
The Changing Face of Infections in Transplant Recipients

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Today's major problems for transplant recipients

- **Organ shortage**
- **Long-term patient and graft survival**
- **Long-term morbidity**

Options for Immunosuppressive Regimens

Induction agent



Thymoglobulin
OKT3
IL2-R
Alemtuzumab

Primary agent



CsA
TAC
Sirolimus

Second agent



AZA
MMF
Sirolimus
FTY

Third agent



Prednisone

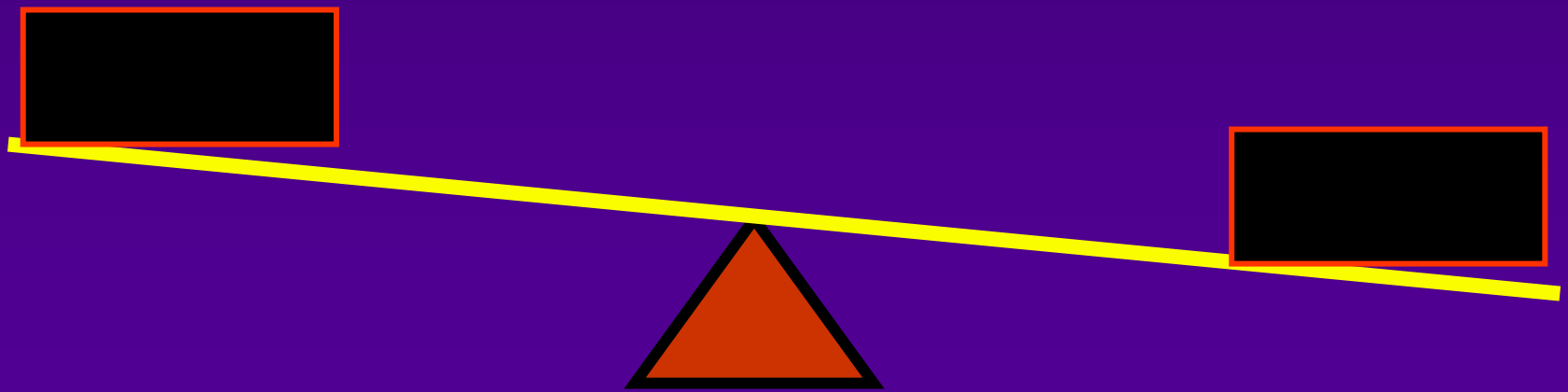
Factors leading to change in transplant infections

Favoring Infections

- Powerful immunosuppression
- Sicker patients
- Comorbid conditions

Against Infections

- Monitoring and diagnosis
- Prophylaxis and preemptive Rx
- More effective antinfective agents



Ways in which infections have changed in transplant recipients

Changes in transplant recipient infections can be divided into 2 broad categories:

- **New emerging infections**
- **Change in the character of existing infections**

**Ganciclovir
Valganciclovir
prophylaxis**

**More potent
immunosuppression
SRL, CAMPATH, others**

CMV

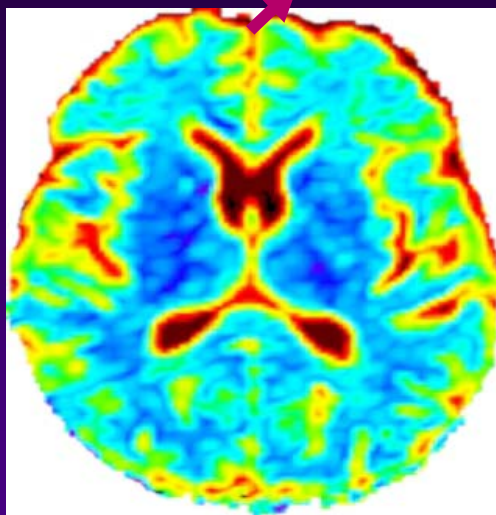
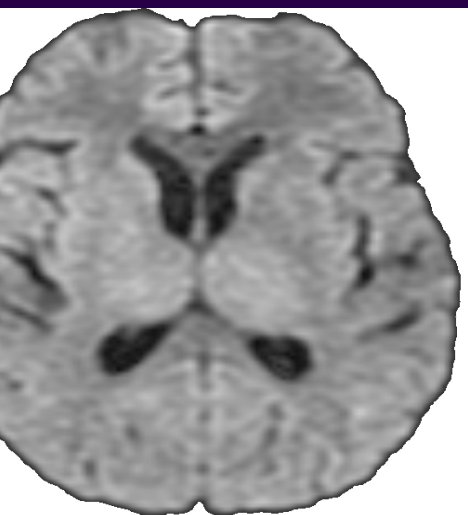
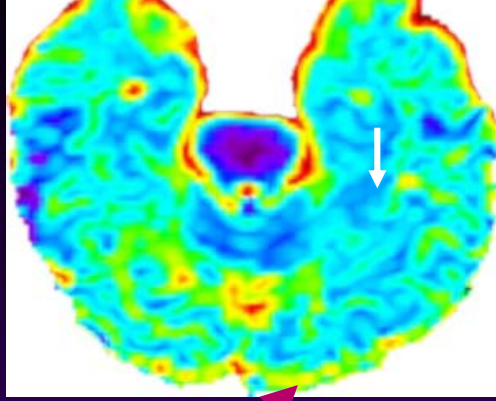
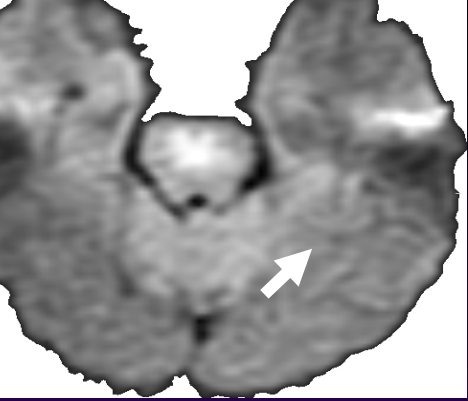
**Modified
presentation**

- Less severe
- Not as often TI

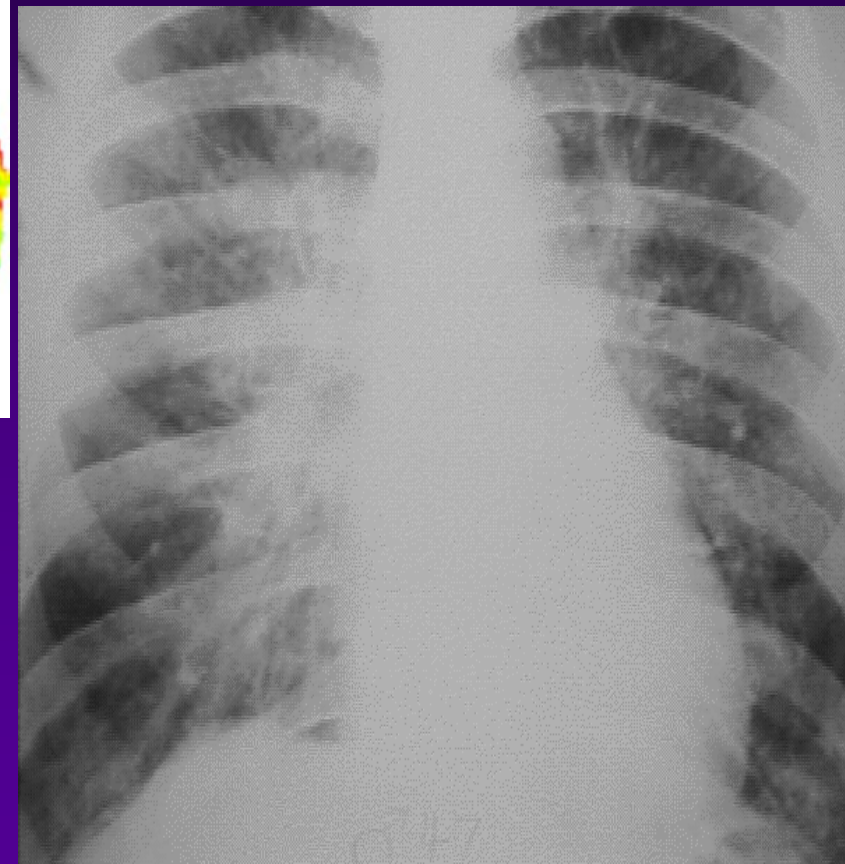
**Drug
resistance**

CMV: WHAT'S NEW

- **Late onset CMV disease**
 - >3 months posttransplant
 - Atypical presentations making diagnosis more difficult
- **Ganciclovir resistance**
 - D+/R- patients
 - Prolonged oral ganciclovir therapy
 - More potent immunosuppression
 - Incidence only about 2%- in some sub populations, up to 10%
 - Alternative therapies for CMV have significant toxicity



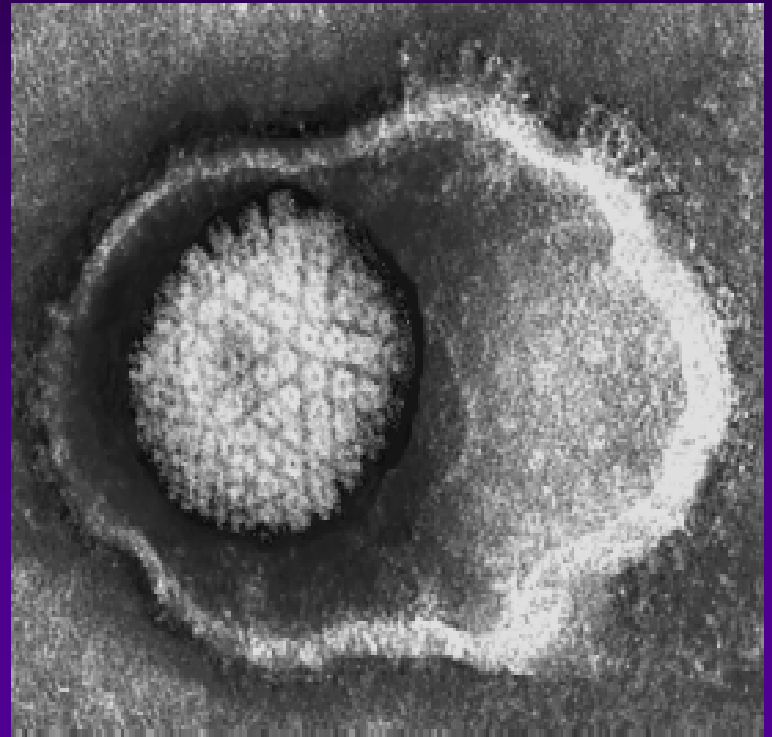
HHV-6 pneumonitis



HHV-6 encephalitis

Human Herpesvirus

- HHV-1/2 – HSV 1/2
- HHV-3 – VZV
- **HHV-4 – EBV**
- HHV-5 – CMV
- HHV-6,-7
- HHV-8 - KSHV

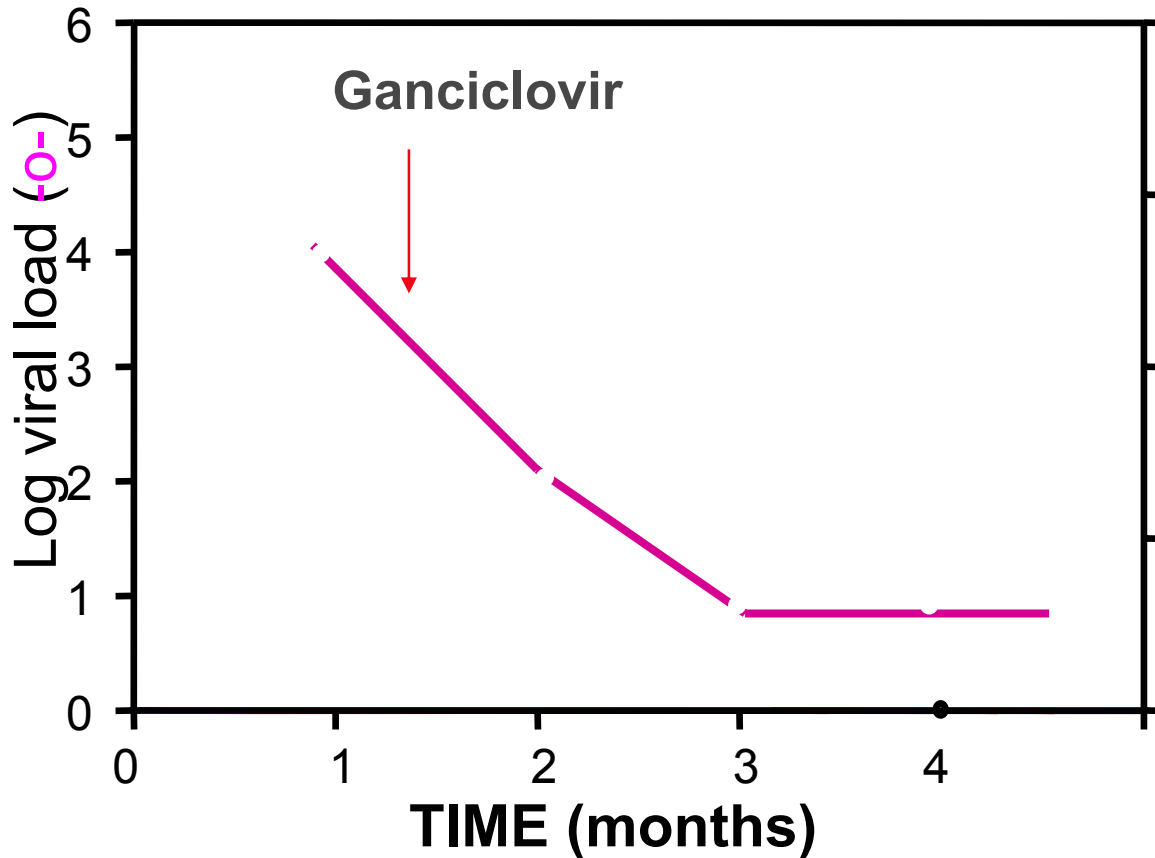


PTLD

DEFINITION:

- An abnormal proliferation of lymphocytes, most-commonly B-cells, usually driven by EBV





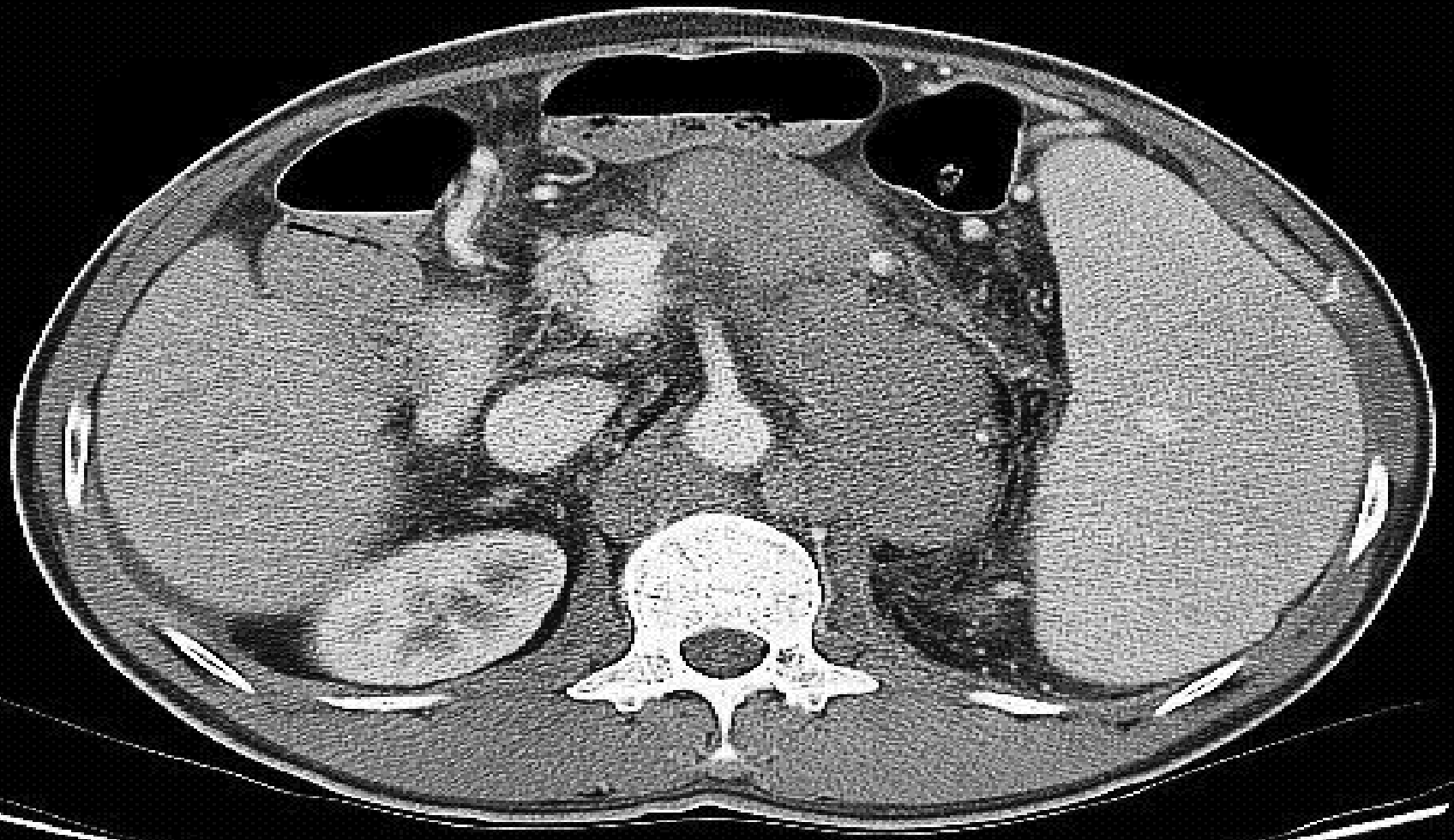
- High viral titres are associated with increased incidence of PTLD
- Viral titres may be reduced with antiviral agents

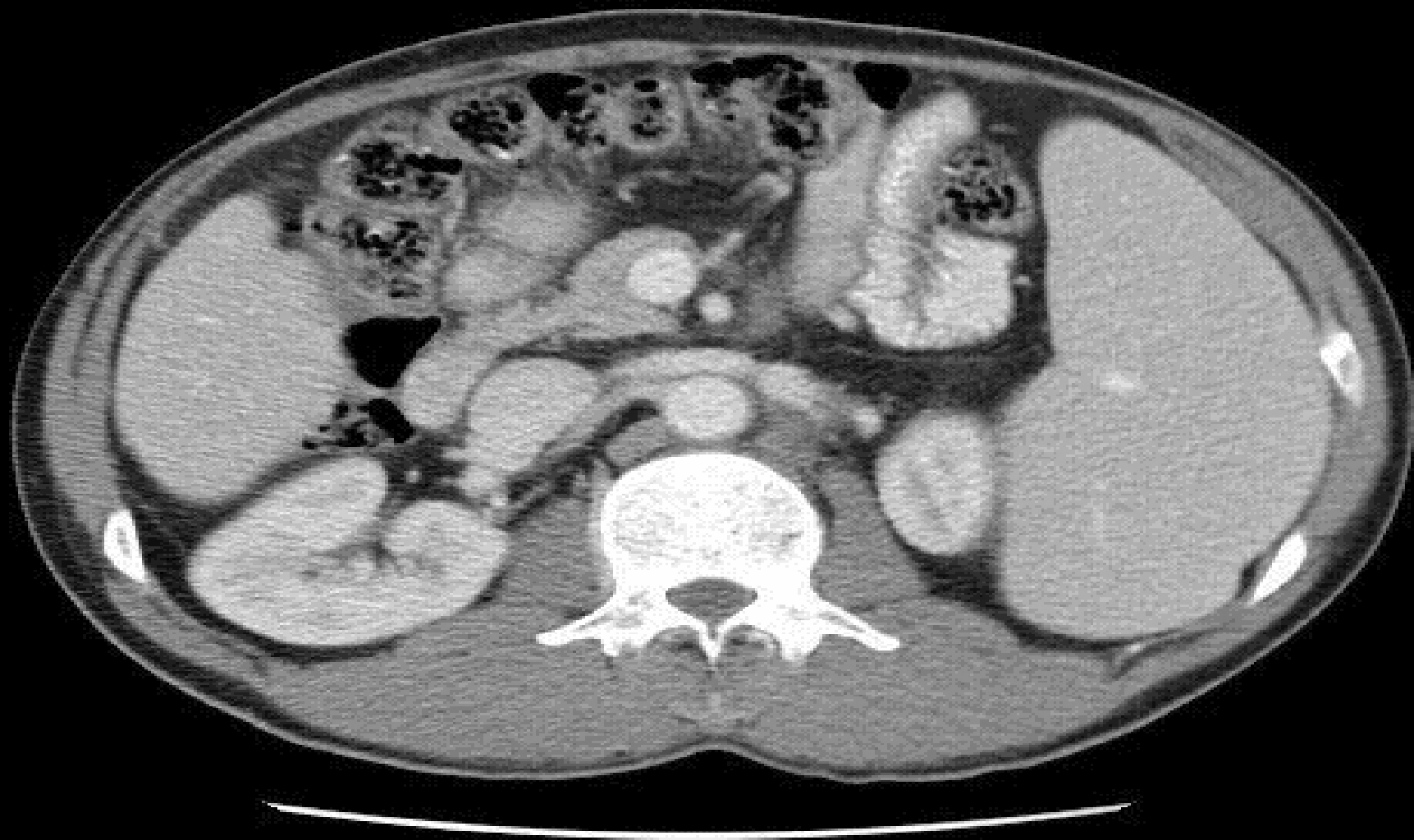
Preemptive Strategies

- **EBV viral load monitoring**
- **High and rising viral load triggering in patients at high risk for PTLD preemptive therapy**
- **This includes reduction in immunosuppression and/or the use of antiviral therapy +/- immunoglobulin or anti B cell therapy**

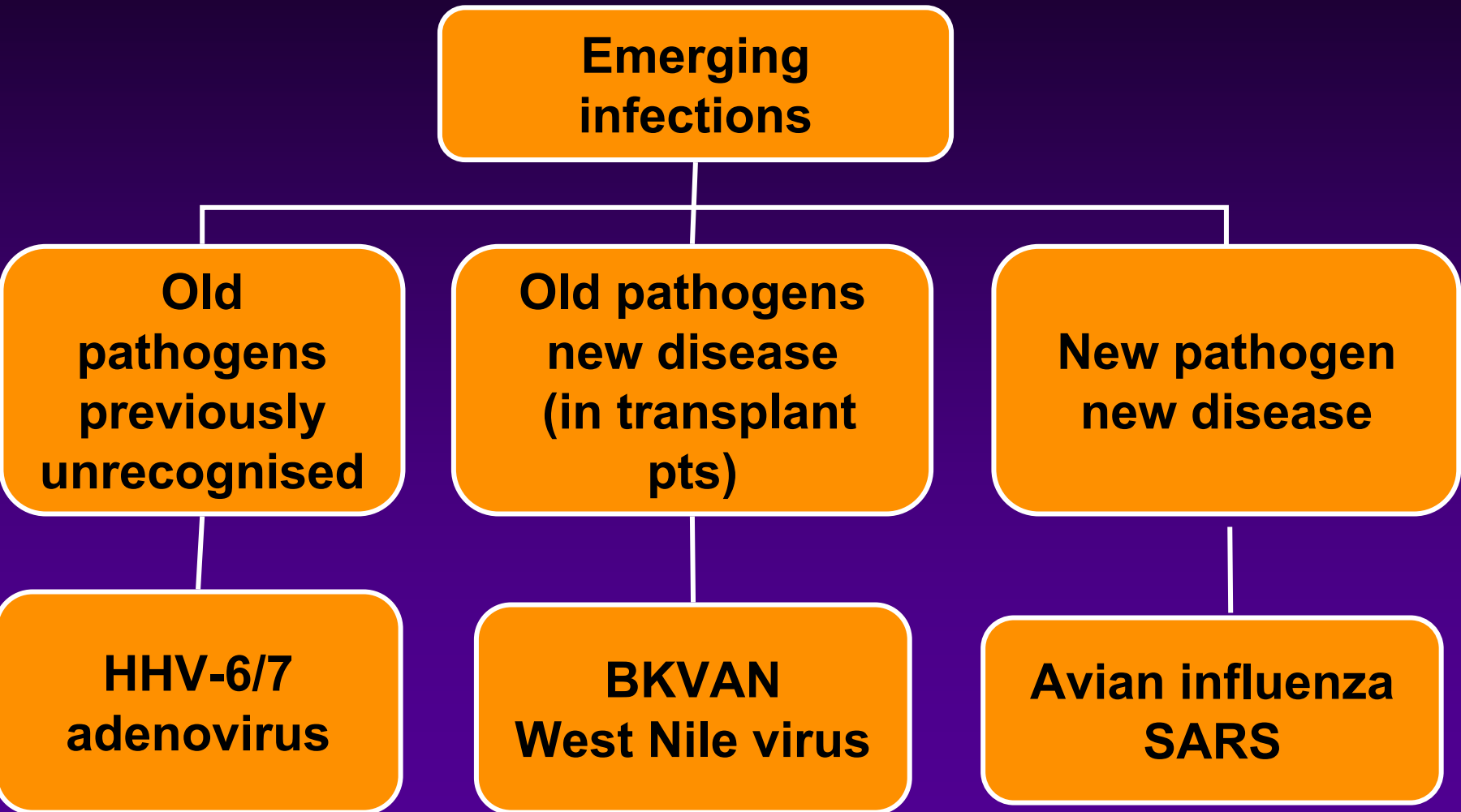
Treatment of FFLD-immunosuppression reduction combined with Monoclonal B cell antibody therapy antiCD20-- Rituximab

- **Most studies show RR of between 60-80%**
- **Most show CR of between 50-60%**
- **Well tolerated regimens**

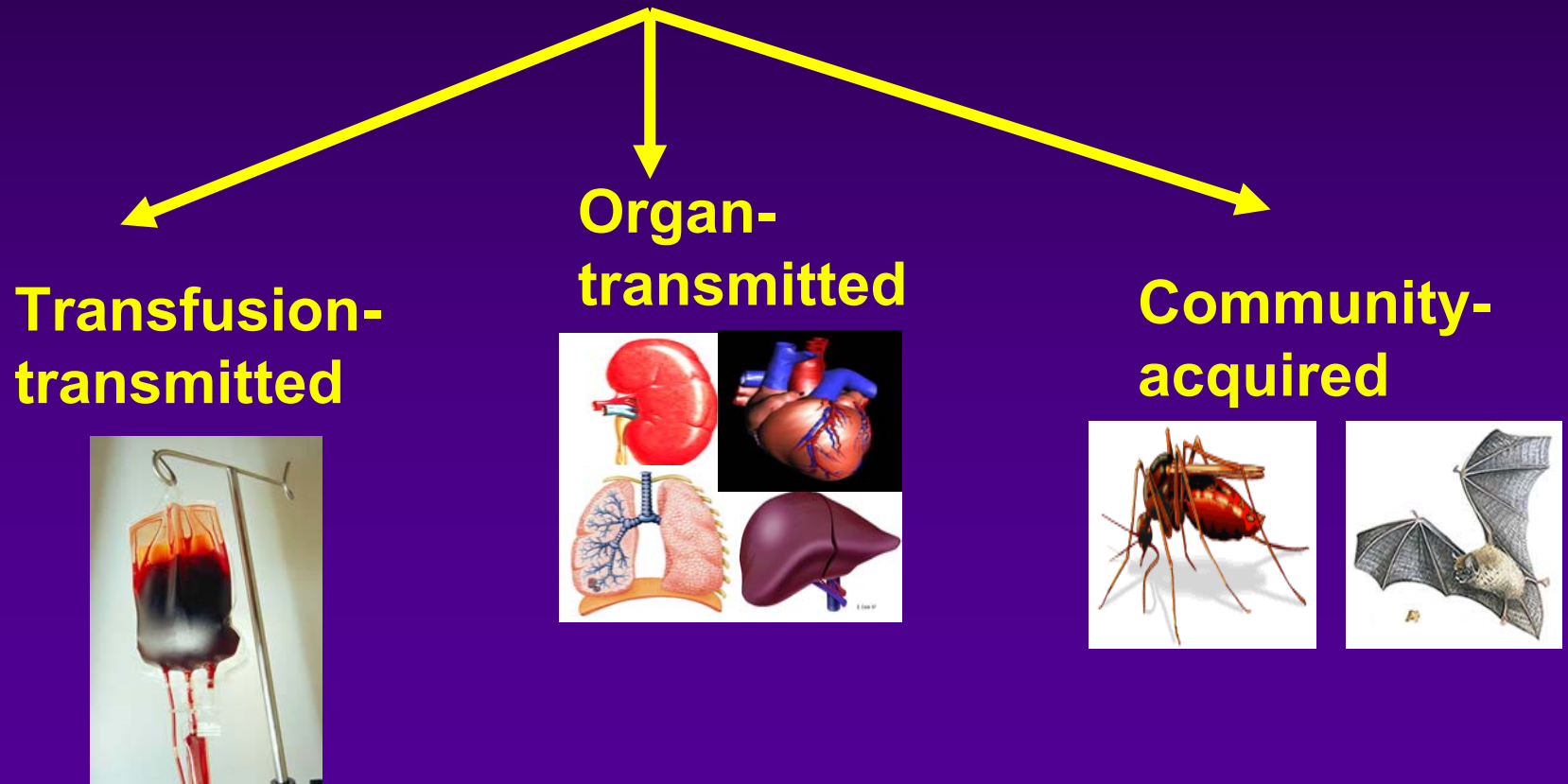




Emerging infections in transplant

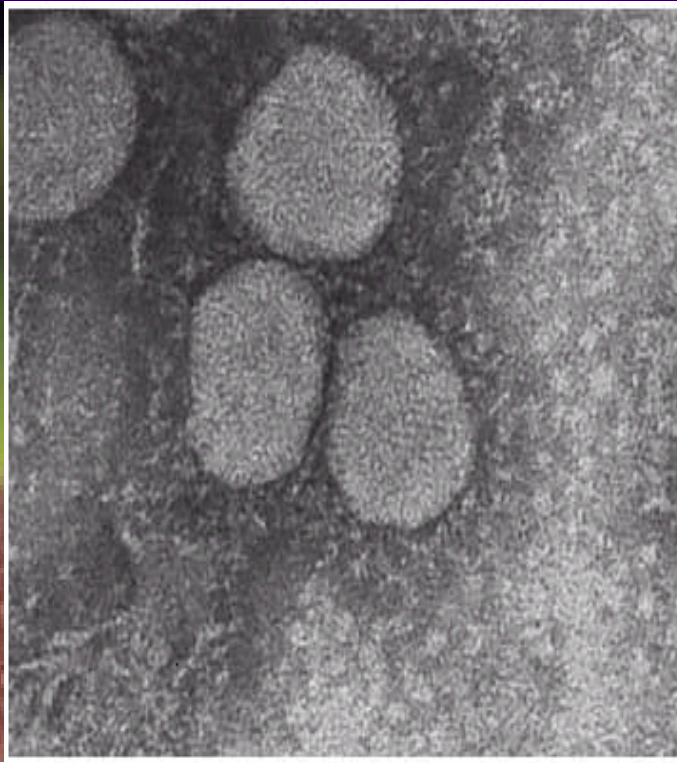


- **Transplant patients can potentially acquire a new pathogen in 3 ways:**



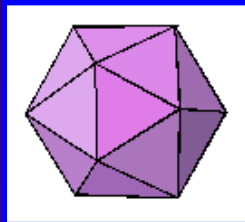
Emerging Infections:

Unusual donor transmitted infections



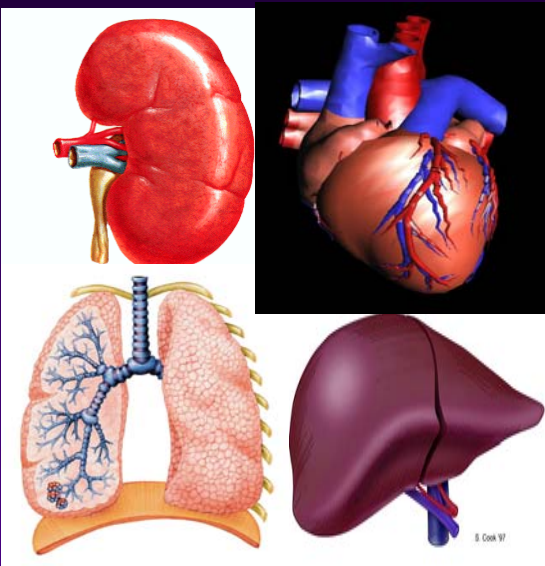
- West Nile Virus
- Rabies
- LCMV
- Others?

WEST NILE VIRUS



Incidence of severe disease (encephalitis, flaccid paralysis): 1:140 infections Or $< 1\%$

816 Transplant Patients



WNV IgG/IgM



Seroprevalence study
(0.25%; 95%CI 0.03-0.88%)



Estimated risk of severe neuroinvasive disease
40% (95%CI 16-80%)

WNV: Transfusion Transmitted

- In the U.S. 23 cases of TTWNV (2002)
- 13/23 developed meningoencephalitis
 - 10 patients Immunocompromised (cancer,transplant,others)
 - Mortality of TTWNV 29%

ORGAN DONOR TRANSMITTED WNV

- **Of the 23 cases of TTWNV-- One of these patient went on to donate 4 organs**
- **3 / 4 recipients meningoencephalitis,**
 - **7-17 days post-transplant**

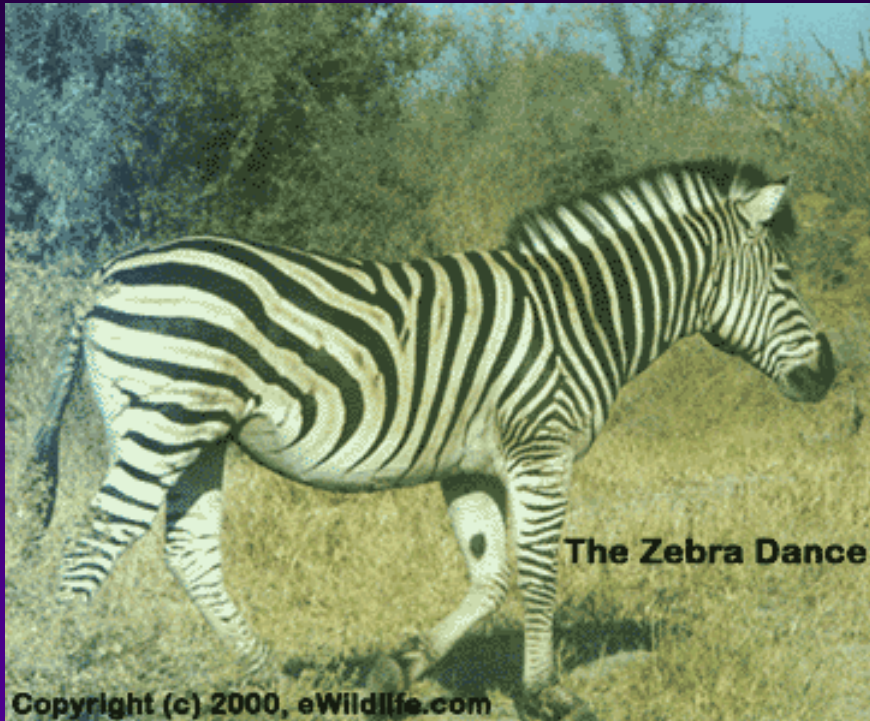
WHAT ABOUT OTHER UNUSUAL INFECTIONS?



RABIES ENCEPHALITIS

- **Four recipients of kidneys, liver, and of an iliac artery graft died of encephalitis of unknown cause.**
 - **Onset within 21-27 days of surgery**
 - **Death a median of 11.5 days (17-23, days later)**
- **Donor presented 4 days prior (fever, mental status changes)**
 - **Cocaine-induced subarachnoid hemorrhage**
 - **In retrospect had a bat bite earlier**
- **Similar case report recently from Germany**

Emerging infections: acquired infections



- Avian Influenza
- SARS
- Others?

“Bird Flu”

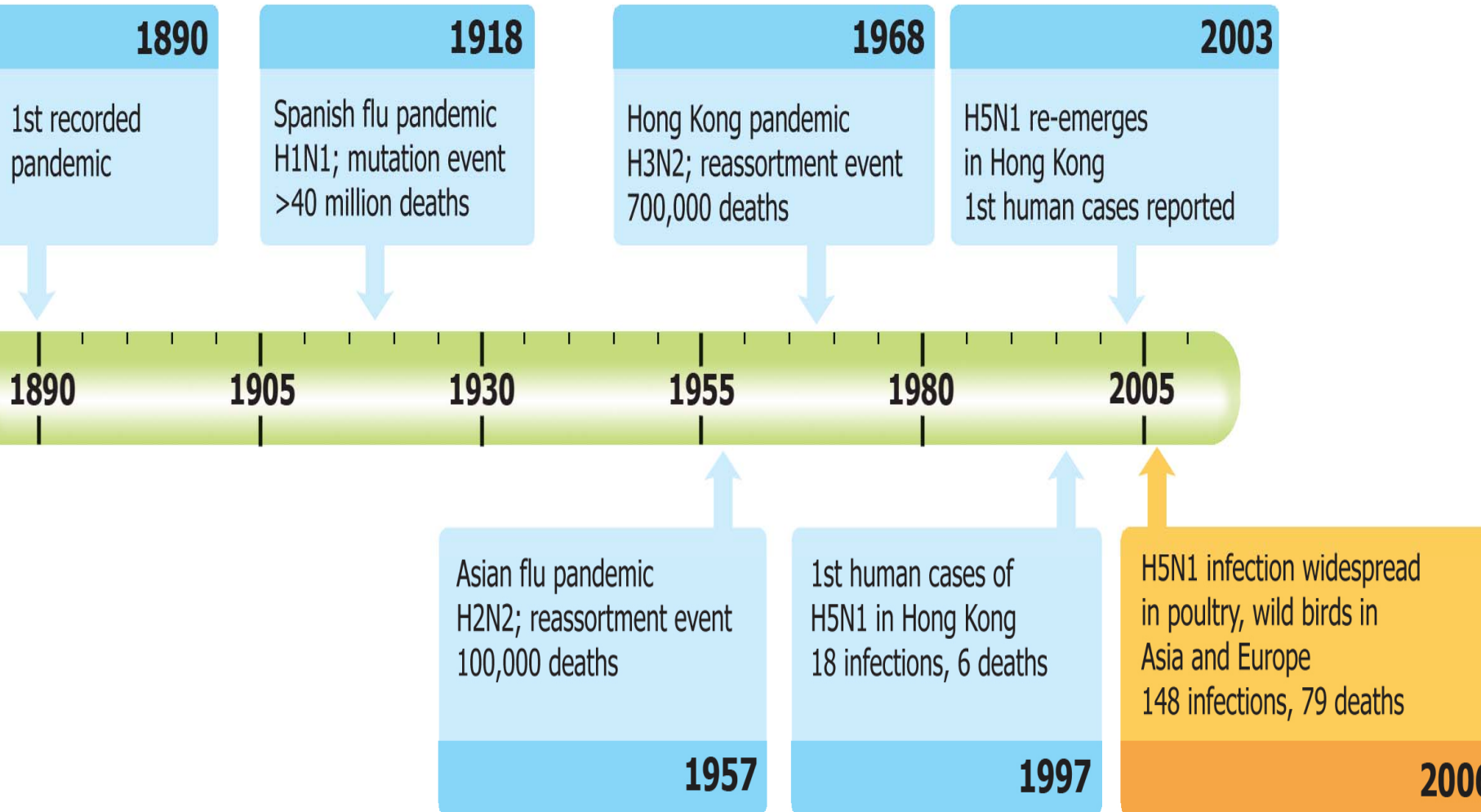
- How might this impact on transplant patients?

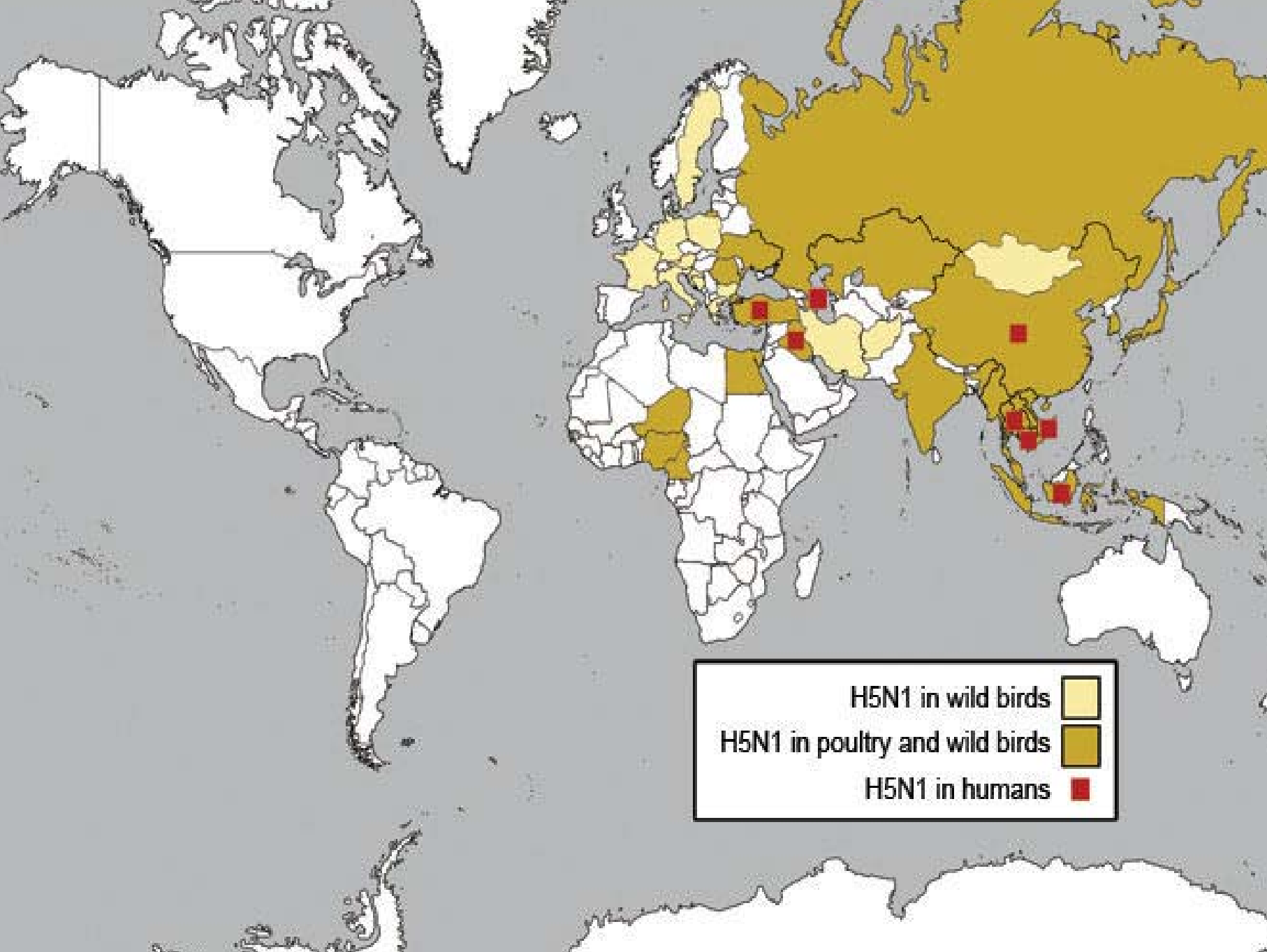


H5N1 Influenza

- **Since 2003 – unprecedented spread of Avian H5N1 virus through Asia/Europe**
- **Sporadic bird-to-human transmission but no efficient human-to-human transmission**
- **Human cases unusually aggressive clinical course with rapid deterioration, primary viral pneumonia and multi-organ failure (~ 50% mortality)**

Timeline Of Pandemics





H5N1 in wild birds



H5N1 in poultry and wild birds



H5N1 in humans

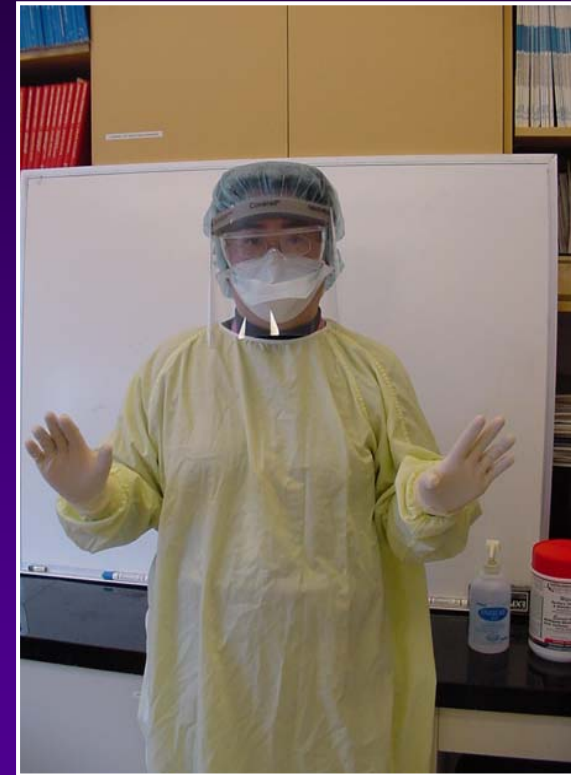


Pandemic Flu and the Transplant Patient

- **More chances of exposure**
- **More likely to develop symptomatic disease if exposed to a pathogen**
- **Once exposed, more rapidly progressive lethal disease**
- **Higher viral burden – longer viral shedding with increased amounts of virus**
 - **Increased infectivity**
 - **Super-spreaders**
- **Lack of response to therapeutic measures**
 - **Standard antiviral may have less efficacy**
 - **Decreased immunogenicity of vaccines**

What about the Transplant Program?

- In the event of a pandemic – it is likely that most transplant programs will close
 - Safety of recipients in hospitals
 - Transmission from donors
 - Concern re utilization of hospital resources



SARS

- Acute respiratory illness due to novel SARS CoV
- 2-10 day incubation period
- Spread primarily via droplets
- Probable origin from an animal coronavirus



SARS-1

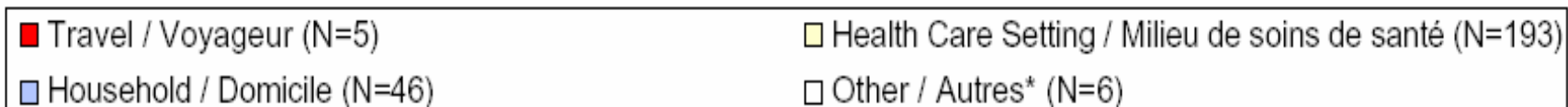
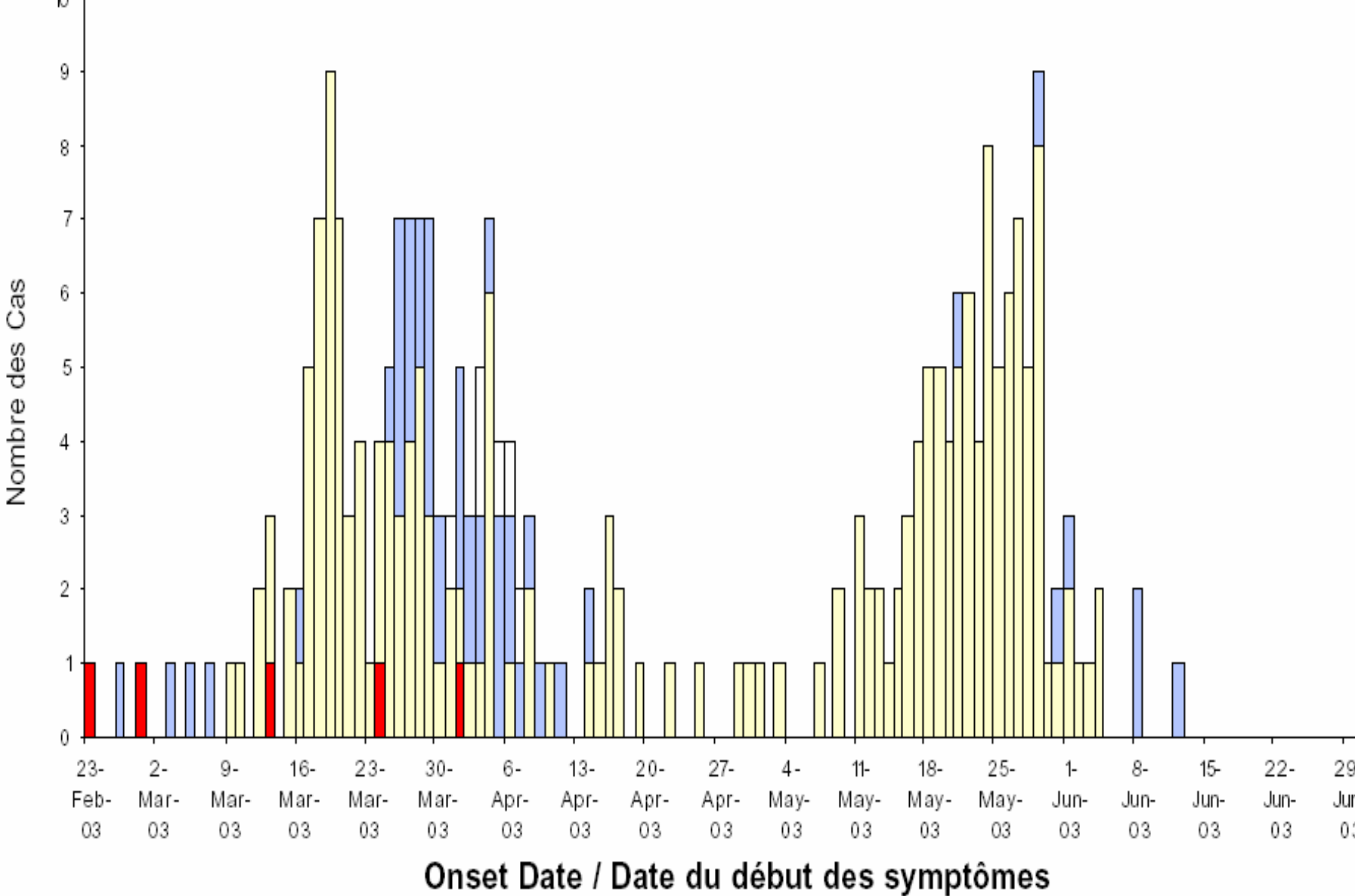
- 74 y.o. 10 years post OLTx; CsA + pred
- Community hospital for outpatient foot doctor appt.
- 5 days later high fever, chills, cough, and myalgias; then progressive SOB, intubation
- BAL positive by RT-PCR for SARS CoV

Contact Tracing

- **Exposed:**
 - wife and two children,
 - FP + office staff;
 - 2 visitors,
 - 11 individuals involved in transfer of the patient
 - 68 staff primarily those involved in the patients ICU care
- **Suspect or probable SARS occurred in 10 persons:**
 - patient's wife, family physician, two visitors, 6 staff at ICU
- **1 death**

TISSUE VIRAL LOADS ($\times 10^3$ copies/gram)

Tissue	Transplant	Non-transplant
Lung	8,760,000	360
Heart	28,000	32
Kidney	740	48
Liver	1600	18
Spleen	140	48
Lymph Node	890,000	710
Large Bowel	370,000	130
Small Bowel	240,000	270



Conclusions

- **Infectious complications continually evolve in transplant patients**
- **Constant vigilance in the face of emerging infections**
- **WNV and SARS provide important lessons:**
 - **Transplant patients are uniquely predisposed to emerging infections**
 - **Transplant programs must continually adapt to new infectious challenges**