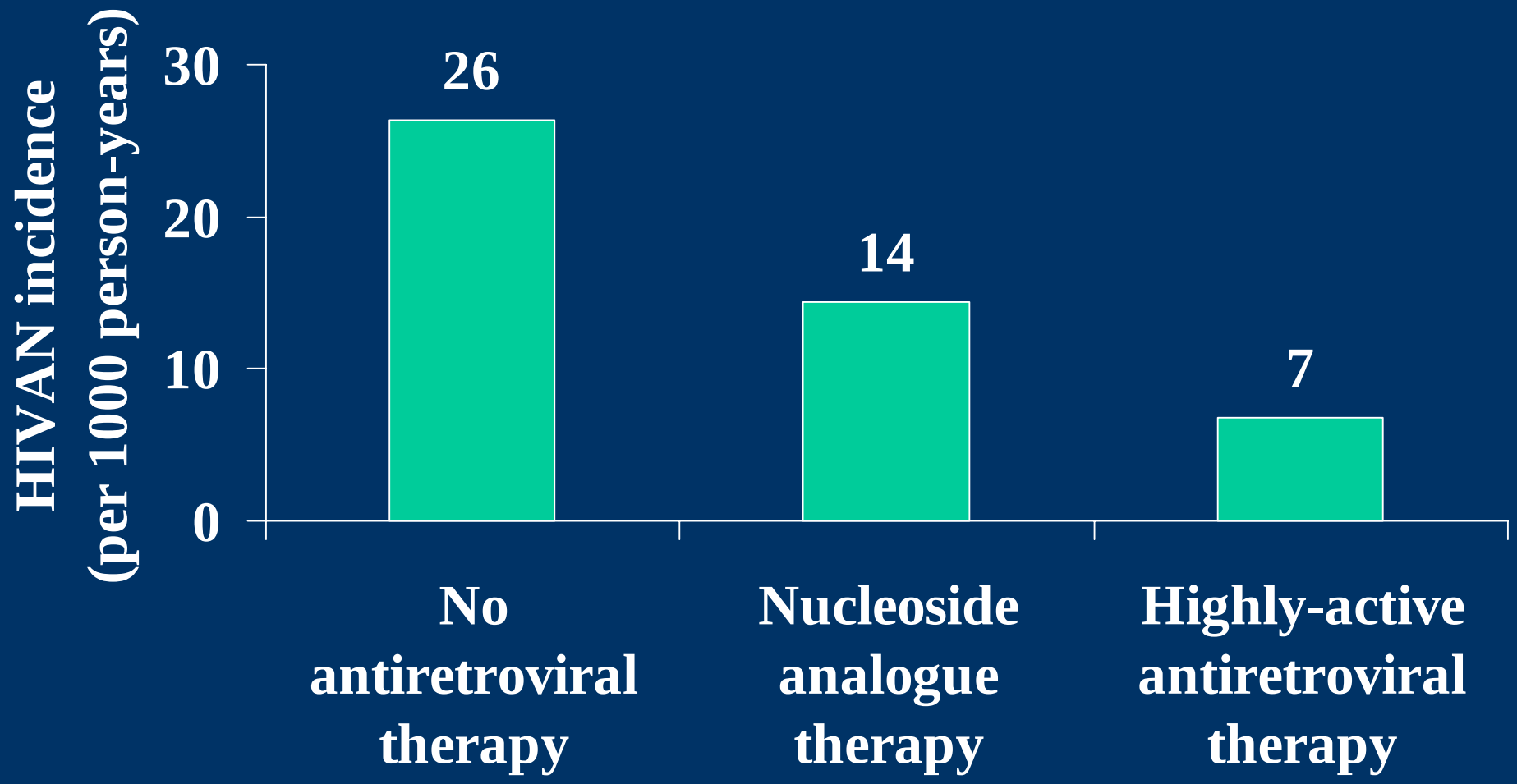
Proposed Framework: CKD as a Risk/Prognostic Factor for Infectious Diseases

Infectious disease (ID)	CKD prevalence	CKD as a risk factor for ID morbidity	CKD as a risk factor for ID mortality
HIV			
HCV			
HBV			
Malaria			
TB			

HIV and CKD

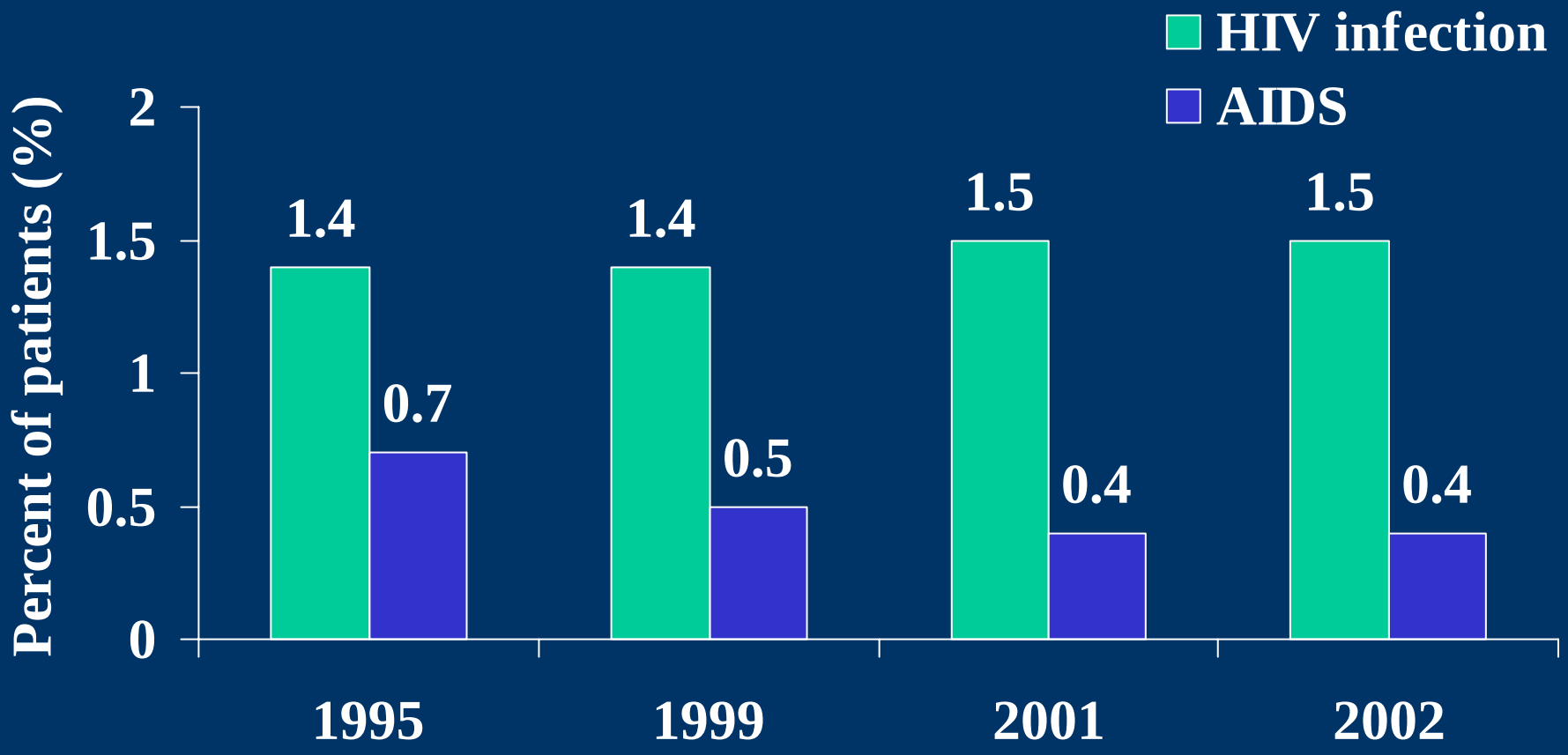


HAART and Incidence of HIVAN: A 12-Year Cohort Study



Lucas GM et al: AIDS 18:541-6, 2004

CDC National Surveillance of Dialysis-Associated Diseases, 1995-2002 U.S. - HIV/AIDS -



Finelli L et al: *Seminars in Dialysis* 18:52-61, 2005

Proteinuria/Increased Serum Creatinine in HIV-Infected Patients

- Markers of HIV-related kidney disease:
  - HIVAN
  - Other HIV-related glomerular diseases
  - Nephrotoxicity of HIV-related drugs
- Indicators of poor health status as a result of:
  - Hypertension
  - Diabetes mellitus
  - Cardiovascular disease

Summary of HIV-CKD Studies

Author	Study design	Sample size	Renal predictor variable	Outcome variable	Results (multivariate analyses)
Lewden C (2002)	Multicenter prospective cohort study (France)	1155 HIV-infected adults	Baseline and post-treatment (4-month) sCr < normal (0.9 [male] or 0.8 [female] mg/dl)	Mortality	•Baseline HR 2.4 (1.3, 4.3) •4-month HR 2.5 (1.0, 6.1)
Gardner LI (2003)	Prospective cohort study (USA)	885 HIV-infected and 425 at-risk HIV negative women	Baseline renal abnormalities: proteinuria (≥ 2+) and/or sCr ≥ 1.4 mg/dl	Mortality	HR 2.5 (1.9, 3.3)
Gardner LI (2003)	Prospective cohort study (USA)	885 HIV-infected adults women	Baseline renal abnormalities: proteinuria (≥ 2+) and/or sCr ≥ 1.4 mg/dl	Condition -specific hospitalizations	• Overall hospitalization HR 1.5 (1.3, 1.8) • Hosp. AIDS defining illness HR 1.7 (1.1, 2.7) • Hosp. renal conditions HR 5.0 (2.3, 11.0) • Hosp. hepatic conditions HR 1.8 (1.1, 2.8)

Summary of HIV-CKD Studies

Author	Study design	Sample size	Renal predictor variables	Outcome variables	Results (multivariate analyses)
Szczech LA (2004)	Prospective cohort study (USA)	2038 HIV-infected women	Proteinuria (≥ 1+ ≥ 2 visits) Inverse sCr decrease	new AIDS-defining illness (ADI) and death before and after widespread use of HAART	<u>Pre-HAART ADI</u> • Proteinuria HR 1.3 (1.1, 1.6) <u>Post-HAART ADI</u> • 1/sCr↓ HR 1.4 (1.0, 2.1) <u>Pre-HAART Death</u> • Proteinuria HR 1.3 (1.1, 1.8) • 1/sCr↓ HR 1.7 (1.1, 2.7) <u>Post-HAART Death</u> • Proteinuria HR 2.2 (1.3, 3.7)
Levin A (2006) [ASN abstract]	Prospective cohort study (Canada)	2629 HIV-infected adults initiating antiretorviral therapy	eGFR (MDRD 4-variable equation) < 60 ml/min/1.73 m^2	Mortality	• eGFR < 60 ml/min/1.73 m^2 HR 1.65 (1.01, 2.71)

Proposed Framework: CKD as a Risk/Prognostic Factor for Infectious Diseases

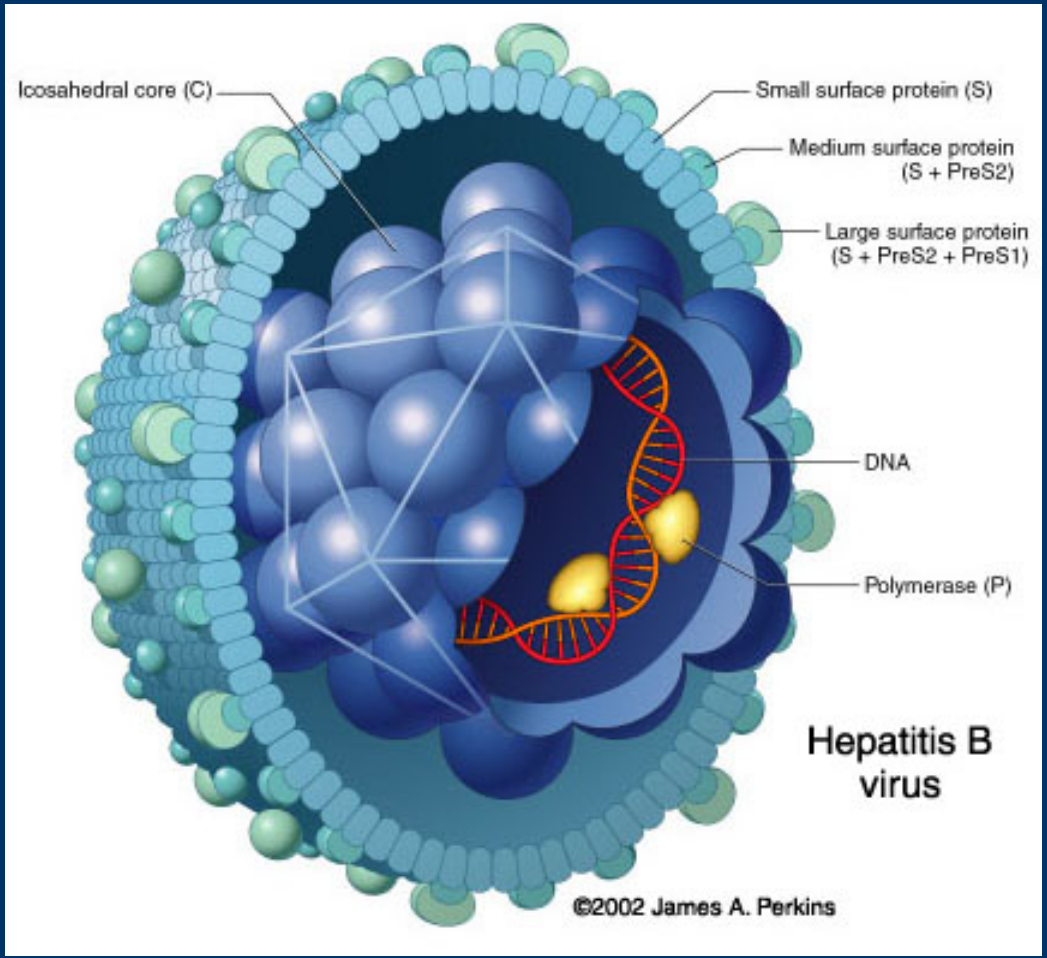
Infectious disease (ID)	CKD prevalence	CKD as a risk factor for ID morbidity	CKD as a risk factor for ID mortality
HIV	HIVAN = 2-10% (likely on decline in countries with access to HAART) Proteinuria (≥ 1-2+) = 14.1-17.8% (female) sCr ≥ 1.4 mg/dl = 5.3% (female) eGFR < 60 ml/min/1.73 m^2 = 3%	++ AIDS defining illness Hospitalization	++++

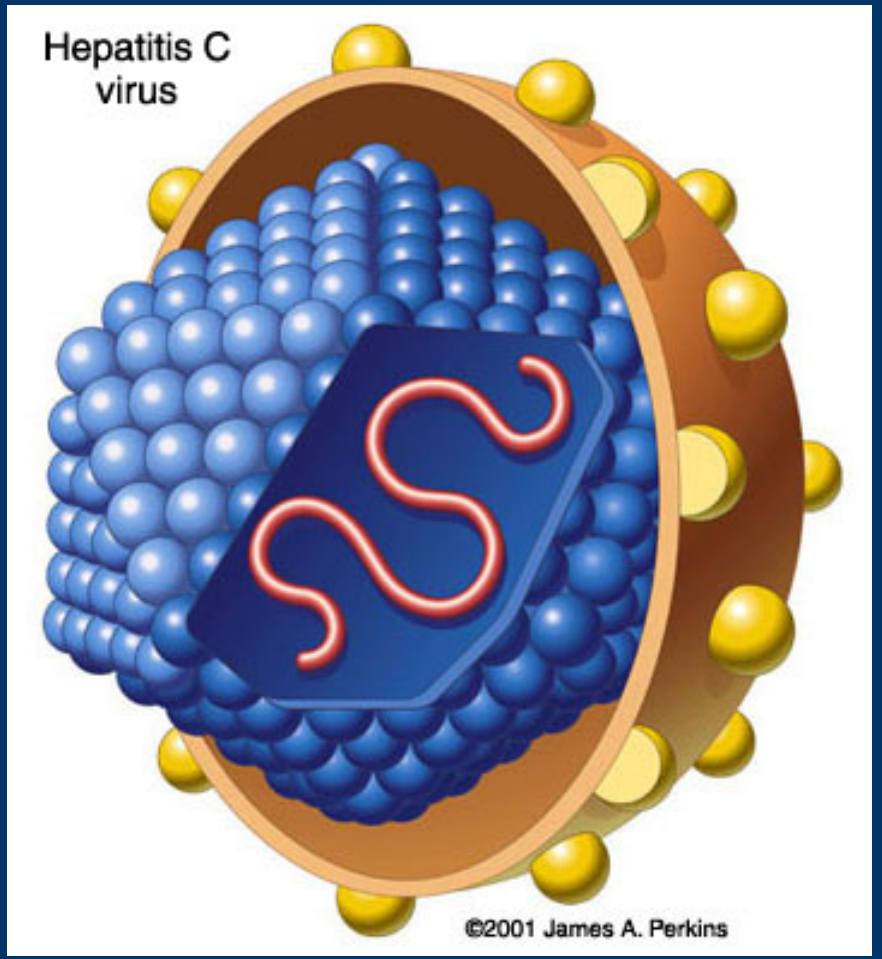
Guidelines for Management of CKD in HIV/AIDS

- **Published Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients**
- **HIV Medicine Association of the Infectious Diseases Society of America (IDSA)**
- **15 members: 7 nephrologists, 8 infectious disease specialists**
- **Guidelines adopt KDOQI Guidelines to estimate kidney function**

Clinical Infectious Disease 40:1559-85, 2005

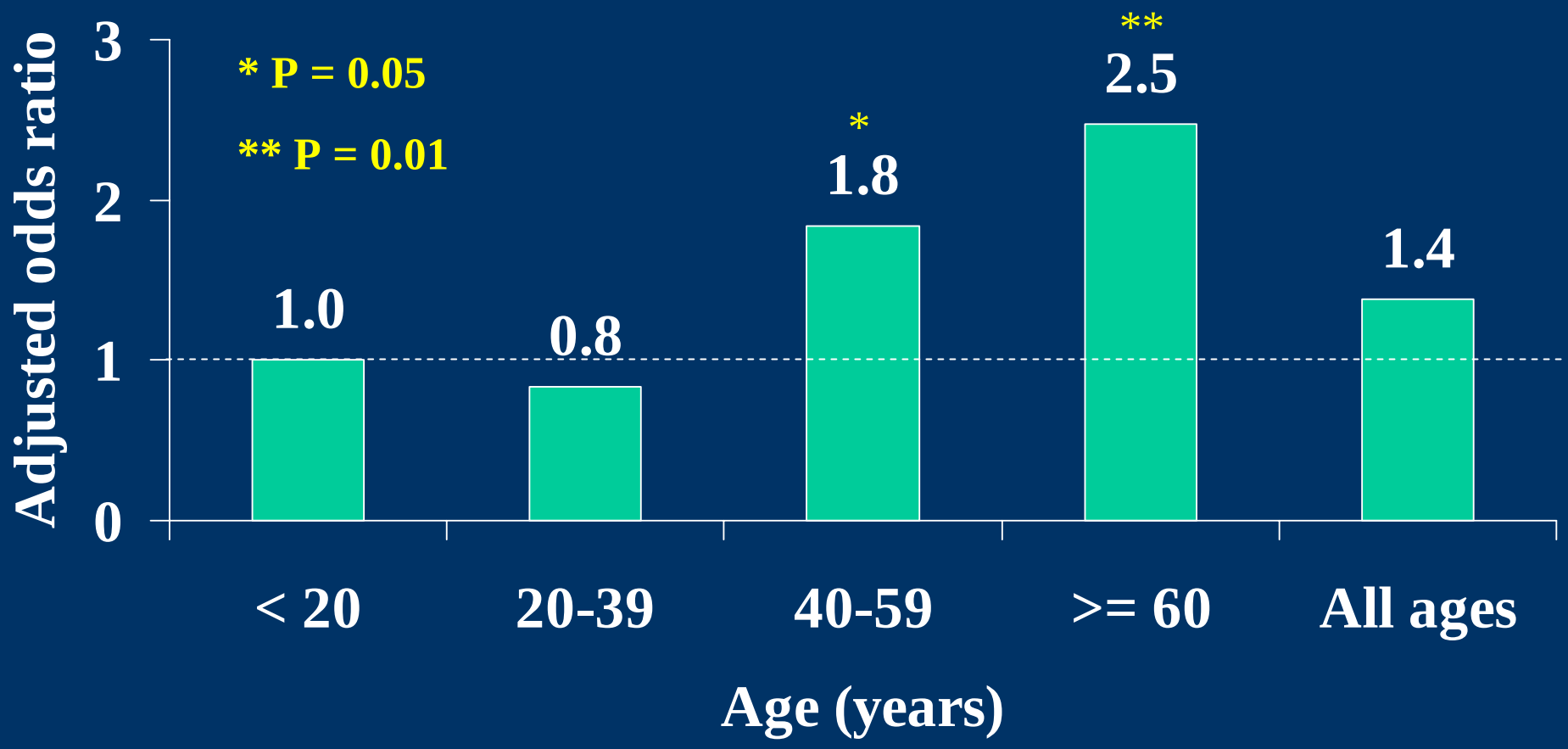
HBV, HCV and CKD





Association between HCV Seropositivity and Albuminuria: NHANES III (N = 15,029)

No association with low eGFR (< 60 ml/min/1.73 m^2)

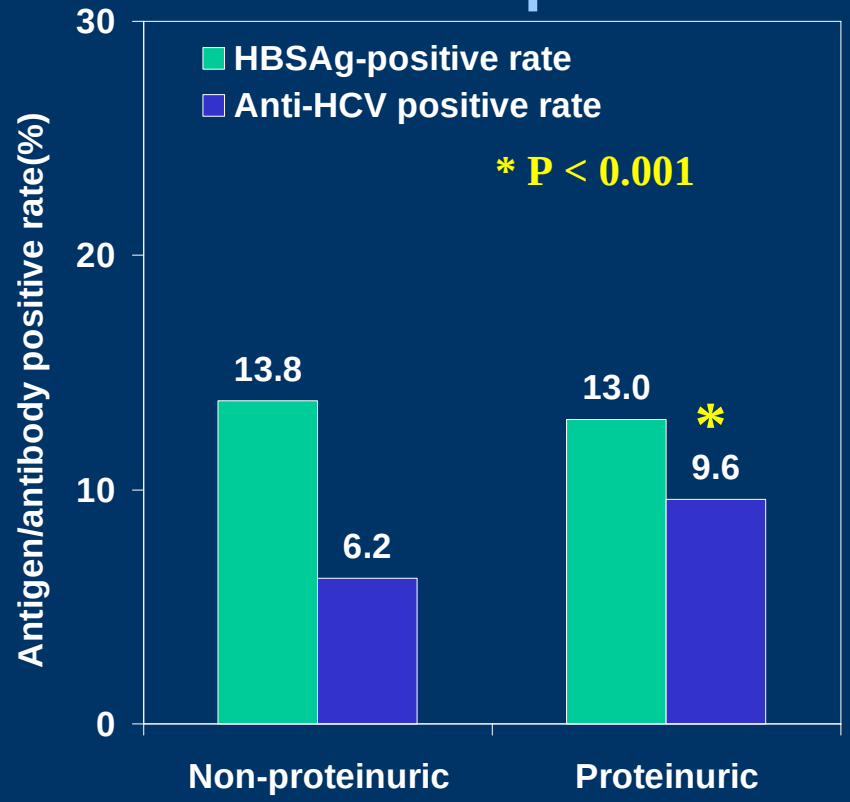


Adjusted for age, gender, race, educational status, smoking status, diabetes, and hypertension

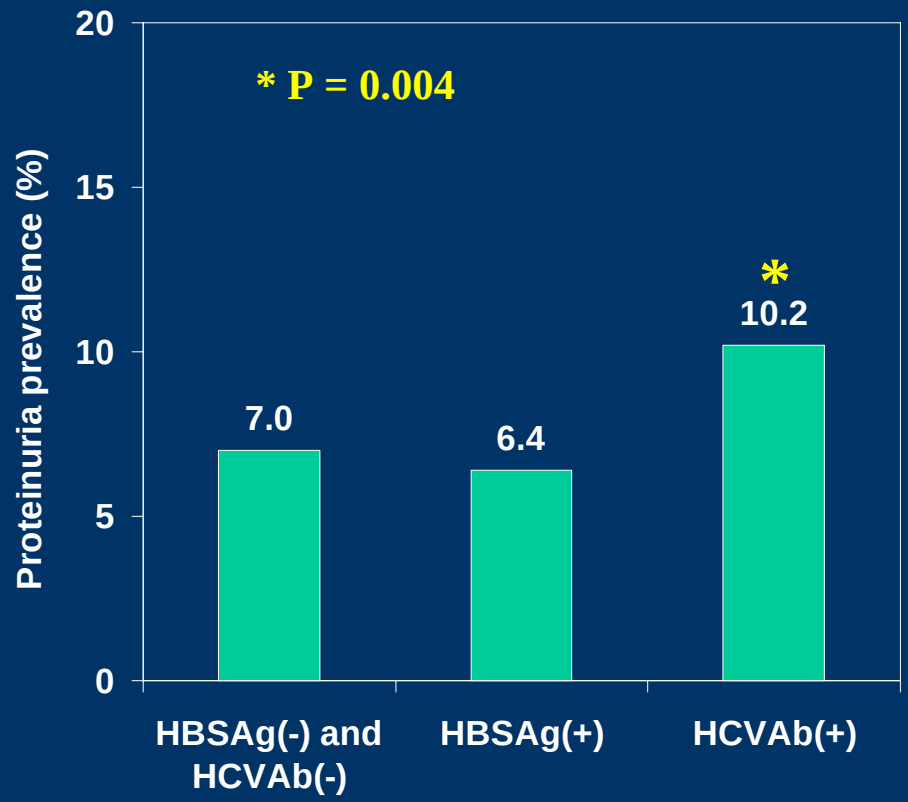
Tsui JI et al: J Am Soc Nephrol 17:1168-74, 2006

HBV, HCV, and Proteinuria (≥ 1+) in Southern Taiwan (n = 9,934)

Prevalence of Viral Hepatitis



Prevalence of Proteinuria



Proteinuria quantified with automated reader on 2 separate visits

Huang JF et al: *J Intern Med* 260:255-62, 2006

Multivariate Analyses of Variables Associated with Proteinuria

9,934 subjects

Variables[a]	OR	95% CI	*P*-value
Diabetes (+)	3.735	3.133–4.453	<0.001
Hypertension (+)	1.974	1.673–2.329	<0.001
Anti-HCV (+)	1.648	1.246–2.179	0.003
BMI (kg m^{-2})	1.078	1.055–1.102	<0.001
Age (year)	1.014	1.000–1.028	0.044
Triglycerides (mg dL^{-1})	1.002	1.001–1.002	<0.001

OR, odds ratio; CI, confidence interval. [a]Variables included: age, sex, body mass index (BMI), alanine aminotransferase (ALT) level, total cholesterol level, triglyceride level, presence of diabetes, presence of hypertension, presence of antibodies to hepatitis C virus (anti-HCV), seropositive for hepatitis B surface antigen (HBsAg). For the continuous variables, OR represents one unit increase in the value of the variable tested.

8,696 nondiabetic subjects

Variables[a]	OR	95% CI	*P*-value
Hypertension (+)	1.963	1.611–2.392	<0.001
Anti-HCV (+)	1.847	1.332–2.561	<0.001
BMI (kg m^{-2})	1.086	1.057–1.116	<0.001
Triglycerides (mg dL^{-1})	1.001	1.001–1.002	<0.001

OR, odds ratio; CI, confidence interval. [a]Variables included: age, sex, body mass index (BMI), alanine aminotransferase (ALT) level, total cholesterol level, triglyceride level, fasting plasma glucose level, presence of hypertension, presence of antibodies to hepatitis C virus (anti-HCV), seropositive for hepatitis B surface antigen (HBsAg). For the continuous variables, OR represents one unit increase in the value of the variable tested.

Huang JF et al: *J Intern Med* 260:255-62, 2006

HBV Pretreatment Characteristics and 6-Month Mortality (N = 154)

Predictor variable	HR (95% CI)	
	Univariate analysis	Multivariate analysis
Creatinine (mg/dl)	3.54 (2.03, 6.18)	5.23 (2.84, 9.63)
Albumin	0.27 (0.14, 0.52)	-
Total bilirubin (mg/dl)	1.56 (1.35, 1.81)	1.69 (1.43, 1.99)
HBV DNA positivity	5.16 (1.21, 21.93)	6.13 (1.41, 26.76)

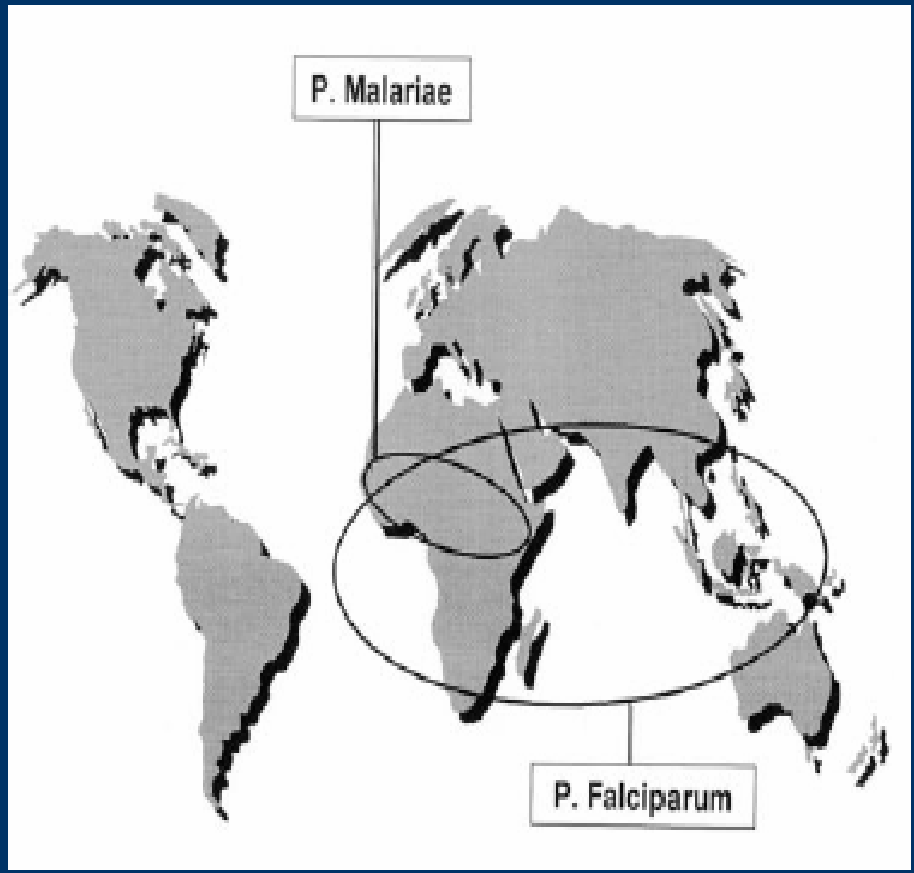
Fontana JF et al: *Gastroenterology* 123:719-727, 2002

Proposed Framework for CKD as Risk Factor for Infectious Diseases

Infectious disease (ID)	CKD prevalence	CKD as a risk factor for ID morbidity	CKD as a risk factor for mortality
HIV	HIVAN = 2-10% (likely on decline in countries with access to HAART) Proteinuria (≥ 1-2+) = 14.1-17.8% (female) sCr ≥ 1.4 mg/dl = 5.3% (female) eGFR < 60 ml/min/1.73 m^2 = 3%	++	++++
HCV	HCV Ab(+): proteinuria (≥ 1+) = 10.2% eGFR < 60 ml/min/1.73 m^2 = 2.0% (95% CI 1.1, 3.6%)	?	?
HBV	HBS Ag(+): proteinuria (≥ 1+) = 6.4%	?	+

Reported Malarial Nephropathies in Endemic Areas

- **Acute malarial nephropathy:**
  - ***Plasmodium falciparum***
  - **Southeast Asia, India, and sub-Saharan Africa**
  - **Incidence:**
    - **Native patients in endemic areas: 1-5%**
    - **Non-immune Europeans: 25-30%**
- **Chronic malarial nephropathy:**
  - ***Plasmodium malaria* and *P. Vivax***
  - **African children**
  - **Chronic glomerulopathy**



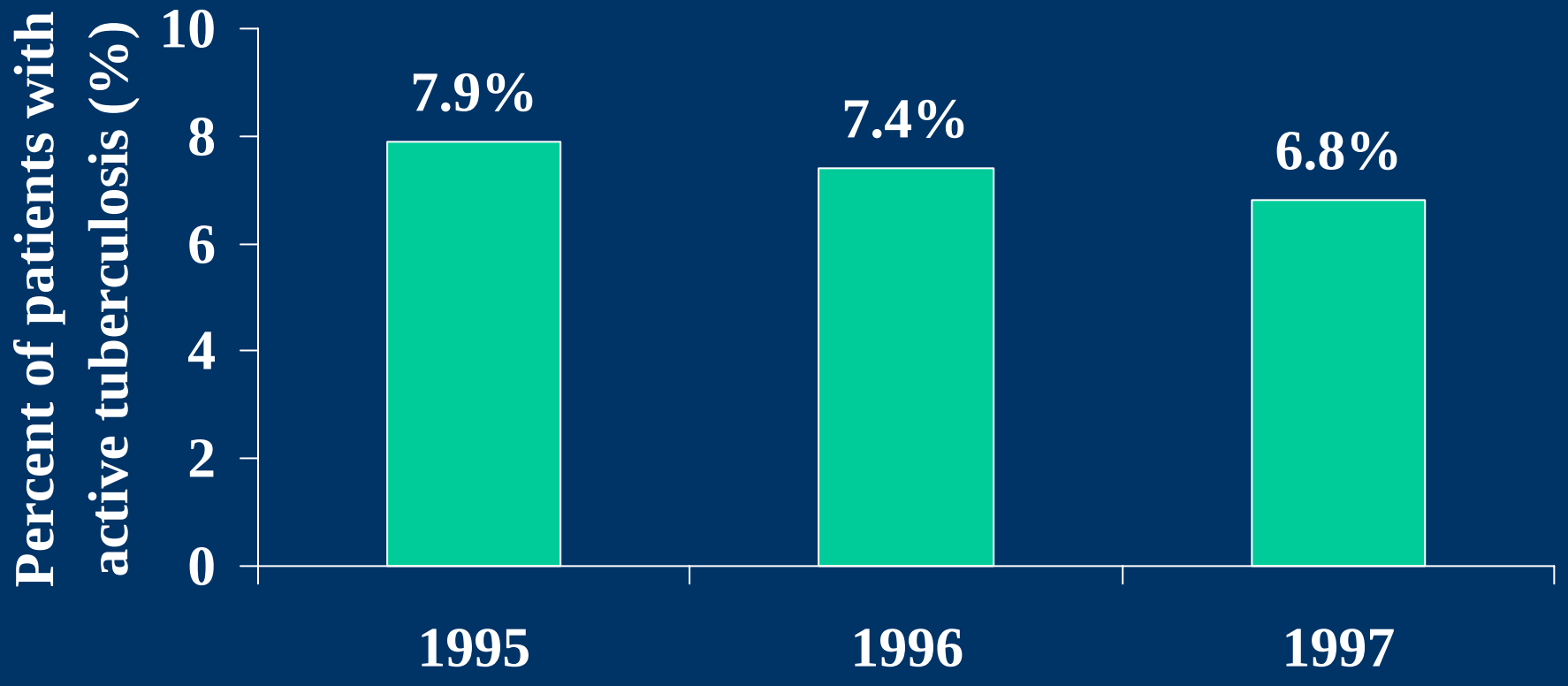
Barsoum RS: J Am Soc Nephrol 11: 2147–2154, 2000

TB and Chronic Kidney Disease

- 7- to 53-fold increased risk of TB in stage-5 CKD compared to the general population
- High incidence of extra-pulmonary disease
- High prevalence of anergy to tuberculin skin test
    - Two-step tuberculin skin testing (booster phenomenon)
    - Annual screening in dialysis units (stage-5 CKD-D)

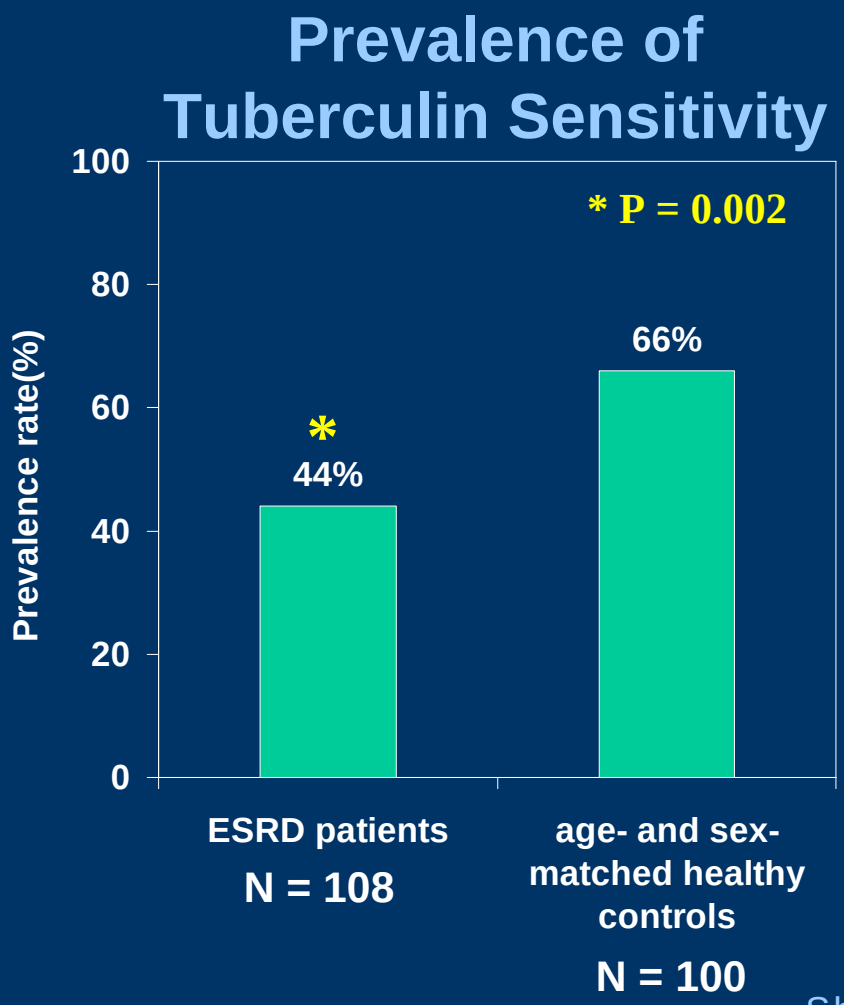
Hussein MM et al: Semin Dial 16:38-44, 2003
Dogan E et al: Ren Fail 27:425-8, 2005

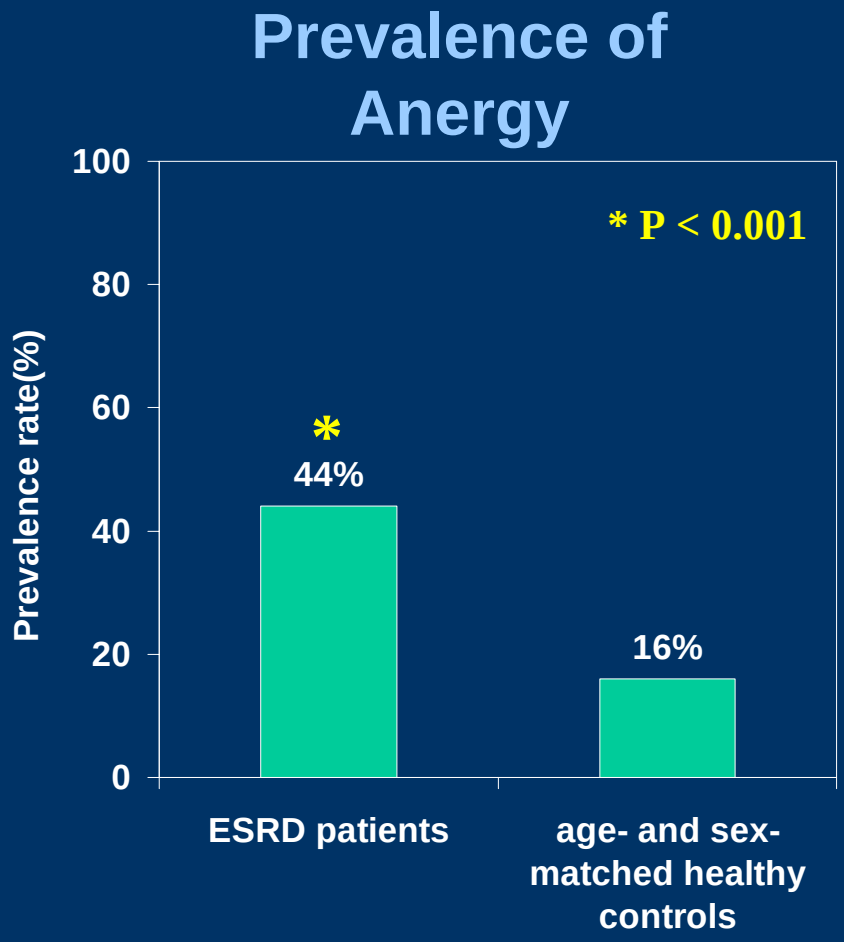
CDC National Surveillance of Dialysis-Associated Diseases, 1995-1997 U.S. - Active Tuberculosis -



Tokars JI et al: *Seminars in Dialysis* 13:75-85, 2000

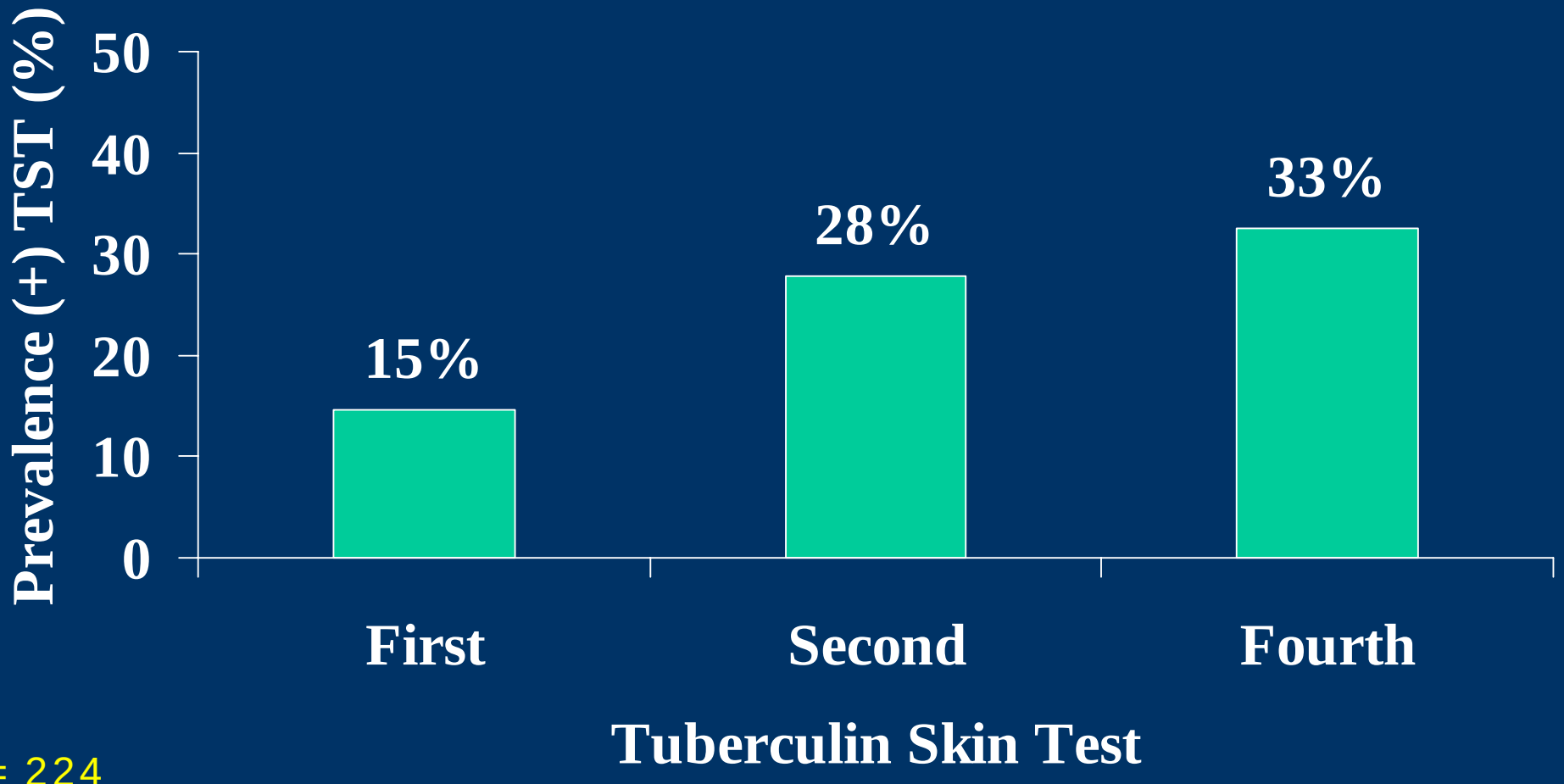
Prevalence of Tuberculin Sensitivity and Anergy in Stage-5 CKD in an Endemic Area





Shankar MS et al: Nephrol Dial Transplant 20:2720-4, 2005

Cumulative Prevalence of a Positive Tuberculin Skin Test in Hemodialysis Patients



N = 224

Booster injection administered at a 7-day interval

Wauters A et al: Nephrol Dial Transplant 19:433-8, 2004

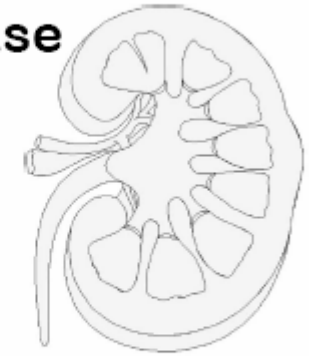
Proposed Framework for CKD as Risk Factor for Infectious Diseases

Infectious disease (ID)	CKD prevalence	CKD as a risk factor for ID morbidity	CKD as a risk factor for ID mortality
HIV	HIVAN = 2-10% (likely on decline in countries with access to HAART) Proteinuria (≥ 1-2+) = 14.1-17.8% (female) sCr ≥ 1.4 mg/dl = 5.3% (female) eGFR < 60 ml/min/1.73 m^2 = 3%	++	++++
HCV	HCV Ab(+): proteinuria = 10.2% eGFR < 60 ml/min/1.73 m^2 = 2% (95% CI 1.1, 3.6%)	?	?
HBV	HBS Ag(+): proteinuria = 6.4%	?	+
Malaria	?	?	?
TB	CKD-5-D point prevalent active TB = 6.8%	?	?

What About Vaccination in CKD?

Guidelines for Vaccinating

Kidney Dialysis Patients and **Patients with Chronic Kidney Disease**



summarized from
Recommendations of the Advisory Committee on Immunization Practices (ACIP)

CDC

CDC Vaccination Recommendations for Patients with CKD

Vaccine	Recommended	May Use if Otherwise Indicated	Contraindicated
Anthrax		X*	
DTaP/Tdap/Td		X*	
Hib		X*	
Hepatitis A		X*	
Hepatitis B	X (see p. 2)		
Influenza (TIV)	X (see p. 3)		
Influenza (LAIV)			X (see p. 4)
Japanese Encephalitis		X*	
MMR		X*	
Meningococcal		X*	
Pneumococcal	X (see p. 4)		
Polio (IPV)		X*	
Rabies		X*	
Rotavirus		X†	
Smallpox		X*	
Typhoid		X*	
Varicella		X*	
Yellow Fever		X*	

*No specific ACIP recommendation for this vaccine exists for renal dialysis patients and patients with chronic renal disease.

†Children with primary immunodeficiency disorders and both children and adults who have received hematopoietic, hepatic, or renal transplants are at risk for severe or prolonged rotavirus gastroenteritis and can shed rotavirus for prolonged periods. ["Prevention of Rotavirus Gastroenteritis Among Infants and Children: Recommendations of the Advisory Committee on Immunization Practices" Unpublished]

Decreased Responses to Vaccination in Patients with Stage-5 CKD

- Protective antibody levels not easily achieved
  - Impaired macrophage function
  - ↓ T-cell activation and proliferation
  - ↓ B-cell count and IgG production
- Protective antibody levels fall rapidly

Doses and Schedules of Hepatitis B Vaccines for Patients with CKD

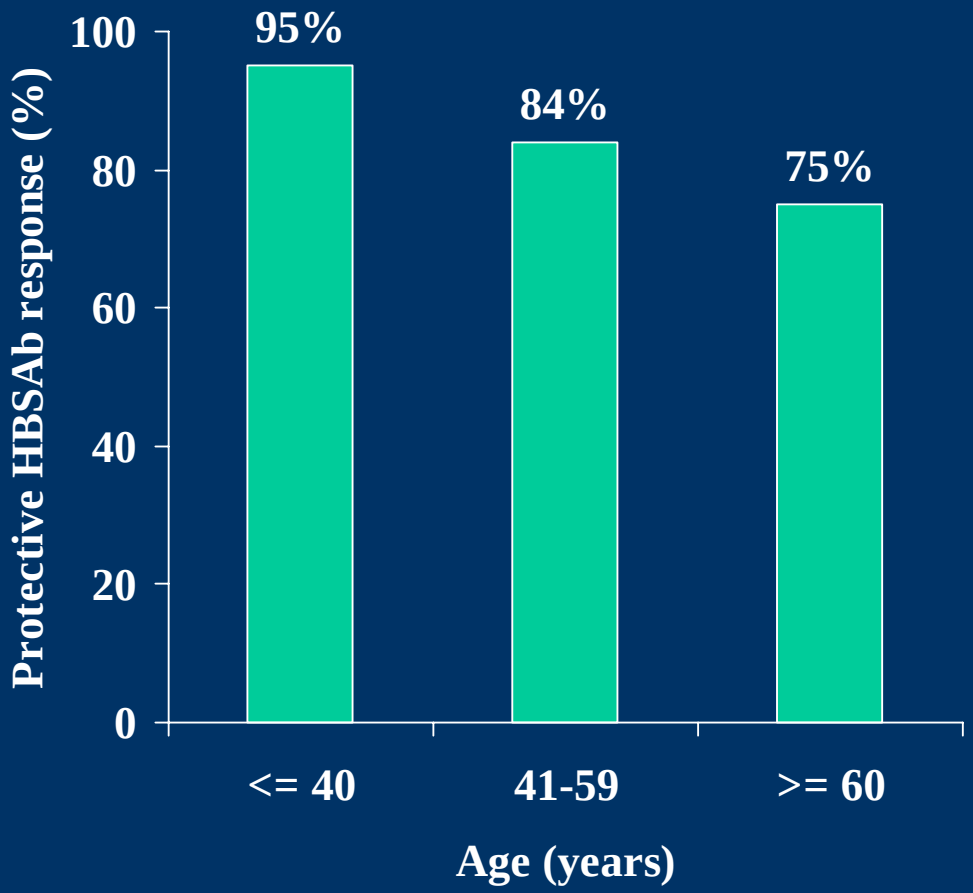
Message lost in translation

Group	Recombivax HB			Engerix B		
	Dose	Volume	Schedule	Dose	Volume	Schedule
≥20 years of age: Predialysis*	10 µg	1.0 mL	3 doses at 0, 1, & 6 months	20 µg	1.0 mL	3 doses at 0, 1, & 6 months
≥20 years of age: Dialysis-dependent	40 µg	1.0 mL†	3 doses at 0, 1, & 6 months	40 µg	Two 1.0 mL doses at one site	4 doses at 0, 1, 2, & 6 months
<20 years of age¶	5 µg	0.5 mL	3 doses at 0, 1, & 6 months	10 µg	0.5 mL	3 doses at 0, 1, & 6 months

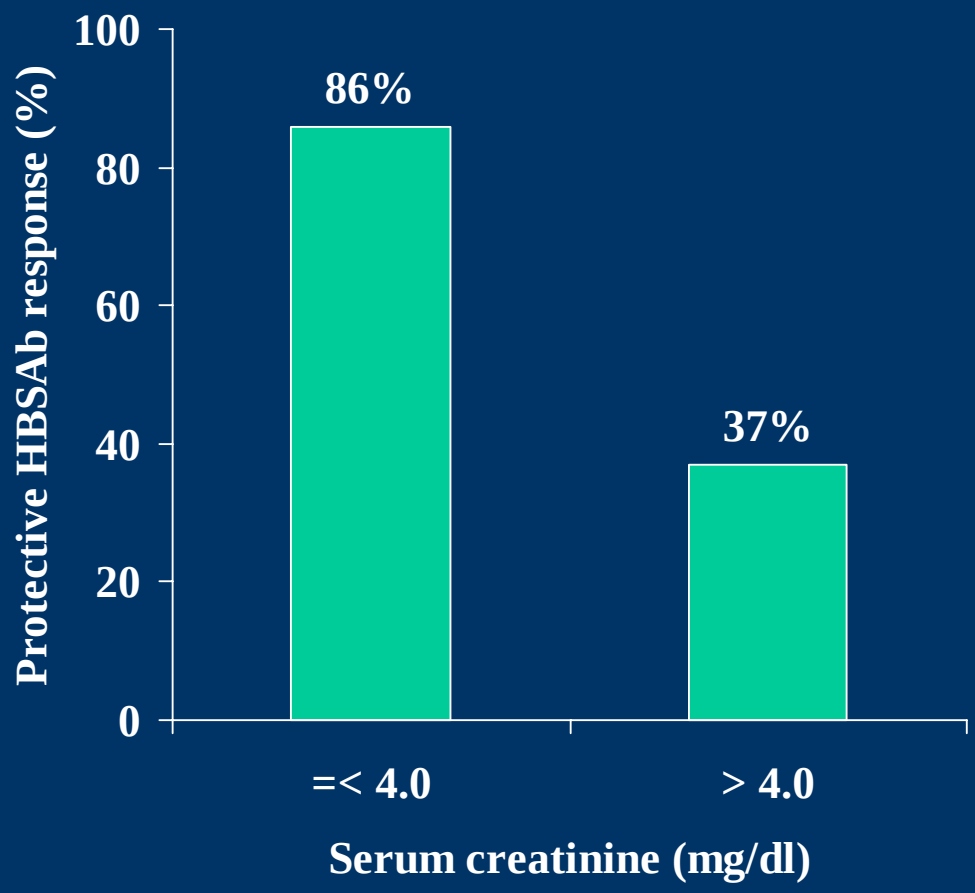
* Immunogenicity might depend on degree of renal insufficiency.
† Special formulation.
¶ Doses for all persons aged <20 years approved by the U.S. Food and Drug Administration. For hemodialysis patients, higher doses might be more immunogenic.

Adapted from CDC. Recommendations for Preventing Transmission of Infections Among Chronic Hemodialysis Patients. *MMWR* 2001; 50 (No. RR-5):Table 3

Immunogenicity of Hepatitis B Vaccine Declines with Age and CKD

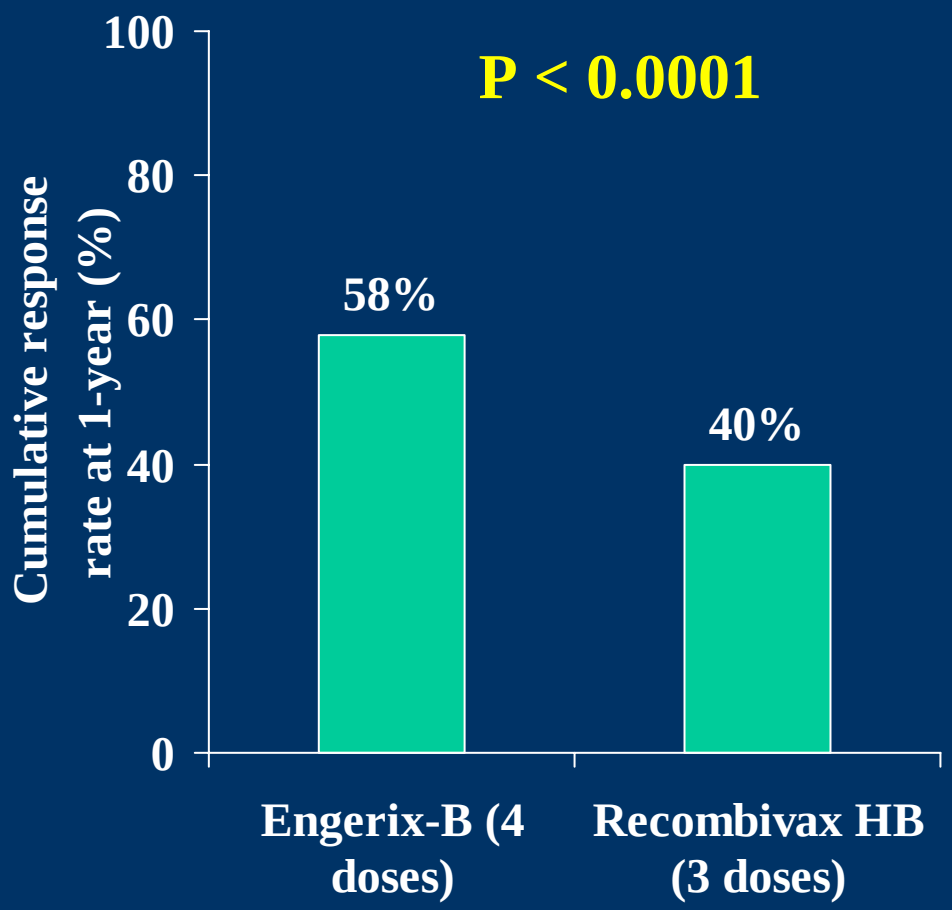


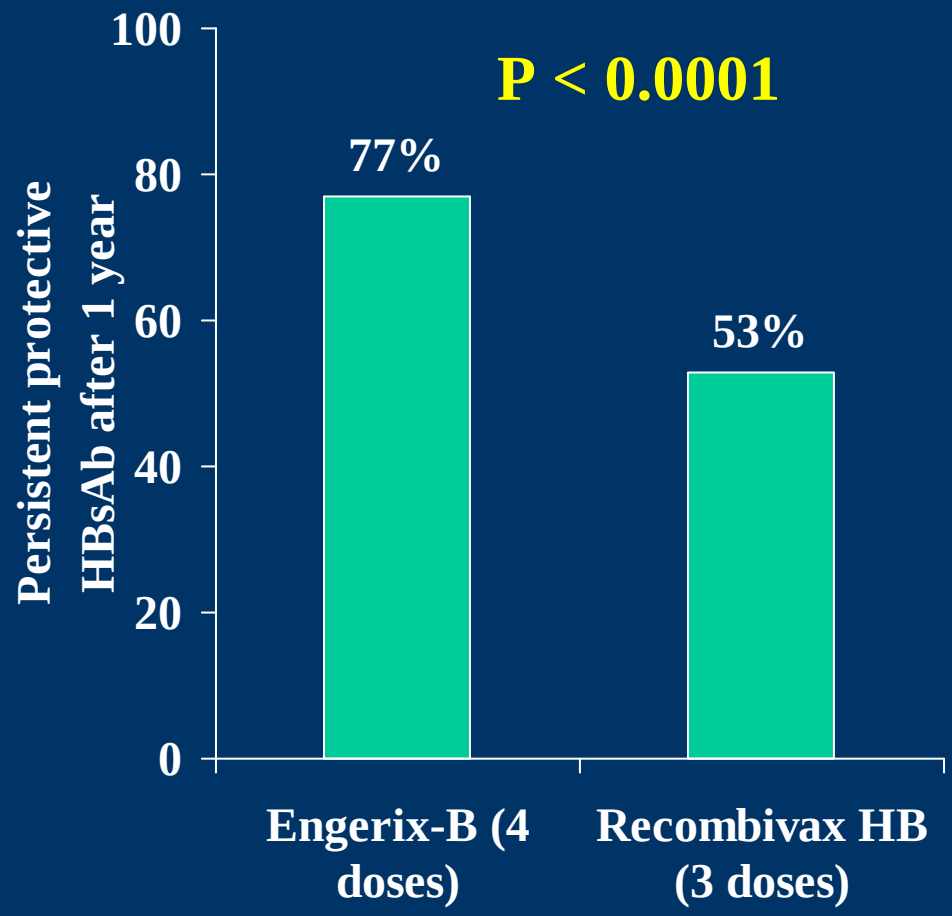
Averhoff F et al: Am J Prev Med 15:1-8, 1998
CDC: *MMWR* 50 (No. RR-5), 2001



Fraser GM et al: J Hepatol 21:450-4, 1994

Antibody Response to Engerix-B and Recombivax-HB Vaccination in Stage-5 CKD-D (N = 14,456)

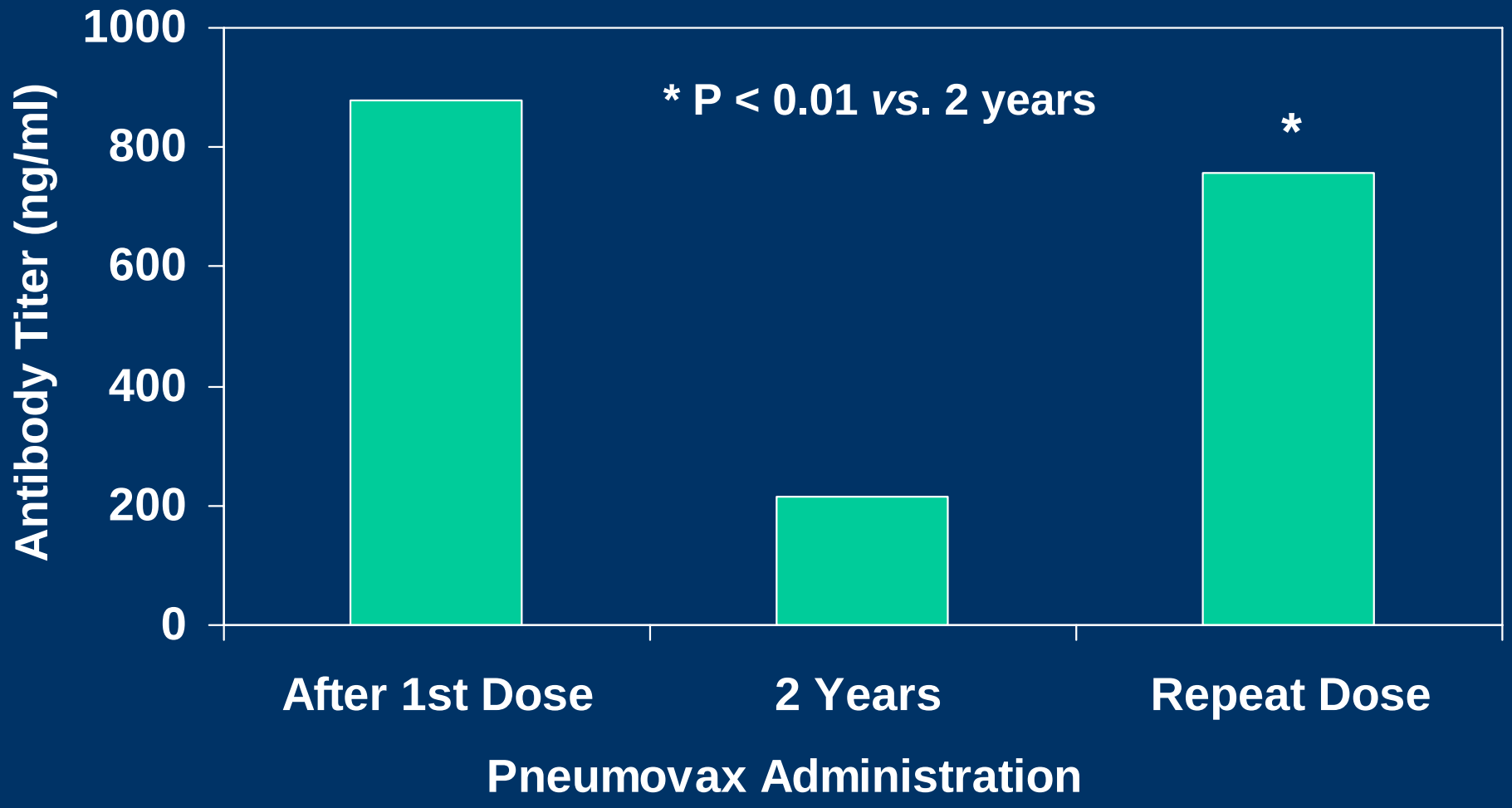




Odds ratio for antibody response to Engerix (vs. Recombivax) = 1.96 (95% CI 1.56, 2.45) adjusted for age, gender, race, diabetes, vintage, BSA, hemoglobin, and eKt/V

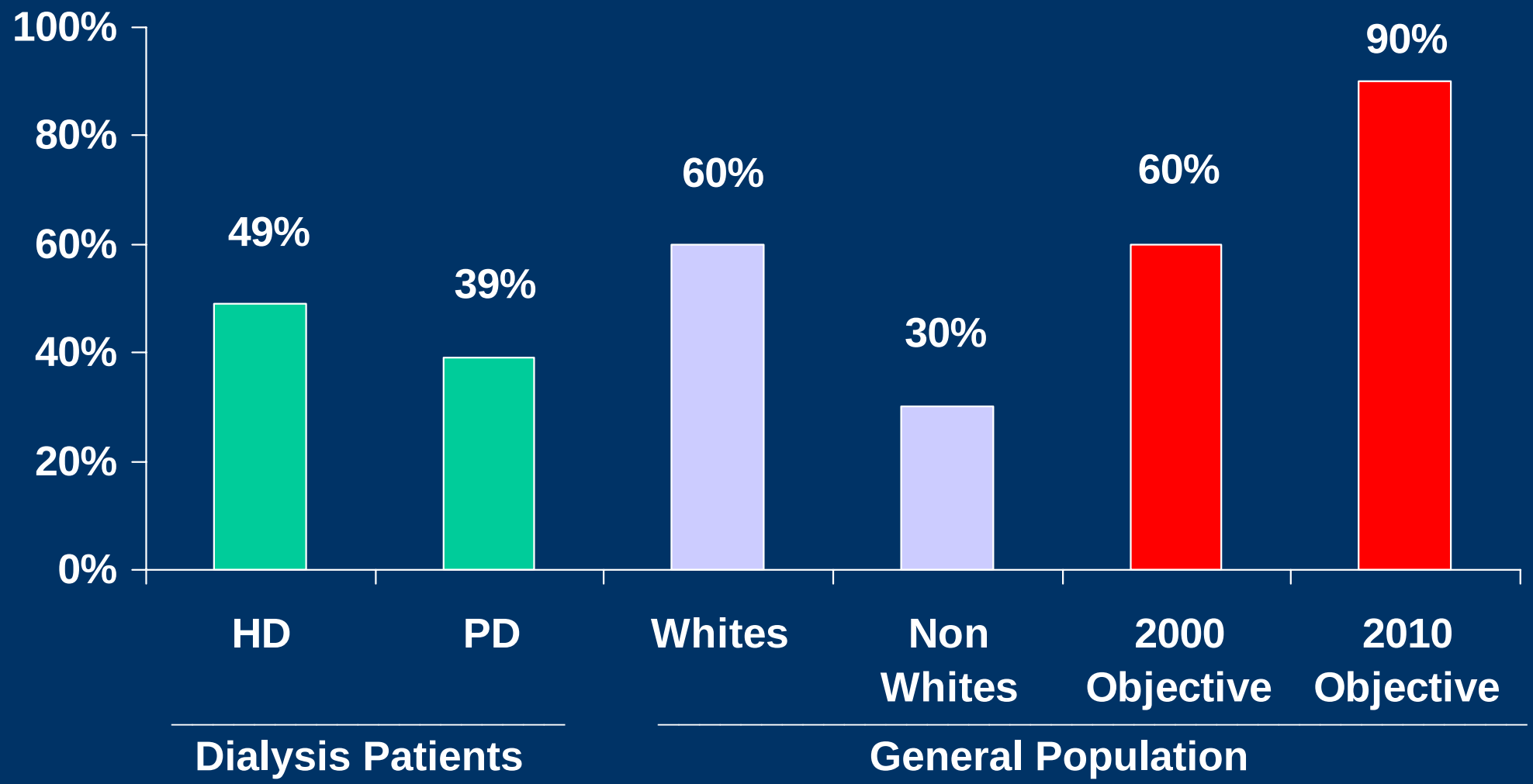
Lacson E et al: Hemodial Int 9:367-75, 2005

Pneumococcal Vaccine: Antibody Response in Dialysis Patients



Linnemann CC et al: *Arch Int Med* 146:1554-6, 1986

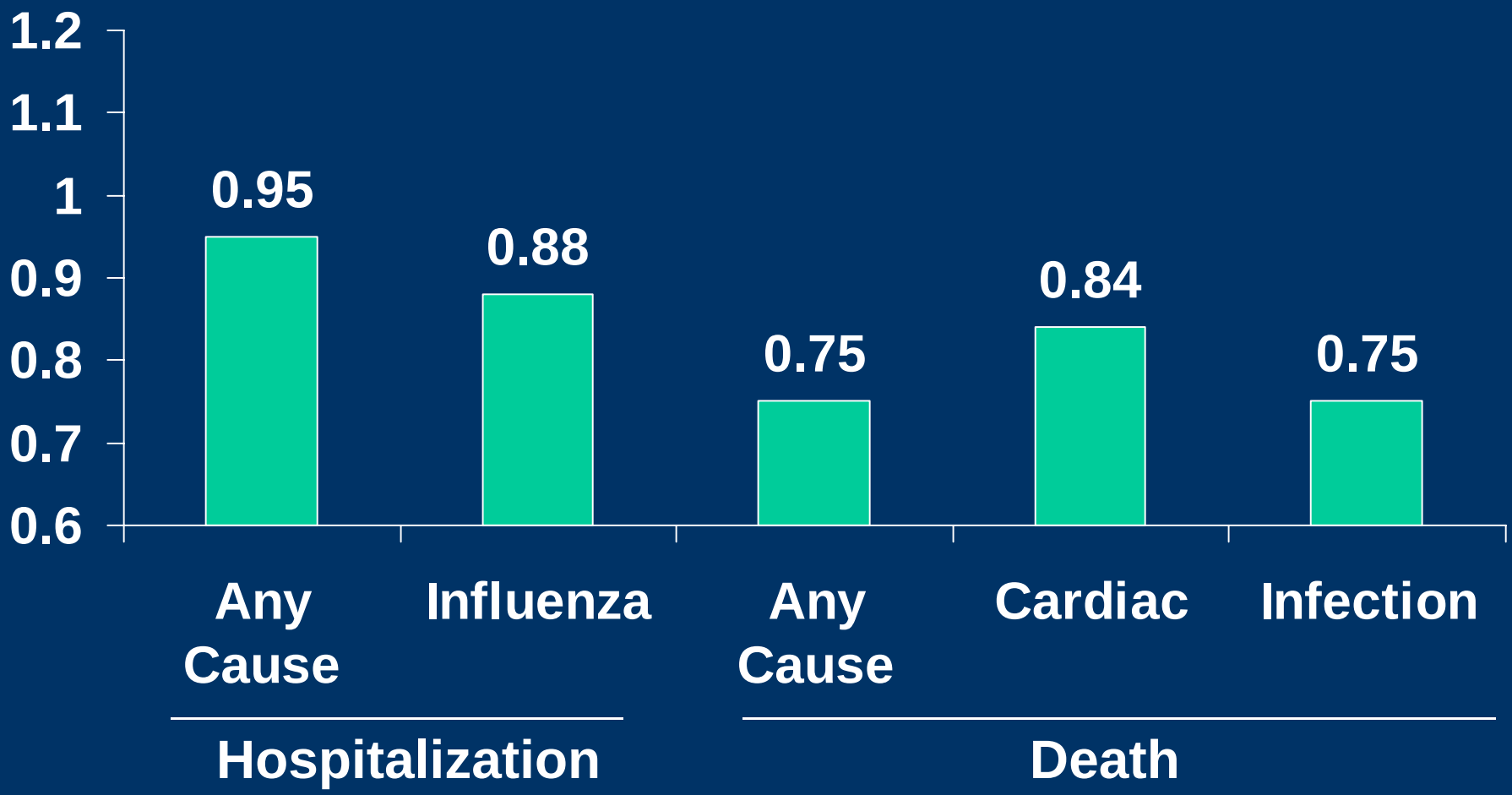
Influenza Vaccination Rates in CKD-5-D are Below U.S. National Objectives



MMWR 50:532-37, 2001

Gilbertson DT et al: *Kidney Int* 63:738-743, 2003

Odds of Hospitalization and Death are Lower among Vaccinated Dialysis Patients



Gilbertson DT et al: *Kidney Int* 63:738-743, 2003

What About Other Vaccines?

- Other vaccines such as diphteria, tetanus, polio (DTP) and are not well studied in CKD
- The usual schedule is recommended if indicated
- Protection is likely to be suboptimal as with other vaccines

Kausz AT & Gilbertson DT: Advances in Chronic Kidney Disease 13:209-214, 2006

Dinits-Pensy M et al: Am J Kidney Dise 46:997-1011, 2005

Workgroup Tasks: Clinical and Research Recommendations

- **Should we screen for CKD in chronic infectious diseases (HBV, HCV, and HIV)?**
- **Should we vaccinate in earlier stages of CKD (e.g. stage 4)?**
- **Do we need better tools to estimate kidney function in chronic infectious diseases (HBV, HCV, and HIV)?**