Epidemiologia delle infezioni nel trapiantato di fegato

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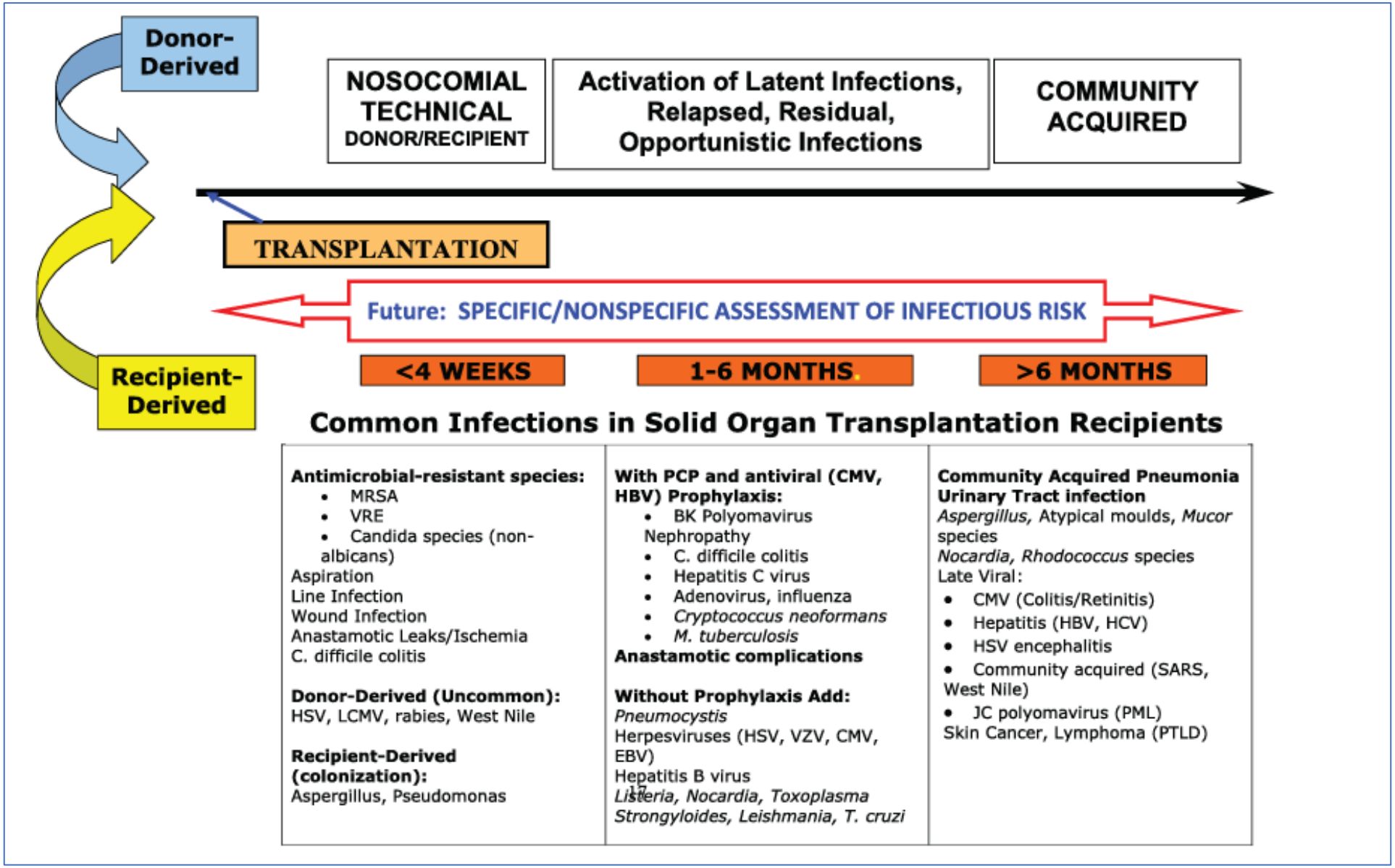
The timeline of post-transplant infections

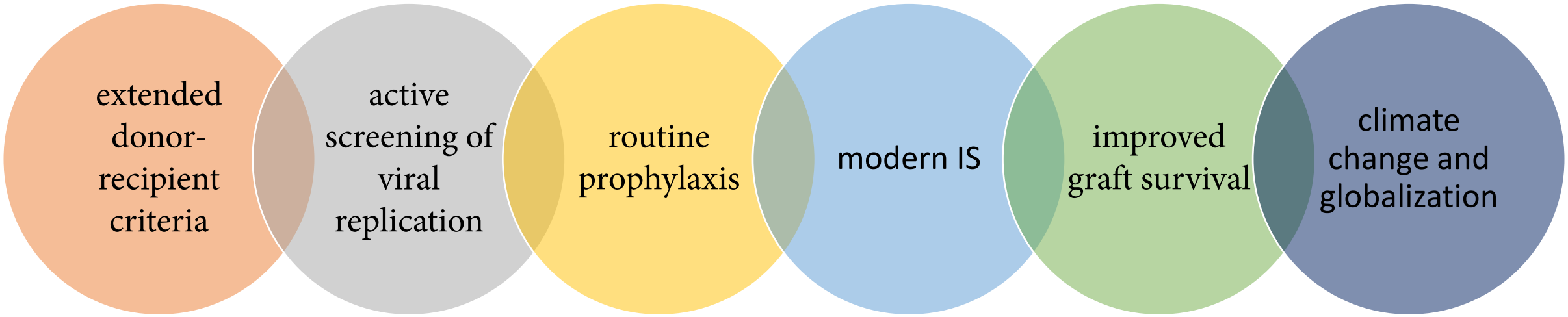


Common Infections in Solid Organ Transplantation Recipients

Antimicrobial-resistant species: • MRSA • VRE • Candida species (non-albicans) Aspiration Line Infection Wound Infection Anastamotic Leaks/Ischemia C. difficile colitis **Donor-Derived (Uncommon):** HSV, LCMV, rabies, West Nile **Recipient-Derived (colonization):** Aspergillus, Pseudomonas	**With PCP and antiviral (CMV, HBV) Prophylaxis:** • BK Polyomavirus Nephropathy • C. difficile colitis • Hepatitis C virus • Adenovirus, influenza • *Cryptococcus neoformans* • *M. tuberculosis* **Anastamotic complications** **Without Prophylaxis Add:** *Pneumocystis* Herpesviruses (HSV, VZV, CMV, EBV) Hepatitis B virus *Listeria, Nocardia, Toxoplasma* *Strongyloides, Leishmania, T. cruzi*	**Community Acquired Pneumonia** **Urinary Tract infection** *Aspergillus,* Atypical moulds, *Mucor* species *Nocardia, Rhodococcus* species Late Viral: • CMV (Colitis/Retinitis) • Hepatitis (HBV, HCV) • HSV encephalitis • Community acquired (SARS, West Nile) • JC polyomavirus (PML) Skin Cancer, Lymphoma (PTLD)

Fishman JA et al. N Engl J Med 1998; 338:1741–51

Consider alterations in the epidemiology and timeline



Specific risk factors of liver transplant recipients

- Pretransplant colonization with MDR bacteria
- Pretransplant bacterial infection
- Surgical approach and surgical complications

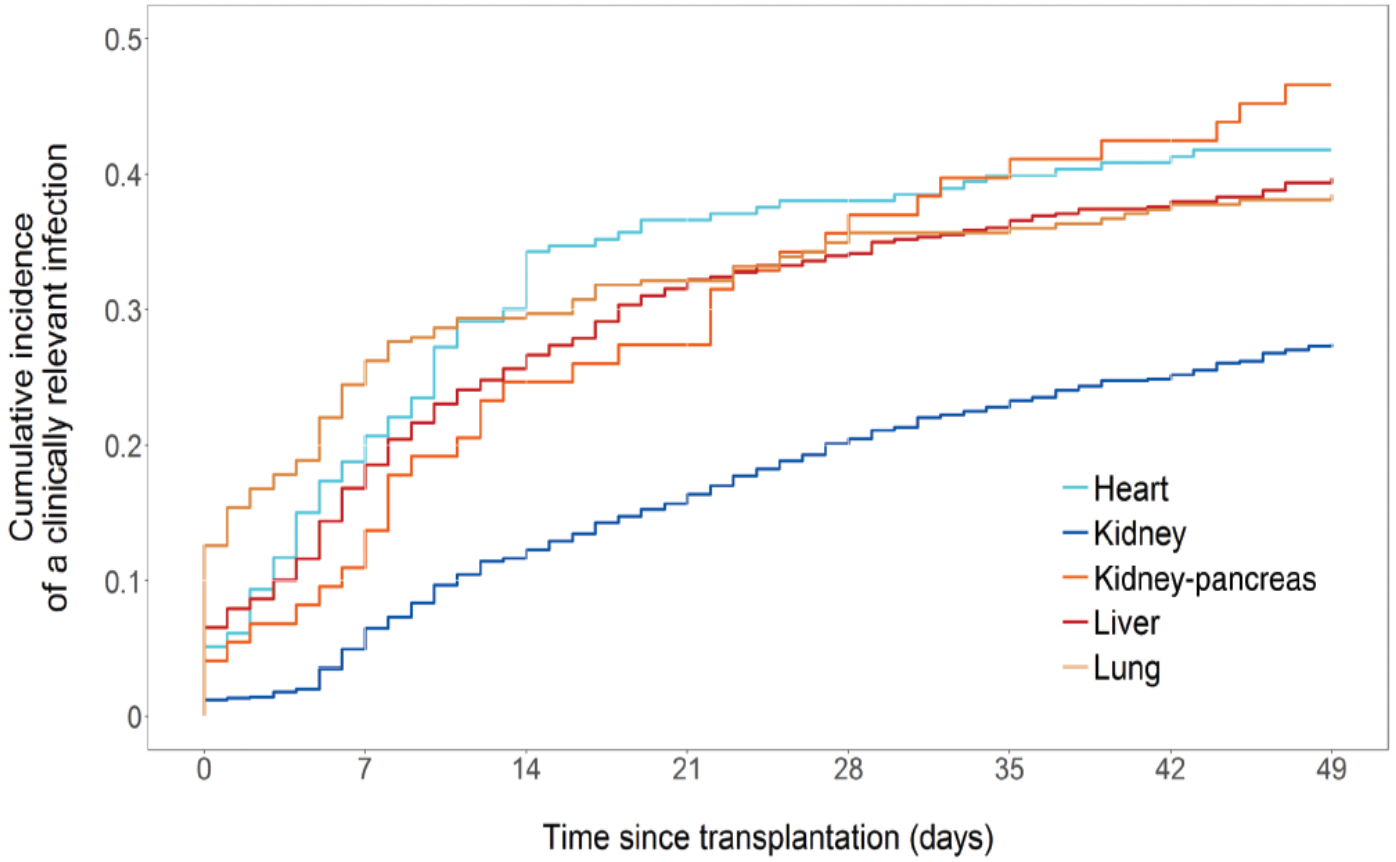
Burden and timeline of infectious diseases in the first year after SOT

prospective study -the Swiss Transplant Cohort

SOT 2008 -2014 with ≥12 months of follow-up: 577/ 2761 (21%) liver transplant

55% suffered 3520 infections during the first year after SOT

Infection accounted for 42% of the deaths



Cumulative incidence 1 year after SOT

- 53% for kidney
- **55% for liver**
- 60% for heart and kidney-pancreas
- 62% for lung transplant

van Delden et al Clinical Infectious Diseases 2020;71(7)

Early post-liver transplantation infections and their effect on long-term survival

- A total of 143/317 (45%) of patients suffered from any infectious episodebduring the first 6 months following liver transplantation

Infectious episodes per patient, no. (%)	
None	174
1 episode	81
2 episodes	38
3 episodes	18
4-5 episodes	6

		95 CI		
Multivariate analysis	HR	Lower	Upper	*P*-value
>1 infection	1.58	1.03	2.43	.03
Gender (male)	0.52	0.34	0.80	.003
Age (y)	1.02	1.00	1.04	.006
MELD score at transplantation	1.02	1.00	1.05	.050

Leibovici et al. Transpl Infect Dis. 2021;23

Rates of infections per 1000 liver transplant-days

0-1 month

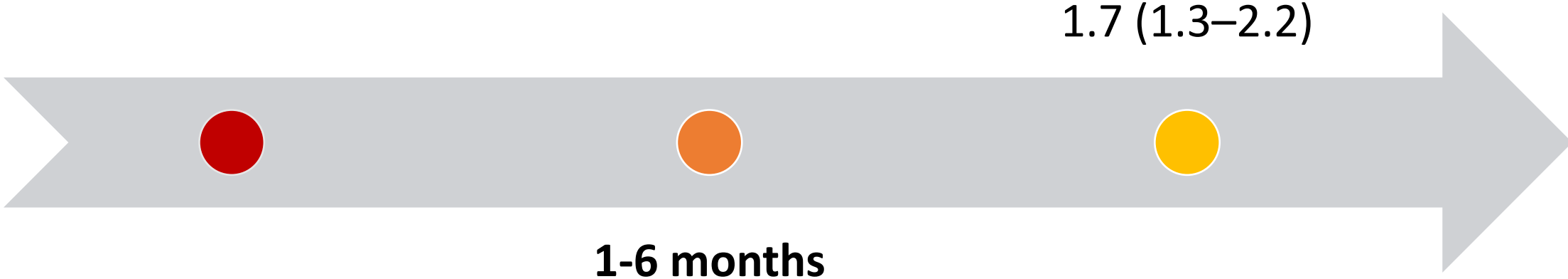
16.4 (14.3–18.8)

1-6 months

3.3 (2.7–3.9)

6-12 months

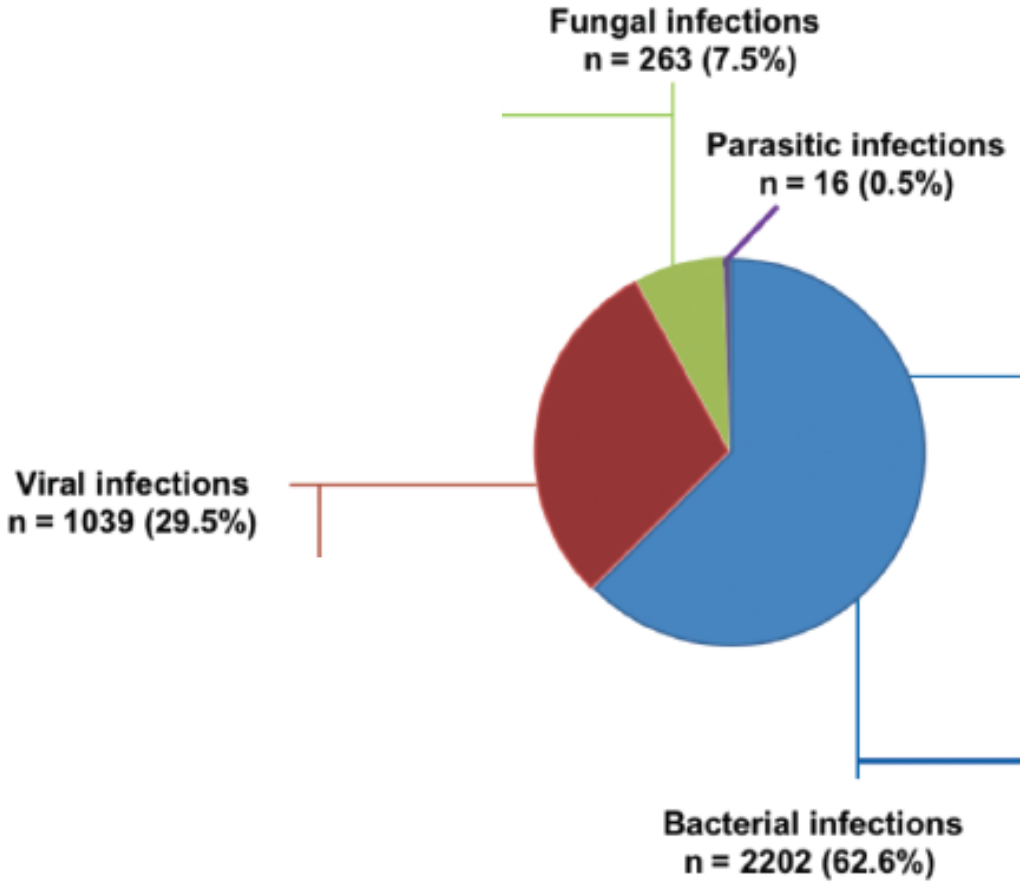
1.7 (1.3–2.2)



van Delden et al Clinical Infectious Diseases 2020;71(7)

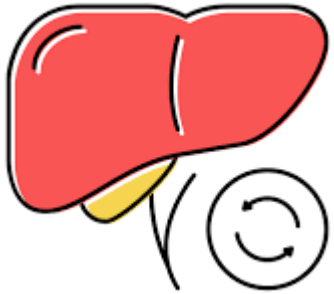
Incidence and distribution of clinically relevant infections

All SOT, n≈ 2761



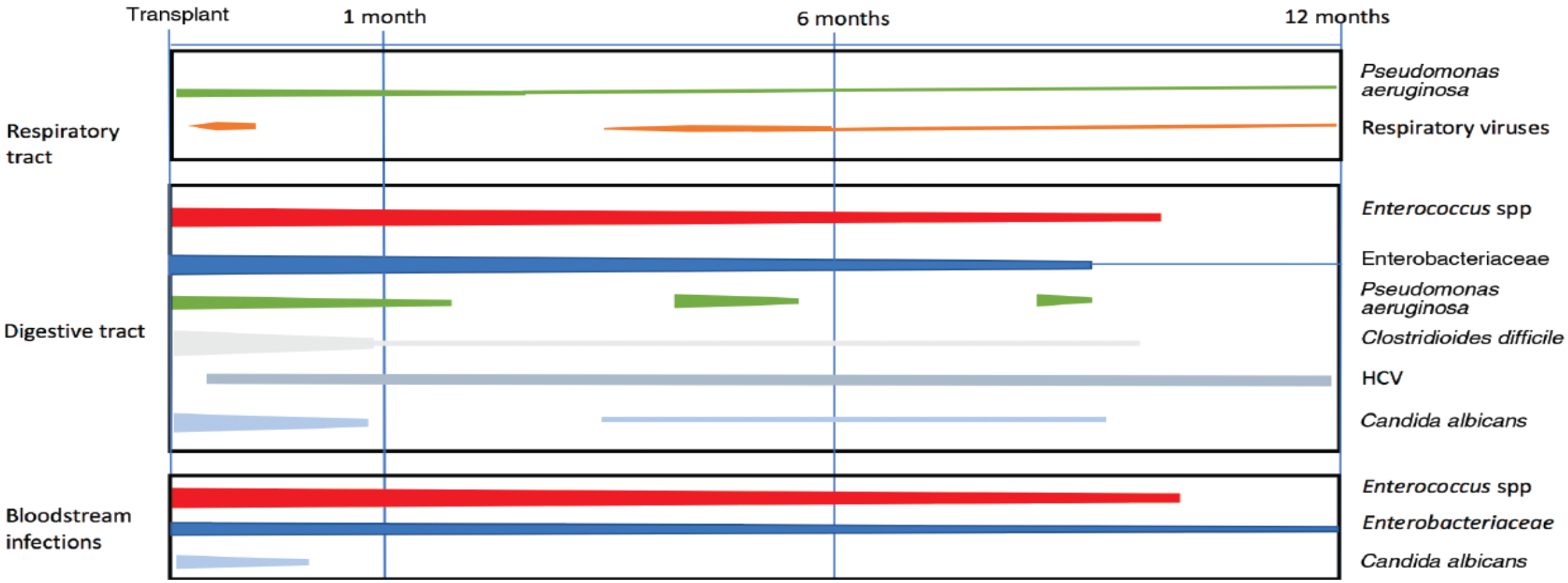
Liver transplant recipients n ≈ 725

- **Bacterial infections 59%**
- **Viral infections 33%**
- **Fungal infections 8%**
- **Parasitic infections 4%**



van Delden et al Clinical Infectious Diseases 2020;71(7)

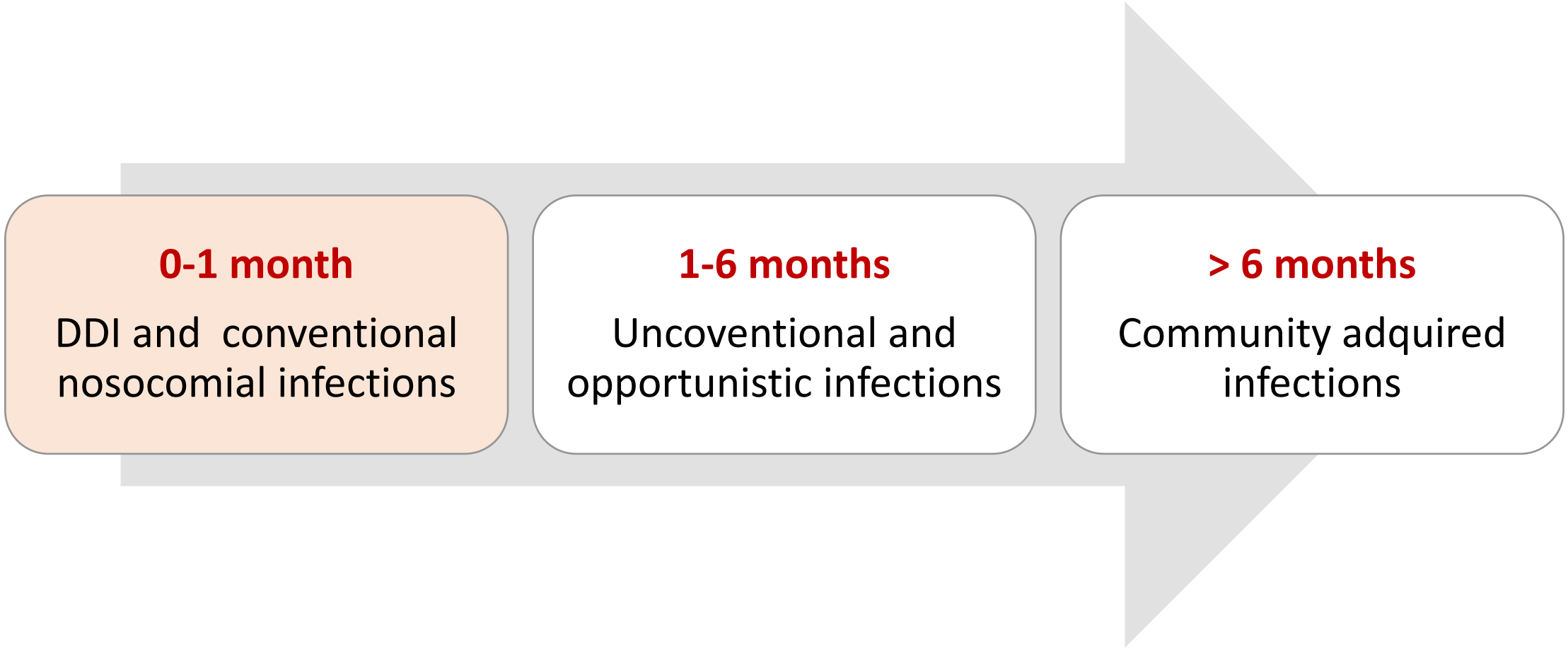
Timelines clinically relevant infections in liver transplant recipients according to predominant infection sites



van Delden et al Clinical Infectious Diseases 2020;71(7)

The timeline of post-transplant infections

The timeline of post-transplant infections



Up to 1 month

- DDI
  - Major hepatitis
  - Bacteremic donor
  - Preservation fluid
- Nosocomial infections
  - SSI
  - Abdominal infections
  - C.difficile

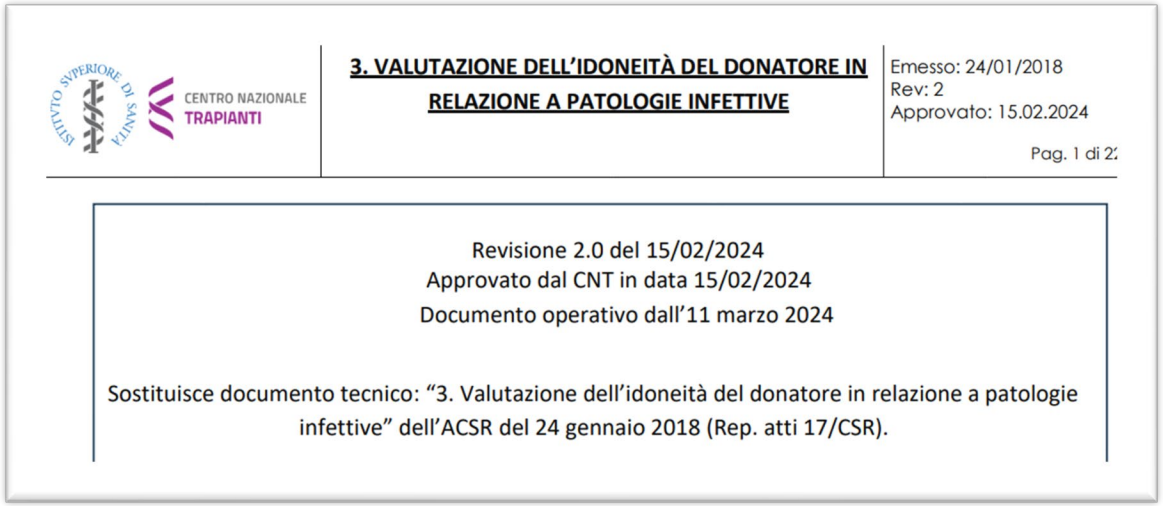
Up to 1 month

- **DDI**
  - **Major hepatitis**
  - Bacteremic donor
  - Preservation fluid
- Nosocomial infections
  - SSI
  - Abdominal infections
  - C.difficile

Expected and unexpected donor derived infections

- **Expected infections**
  - **the donor is known to have an infection**
  - positive serology or NAT results (CMV, EBV, HBV, HCV) or positive cultures in the donor at donation
  - microbiologic monitoring, pre-emptive therapy and/or universal prophylaxis to minimize the impact of the disease transmissions
- **Unexpected infections**
  - **the donor is not known to be infected prior to donation** : not recognized or not screened
  - viral pathogens (HIV, HCV, LCMV, rabies, WNV), fungal infections, *Mycobacterium tuberculosis* or MDR bacteria

- https://www.trapianti.salute.gov.it/imgs/C_17_cntPubblicazioni_620_allegato.pdf
- https://www.edqm.eu/en/guide-quality-and-safety-of-organs-for-transplantation



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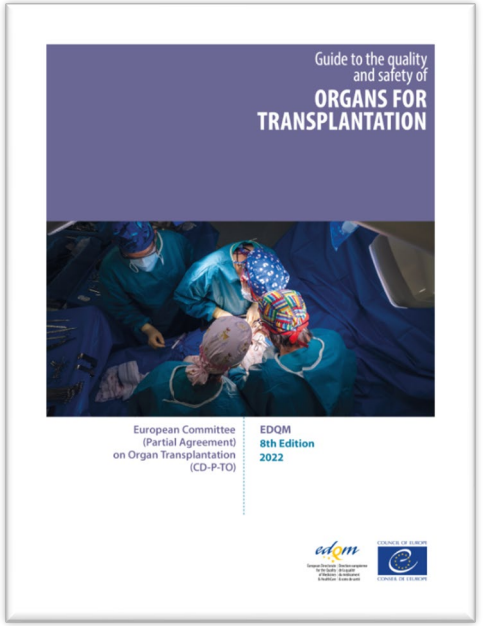
3. VALUTAZIONE DELL'IDONEITÀ DEL DONATORE IN RELAZIONE A PATOLOGIE INFETTIVE

Emesso: 24/01/2018
Rev: 2
Approvato: 15.02.2024
Pag. 1 di 2

Revisione 2.0 del 15/02/2024
Approvato dal CNT in data 15/02/2024
Documento operativo dall'11 marzo 2024

Sostituisce documento tecnico: "3. Valutazione dell'idoneità del donatore in relazione a patologie infettive" dell'ACSR del 24 gennaio 2018 (Rep. atti 17/CSR).



- HBcAb positive donor
- HBsAg positive donor
- anti-HCV positive donor

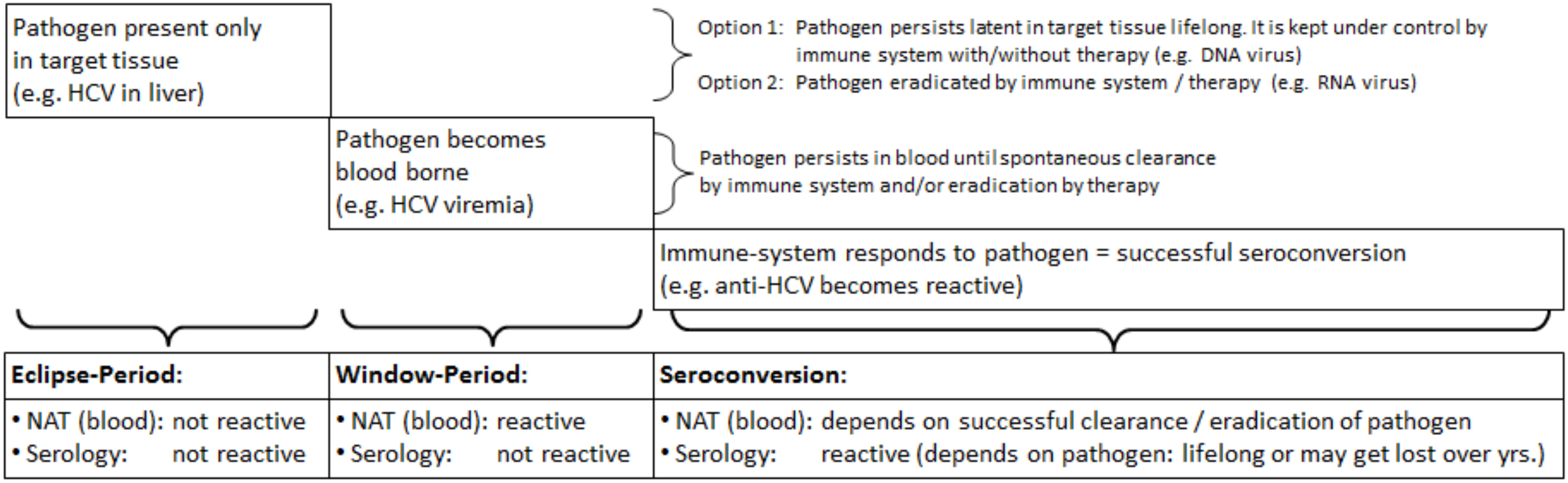
Behaviors at high risk of acquiring blood-born infections if present in the 30 days before organ procurement

HIV, HBV, HCV NAAT mandatory before organ procurement

- Use of parenteral or inhaled drugs for non-medical reasons
- Exposure to blood from a person suspected of being infected with HIV either by inoculation or by contamination of skin or mucous wounds
- Incarceration (confinement in jail, prison, or juvenile correction facility) for ≥72 consecutive hours
- Infants breastfed by an HIV-infected mother
- Children born from mothers infected with HIV, HBV or HCV
- Unknown medical or social history
- Sexual habits that can increase the risk of transmission of diseases
  - sexual relations with people affected or suspected of being affected by HIV, HCV, HBV
  - habitual and repeated sexual behavior (promiscuousness, casualness, sexual relations with the exchange of money or drugs)
  - sexual relations with people with a history of mercenary sex
  - sexual relations with subjects who have used parenteral or inhaled drugs
  - sex in exchange for money or drugs
  - people who have been diagnosed or have been treated for syphilis, gonorrhea, *chlamydia* or genital ulcers

Grossi et al Transpl Int 2024 Oct 2:37:12803

Timeline from infection until final seroconversion, including the eclipse-period and window-period



Grossi et al Transpl Int 2024 Oct 2:37:12803

Other mayor hepatitis virus…and unexpected DDI

- HAV
- HEV
  - In Europe, pigs and wild boars are the main reservoirs for HEV-3 and HEV-4
  - First case of liver transplant transmission described in 2012 in Germany
  - HEV RNA positivity ranging from 0.02 to 0.14% in blood donors
  - Donor screening with HEV RNA currently done in UK, Spain, Germany and France for deceased and living donors

Solignac et al. Virology Journal (2024) 21:136

Up to 1 month

- **DDI**
  - Major hepatitis
  - **Bacteremic donor**
  - Preservation fluid
- Nosocomial infections
  - SSI
  - Abdominal infections
  - C.difficile

Bacteremic donor: liver recipients may be at higher risk of donor transmitted bacteremia

- Blood donor cultures obtained routinely at the time of donation
- **5%-7%** of organ donors have bacteremia at organ procurement, but transmission of the infection to the recipient is low
- Risk factors for DDI-bacteremia:
  - microorganisms resistant to perioperative prophylaxis
  - GNB > GPB (except for S.aureus)
  - **Liver transplant > non –liver transplant**

Siddiqi U et al.. Clin Transplant. 2023

Transmission of bacterial infections from a donor with bacteremia

overwhelming infection, vascular anastomosis dehiscence with risk for transplantectomy and death
? worsening of graft function ?

Administration of effective antimicrobial therapy in donor and recipient at time of the donation, decreases dramatically the risk of transmission

Wolfe CR et al. Clin Transplant. 2019;33(9):e13547

Organs from donors with positive blood cultures may be safely used if …

- Donors have received an appropriate antimicrobial for at least 24–48 h optimally with
  - negative blood cultures (often not feasible)
  - degree of clinical response (improved WBC, hemodynamics, defervescence of fever)

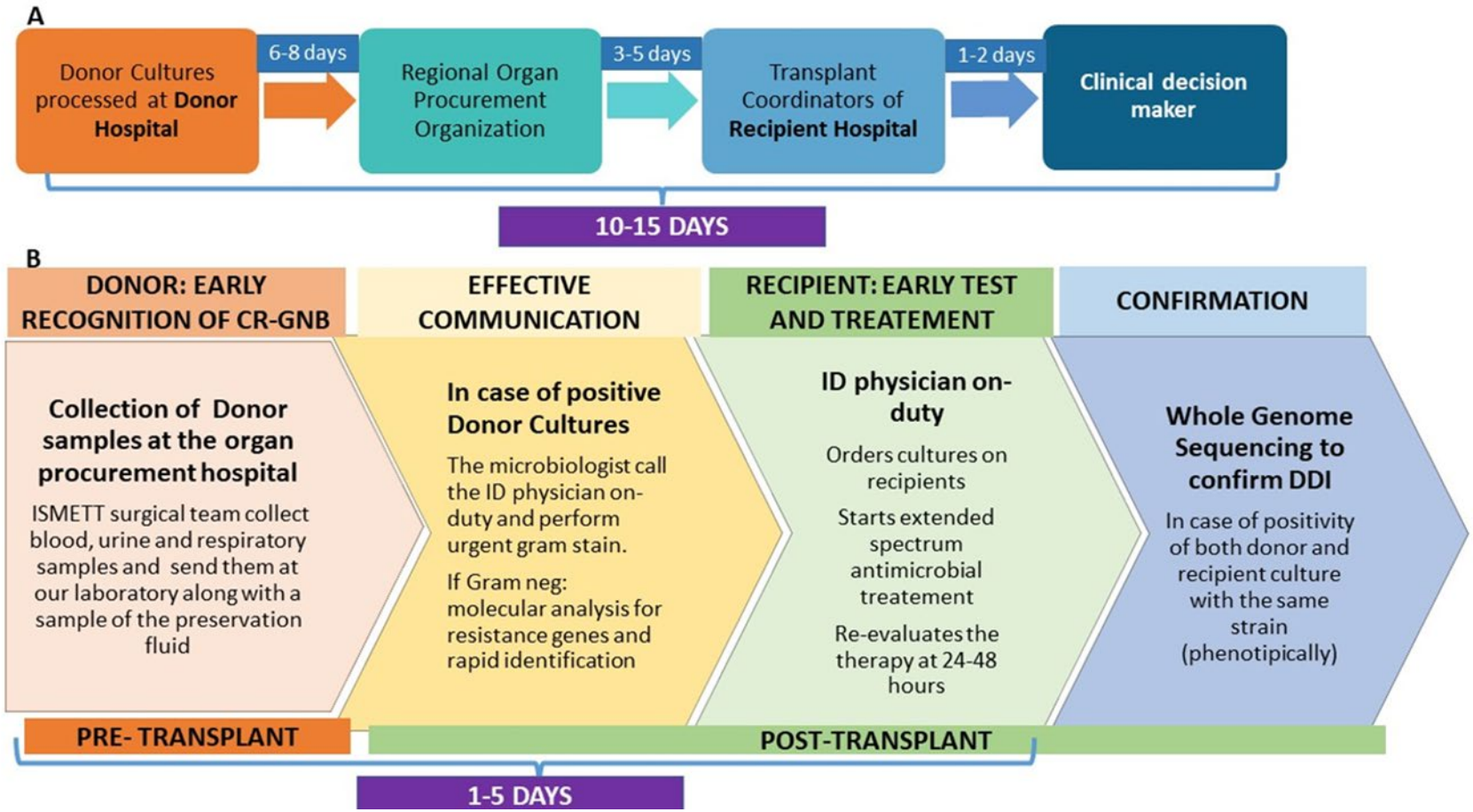
- Recipient should continue a complete course of therapy: range 7-14 days depending on
  - the presence of virulent microorganism (such as *S.aureus* and *P.aeruginosa*)
  - the characteristics of antimicrobial treatment

- Recipients should be submitted to systematic surveillance cultures after transplantation

Grossi P. et al. Curr Opin Organ Transplant. 2024 Apr 1;29(2):131-137

Donor-derived carbapenem-resistant GNB infections in SOT
Active surveillance enhances recipient safety

Prospective study (2015-2021) : 791 SOT



Mularoni A et al. AJT 2024 Feb

CR-GNB DDI

- **38 (4.8%) at high risk of unexpected CR-GNB DDI**:
  - 25 for CRE
  - 13 for CRAB

Positive donor sample / Organ transplanted	Blood	Urine	Respiratory specimen	Preservation Fluid
Liver	**High Risk**	Low Risk	Low Risk	**High Risk**
Kidney	**High Risk**	**High Risk**	Low Risk	**High Risk**
Heart	**High Risk**	Low Risk	Low Risk	**High Risk**
Lung	**High Risk**	Low Risk	**High Risk**	**High Risk**
Pancreas	**High Risk**	Low Risk	Low Risk	**High Risk**

- Transmission was prevented in 71%
- Transmission occurred in 11/38 (29%)
  - 9/25 (36%) of CRE after a median of 24 hours from SOT
  - 2/13 (15%) of CRAB cases after a median of 5 days from SOT

- **Highest risk of DDI:**
  - **recipients of organs with CRGNB– positive preservation fluid**
  - **liver recipients from a donor with CRE infection**

- Survival at 60 days after SOT was not different in patients with DDI (n=11) and in patients without DDI (n=780) (p=0.68)

Mularoni A et al. AJT 2024 Feb

Up to 1 month

- **DDI**
  - Major hepatitis
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  - **Preservation fluid**
- Nosocomial infections
  - SSI
  - Abdominal infections
  - C.difficile

Positive cultures of preservation fluid

- Preservation-fluid contamination may be
  - endogenous : include bacteria and fungi present in the donor's organ
  - exogenous: during the procurement process

- Meta-analysis (17 studies)
  - PF contamination : 13% (95% CI 9.0-17.0%)
  - PF-related infection- early post-transplant DDI : 4 %
  - PF-related infection mortality: 35%

- Routine culture of preservation fluid is not the standard of care in most SOT centres wordwide

Yahav et al. Clin Microbiol Infect 2019 May;25(5):536-537

Performance and interpretation of cultures of PF in the prevention of DDI is controversial

- Pre-emptive antibiotic/antifungal therapy according to preservation-fluid culture VERSUS close clinical and microbiological monitoring

- Balancing benefits (decrease in donor-derived infection and improved transplant outcomes) and risks (infection by MDR organisms, fungi)

DONOR DERIVED INECTIONS

ANTIBIOTIC OVERUSE

Yahav et al. Clin Microbiol Infect 2019 May;25(5):536-537

Graft site arteritis development in and positive preservation fluid in liver recipients

- Liver recipients with a PF yielding a high-risk pathogen showed a significantly increased risk of arteritis development compared to low-risk/negative PF (OR 16.78, 95%CI 2.95–95.47)

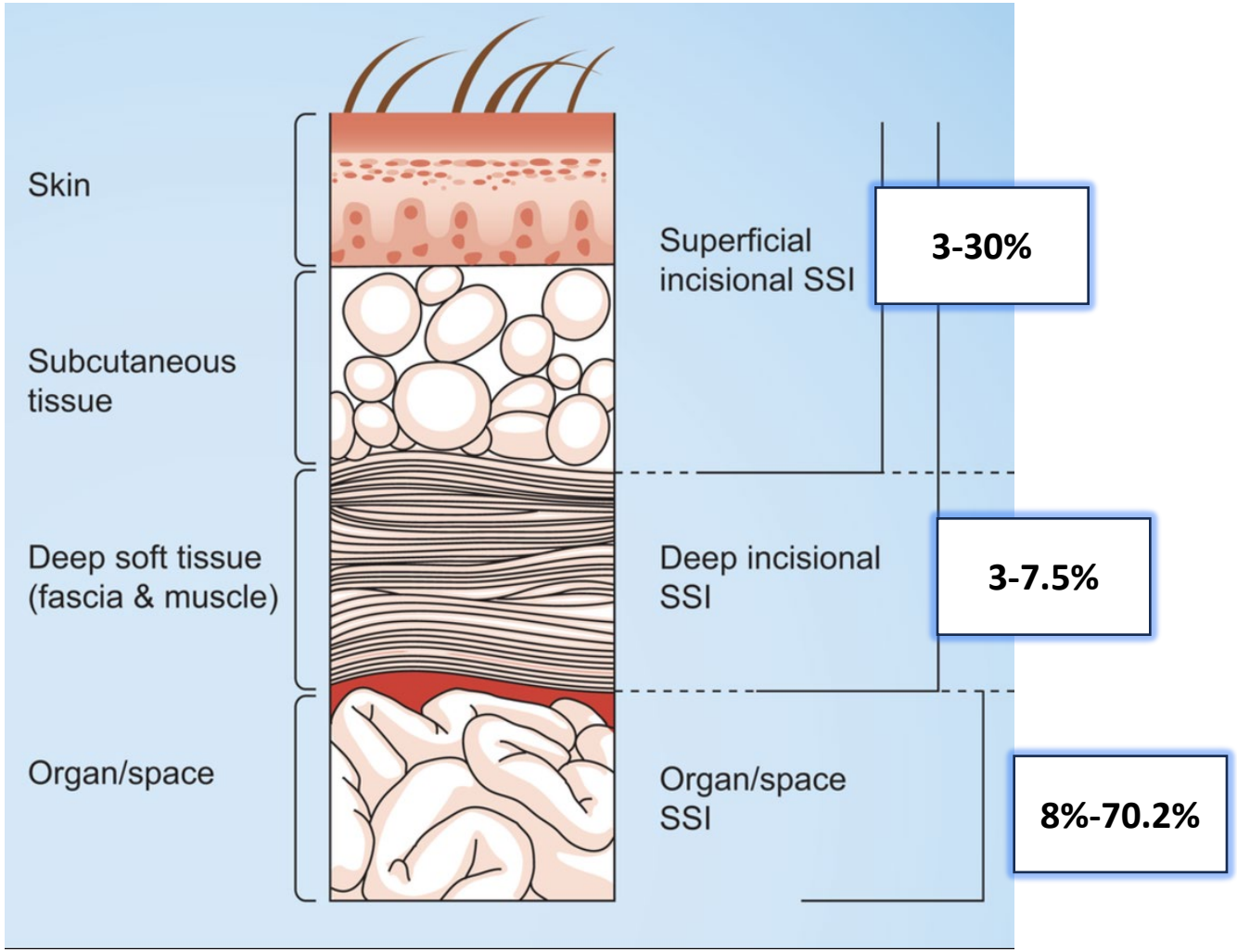
Rinaldi M. et al. Transpl Infect Dis 2022 Dec;24(6).

Up to 1 month

- DDI
  - Major hepatitis
  - Bacteremic donor
  - Preservation fluid
- **Nosocomial infections**
  - **SSI**
  - Abdominal infections
  - C.difficile

Surgical site infection

8-37% of liver transplant recipients



S. aureus, CNS, Enterobacteriaceae, Enterococcus, *Acinetobacter and Candida*
MDRO :14.3%-30%

Rolak al. Transplantation 2024 May 1;108(5):1179-1188
Freire et al. Diagnostic Microbiology and Infectious Disease 99 (2021)

Up to 1 month

- DDI
  - Major hepatitis
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- **Nosocomial infections**
  - SSI
  - **Abdominal infections**
  - C.difficile

Anatomy and the physiology of the biliary tree

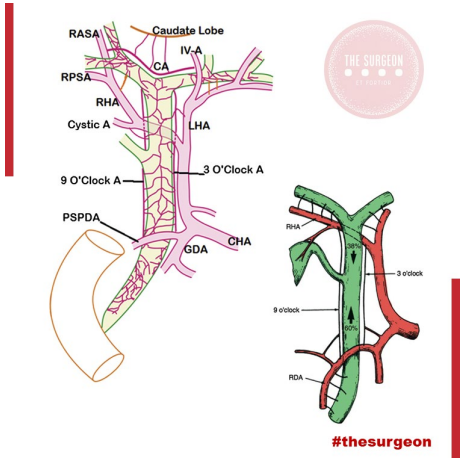


Table 3. Risk Factors for Biloma Formation by Multivariable Analysis

Risk Factor	Adjusted OR 95% (CI)	*P* Value
Hepatic artery thrombosis	90.9 (6.1–500)	<.001
Hepatic artery stenosis	13.1 (3.2–52.6)	<.001
Roux-en-Y choledochojejunostomy	5.8 (1.2–27.7)	.03
Ursodiol use	0.1 (0.0–0.4)	<.001

Goodness-of-fit test by pearson's Chi-square, $P = .73$; receiver operating characteristic curve c-statistic, 0.90.

- bile ducts are nourished by their own arterial supply, the peribiliary plexus
- peribiliary plexus originates from the hepatic artery and is strictly arranged around the intrahepatic bile ducts
- blood supply to the biliary system principally depends on the hepatic artery flow
- it is of the greatest importance to check the vascular patency in any patient who presents a biliary complication after LT

Zanus t al. Transplantation Proceedings, 49, 736e739 (2017)

Biliary tract infections

- Leading cause of postoperative morbidity and mortality
- 38% of all bacterial infections during the first year post-transplantation
- Not restricted to the early post-transplantation period:
  - 21.8 per 1000 person-years 1 to 5 years post-liver transplant
  - 2.5 per 1000 person-years only 11–15 years post-liver transplant
- Microbiological etiology:
  - < 6 months: Gram positive (> Enterococcus spp)
  - > 6 months : Gram negative: Enterobacterales, P. aeruginosa, Candida > MDR

Type of infection	Incidence
Biliary tract	3.5-8.8 %
Cholangitis	10 %
Bilioma	11.5%

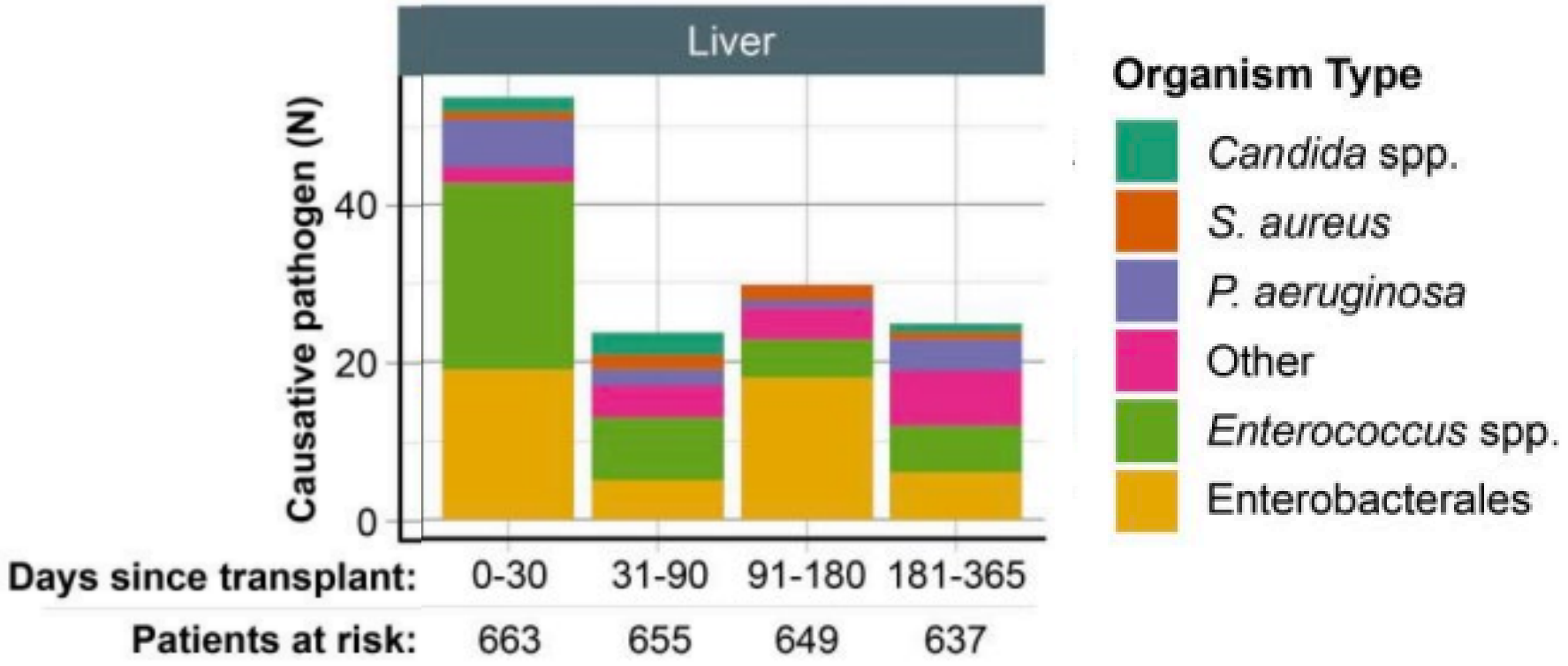
Courjon et al Curr Opin Organ Transplant 2024, 29:155–160

Bloodstream infections after solid organ transplantation: clinical epidemiology and antimicrobial resistance (2016–21)

single-centre retrospective study

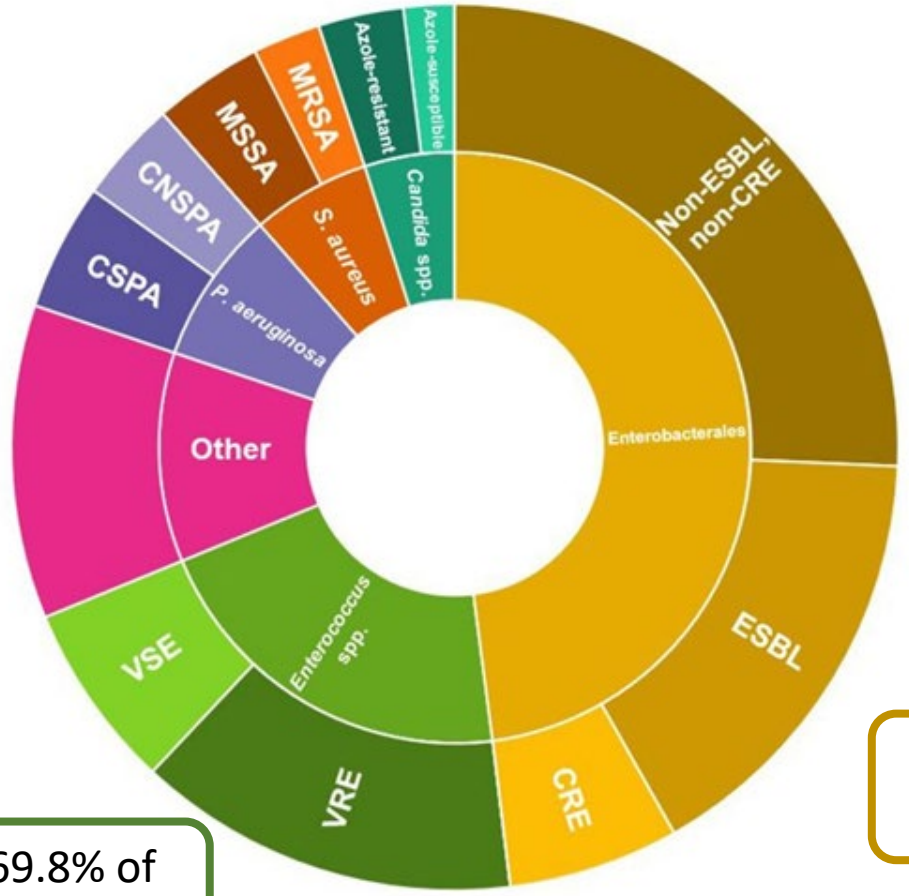
2293 patients: 1251 (54.6%) kidney, 663 (28.9%) liver, 219 (9.6%) heart and 160 (7.0%) multi-organ

8.5% of patients developed a BSI



Adelman M et al. JAC AMR Jan 2024

45.5% of BSI were caused by MDR bacteria



- **BSIs were most common** after multi-organ (23.1%) and **liver (11.3%) transplantation (P < 0.001)**
- **MDR most common after liver transplant (53.4%)**
- Mortality after BSI was 9.7%
- VRE was independently associated with mortality (OR 6.0, 95% CI 1.7–21.3)

VRE: 69.8% of Enterococci

EBSL: 29.2% of Enterobacterales

CRE: 27.2% of Enterobacterales

Adelman M et al. JAC AMR Jan 2024

Up to 1 month

- DDI
  - Major hepatitis
  - Bacteremic donor
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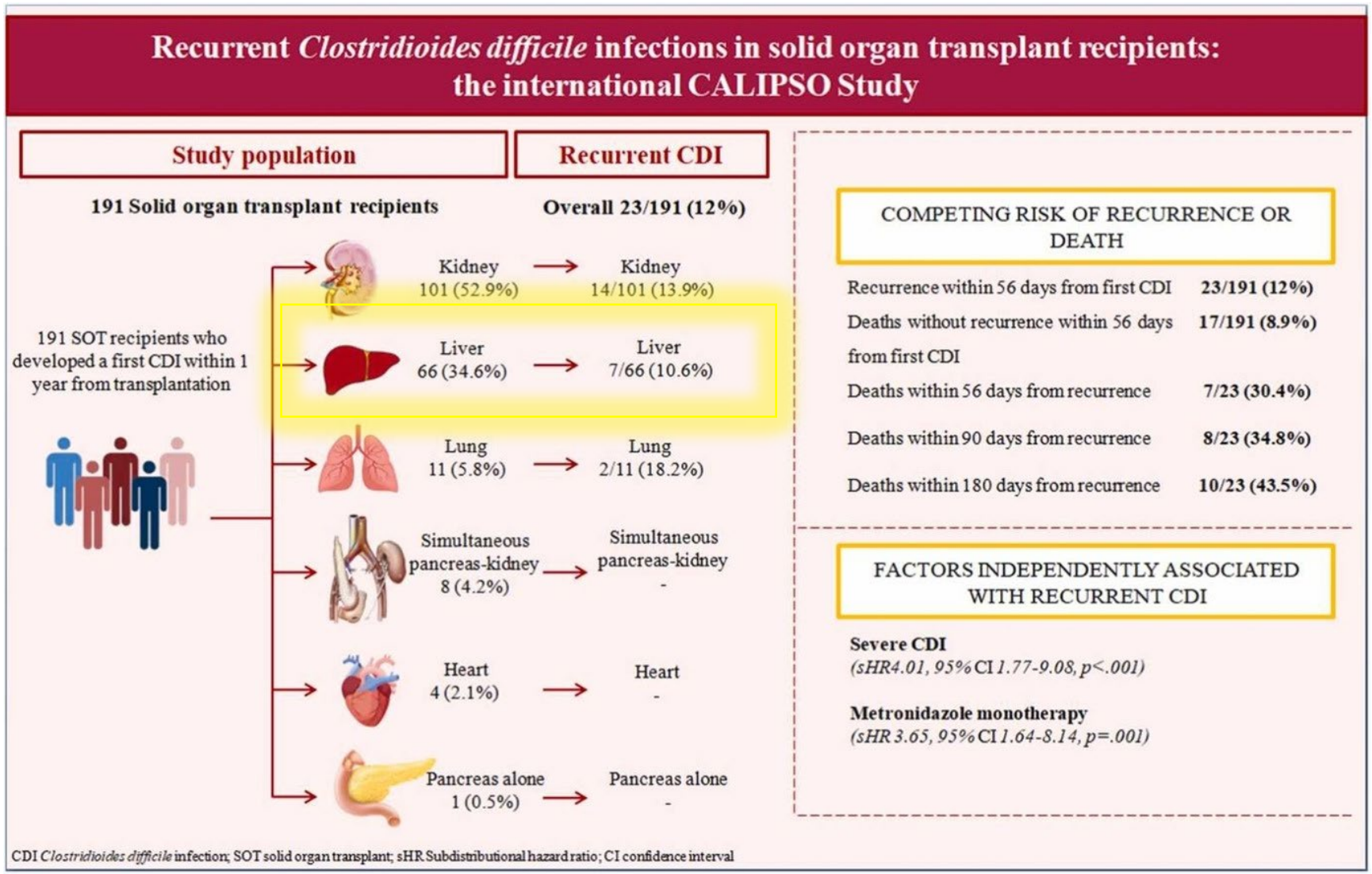
- **Nosocomial infections**
  - SSI
  - Abdominal infections
  - **C.difficile**

Liver transplant patients have a higher prevalence of CDI as compared to non liver transplant patients (2.7%-9%)



Tiseo et al. Journal of Infection Oct 2024


0-1 month
DDI and conventional nosocomial infections
1-6 months
Uncoventional and opportunistic infections
> 6 months
Community adquired infections

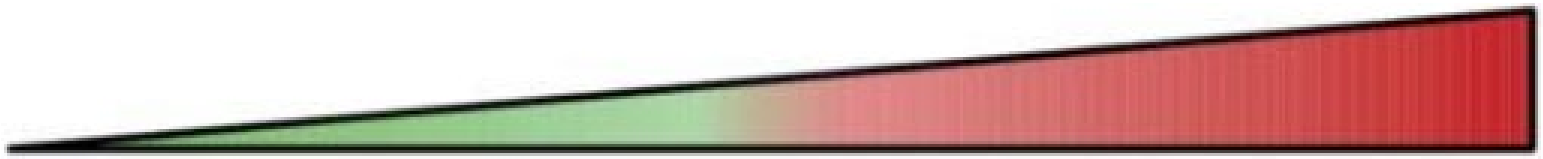
1 to 6 months

- Opportunistic infections
  - CMV
  - IFI
    - P.jiorvecii

1 to 6 months

- **Opportunistic infections**
  - **CMV**
  - IFI
    - P.jiorvecii

The hierarchy of risk with respect to CMV infection



Donor	−	−	+	+
Recipient	−	+	+	−
Transplanted organ	Liver	Kidney	Heart	Lung
Immuno-suppressive therapy	mTOR inhibitors	Tacrolimus	MMF	Belatacept or ATG*

Courtesy of professor Palo Antonio Grossi

CMV

	Prophylaxis	Preemptive therapy
Early CMV DNAemia	Rare	Common
Prevention of CMV disease	Good efficacy	Good efficacy (less optimal in high-risk populations)
Late CMV (infection/disease)	Common	Rare
Resistance	Uncommon	Uncommon
Ease of implementation	Relatively easy	More difficult
Other herpes viruses	Prevents HSV, VZV	Does not prevent
Other opportunistic infections	May prevent	Unknown
Cost	Drug costs	Monitoring costs
Safety	Drug side effects	Less drug toxicity
Prevention of rejection	May prevent	Unknown
Graft survival	May improve	May improve

Comparison of prophylaxis versus preemptive therapy

Grossi et al. Curr Opin Organ Transplant 2024, 29:131–13

CMV and liver transplant

- **Preemptive:** without prophylaxis, most common 1 to 6 months after transplantation: overall 50-60% viremia ; 20-30% CMV-related disease
  - R-/D+: 91.9% of viremia and 50–65% of symptomatic infection < 90 days
  - R + : 40–60% of viremia
  - R- /D- : 4% of transmission (transfusion or sexual contact)

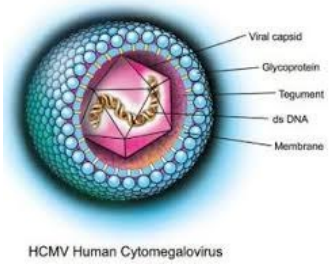
- **Prophylaxis**
  - after the cessation of prophylaxis with 25–40% developing symptomatic disease

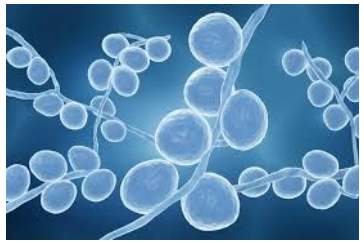
- CMV hepatitis may be difficult to distinguish from graft rejection

Kotton et al. Transpl Infect Dis. 2022 Dec;24(6):e13977

1 to 6 months

- Opportunistic infections
  - CMV
  - **IFI**
    - P.jiorvecii





IFI in liver transplant recipients

- Incidence: 4 to 40%

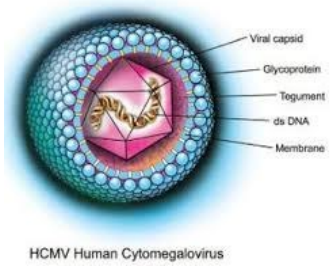
- Rates
  - 1 year after SOT:1.8% (7.4% for lung, 5.4% for heart, 1.1% for kidney)
  - 5 years after SOT: 2.9%
  - 10 years after SOT: 5%

- Causative agents
  - Candida 68–93%: > 1-3 months after transplant
  - Aspergillus 1–9%
  - Cryptococcal 0.5–5%

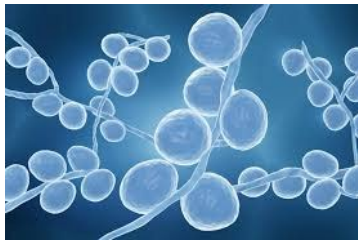
Senoner et al J. Clin. Med. 2023, 12, 3238
Hosseini-Moghaddam SM et al. TID 2020

1 to 6 months

- Opportunistic infections
  - CMV
  - IFI
    - **P.jiorvecii**



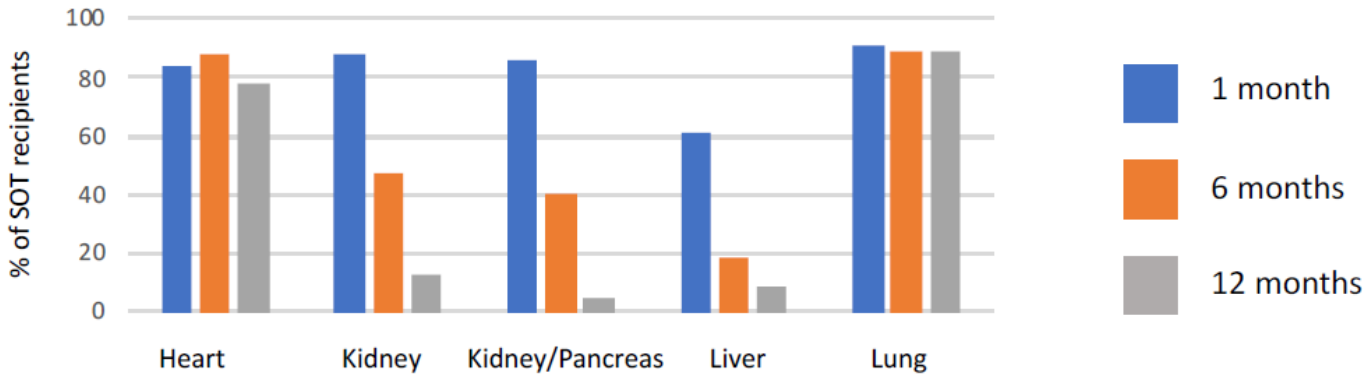
HCMV Human Cytomegalovirus



Questions a one-size-fits-all approach to PJP prophylaxis in liver transplant recipients

- Guidelines recommend anti-PJP prophylaxis for at least 6–12 months for all SOT recipients due to the higher degree of immunosuppression during first months
- incidence threshold of 3–5% for using prophylaxis
- It is uncertain wheather universal PJP prophylaxis is still applicable in the contemporary LT setting

Panel A: anti-Pneumocystis



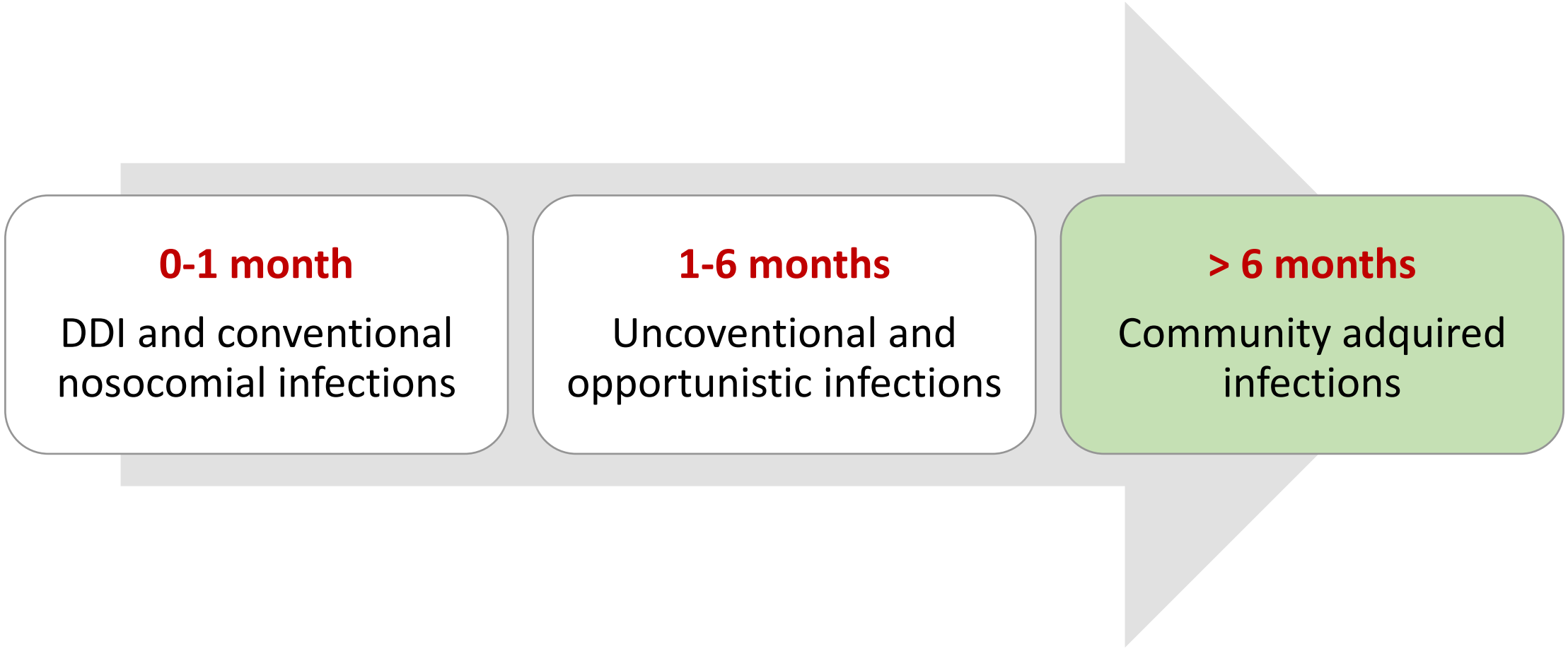
van Delden et al Clinical Infectious Diseases 2020;71(7)
Fortea et al. J. Clin. Med. 2020, 9, 3573;

Epidemiology of PCP in liver transplant recipients

- Incidence of PCP in liver transplant recipients varies substantially across centers
- Low incidence of PJP in unprophylaxed cohort
- Recent series in which PJP incidence is below 3% and even similar to incidences from LT recipients using prophylaxis
- Most cases occurring beyond the usual recommended period of prophylaxis
- Outbreak described in liver transplant recipients
  - infections by *P. jirovecii* strains with increased virulence
  - changes in the immunosuppressive treatments
  - increased infectious pressure
  - nosocomial transmission by healthcare workers

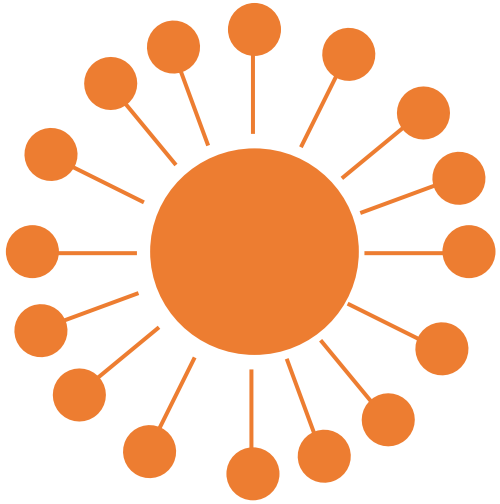
Montantes et al. Transpl Infect Dis. 2018;20:e12956.
Fortea et al. J. Clin. Med. 2020, 9, 3573;

The timeline of post-transplant infections



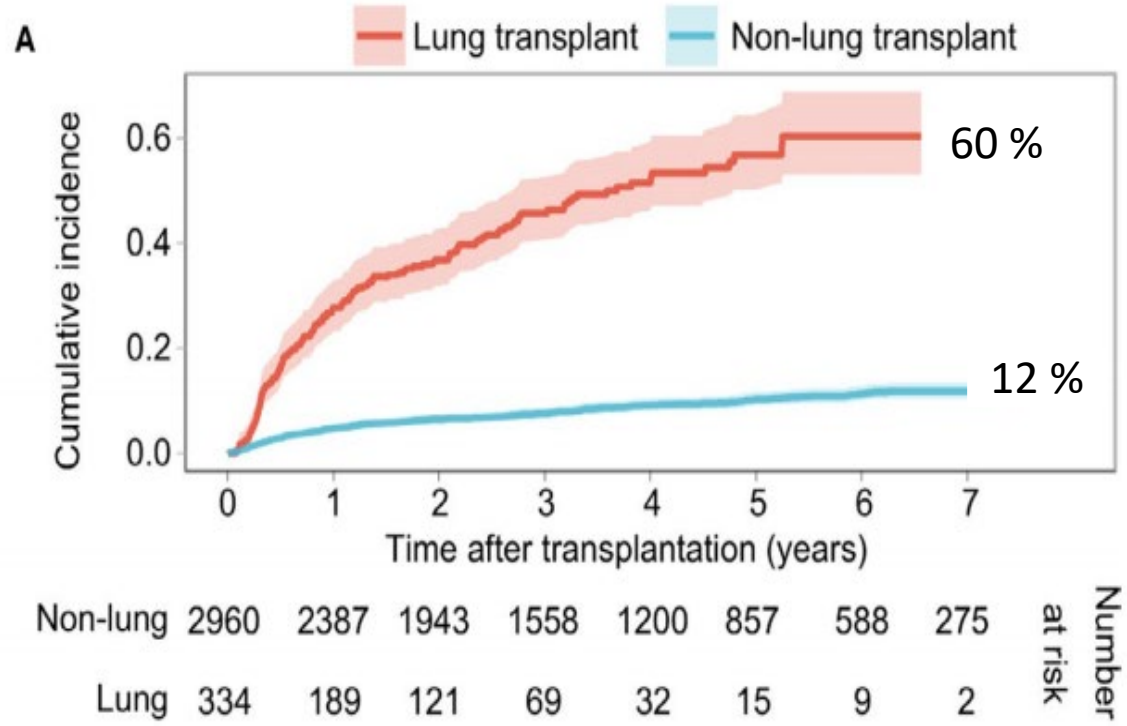
> 6 months

- Respiratory viruses



Burden, epidemiology, and outcomes of RV infections in SOT a nationwide, prospective Swiss Transplant Cohort Study

- 3.294 SOT (334 LTR, 2960 Non-LTR) from 2008 to 2015 in Switzerland
- Follow-up was 3.4 years (IQR 1.61–5.56): 696 RV

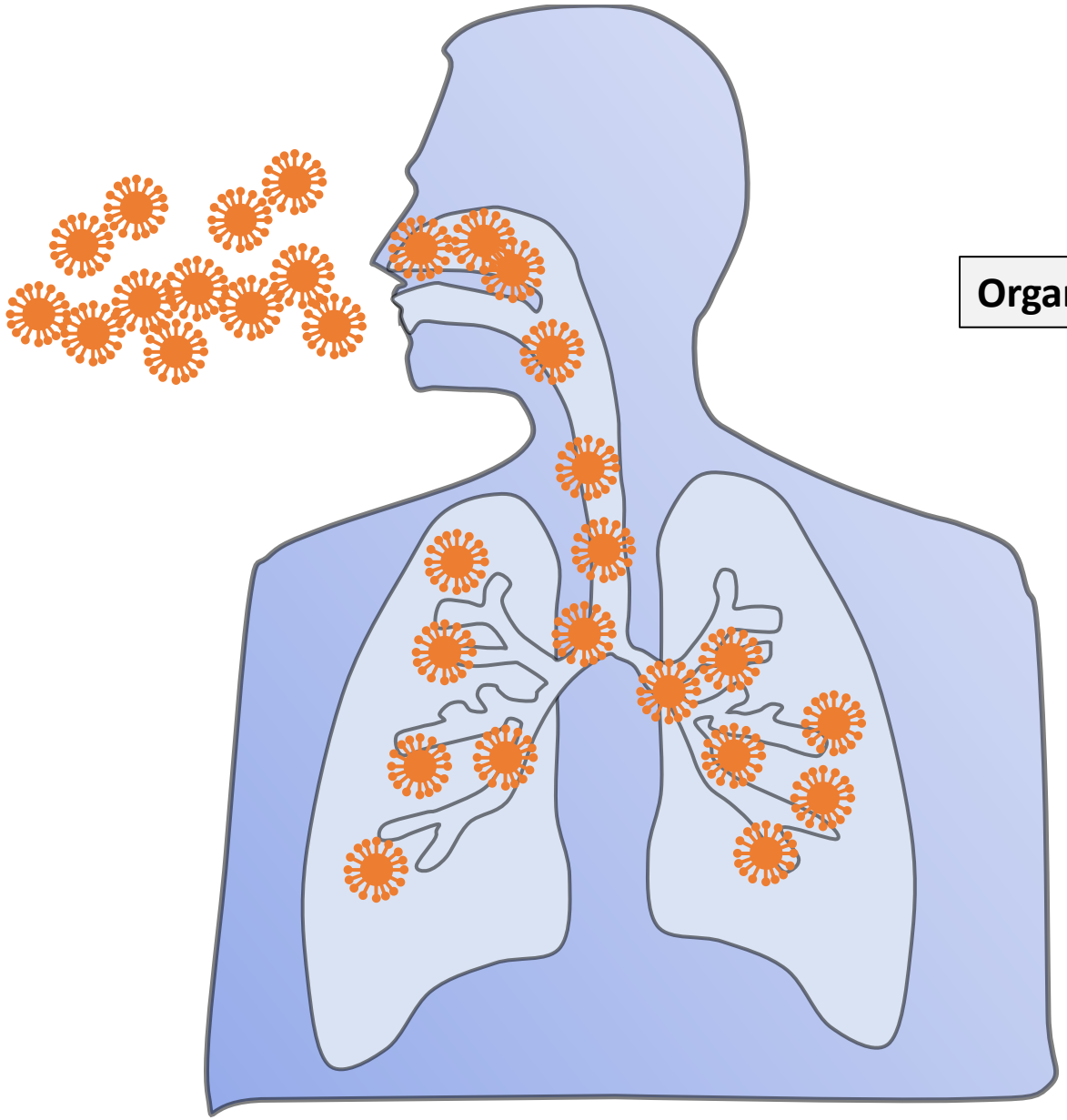


Incidence rate
LTR 320 /1000 person-years

Incidence rate
Non-LTR 30.6 /1000 person-years

Mombelli et al. Am J Transplant. 2021;21:1789–1800

Direct, cytopathic and tissue-invasive effects



Upper Respiratory Tract Infection, URTI

Organ transplantation

Lower Respiratory Tract Infection, LRTI

Hospital and ICU admission

Respiratory failure>>MV

Death

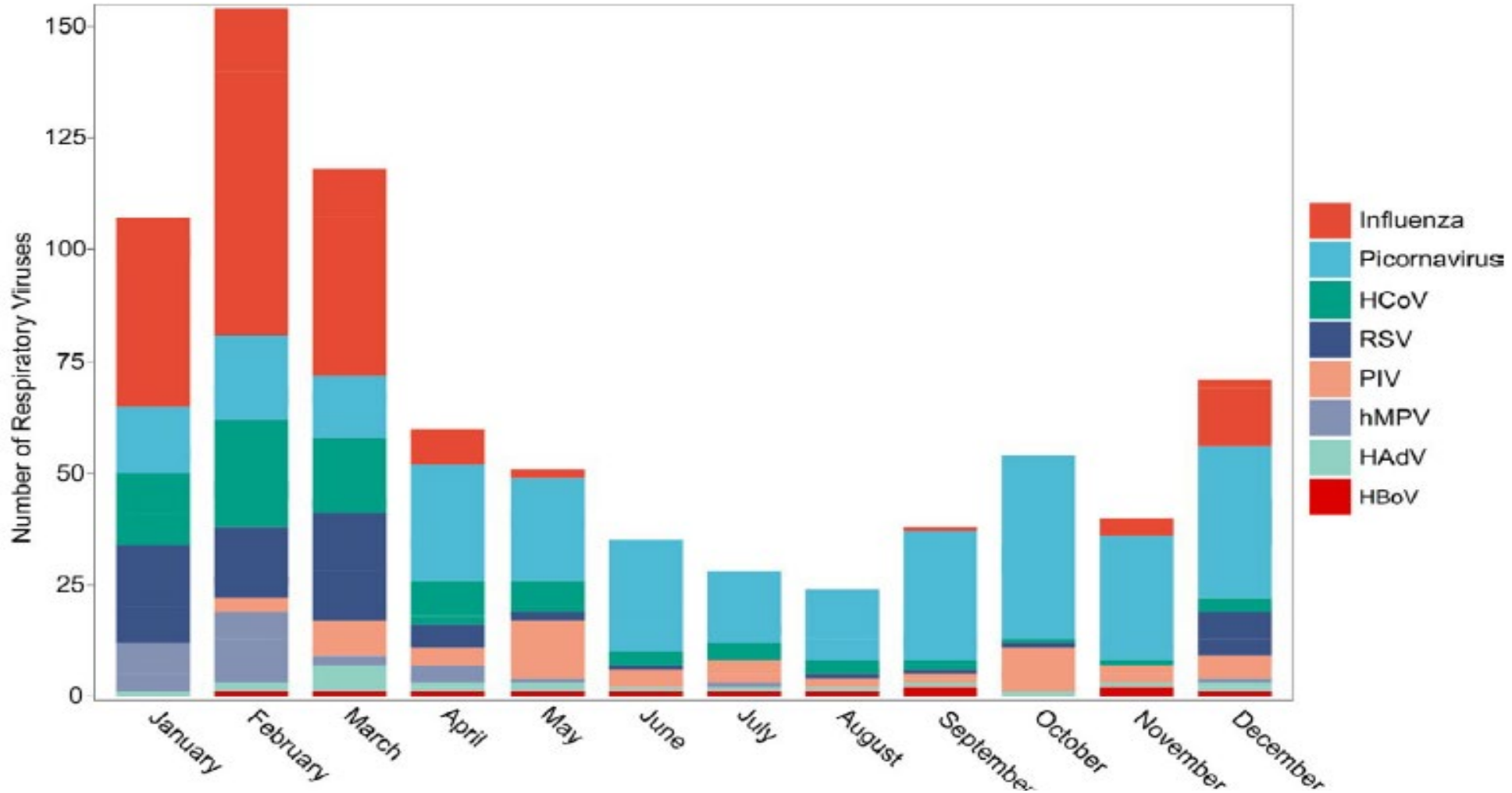
Indirect complications

Distribution of major respiratory virus in SOT before the pandemic

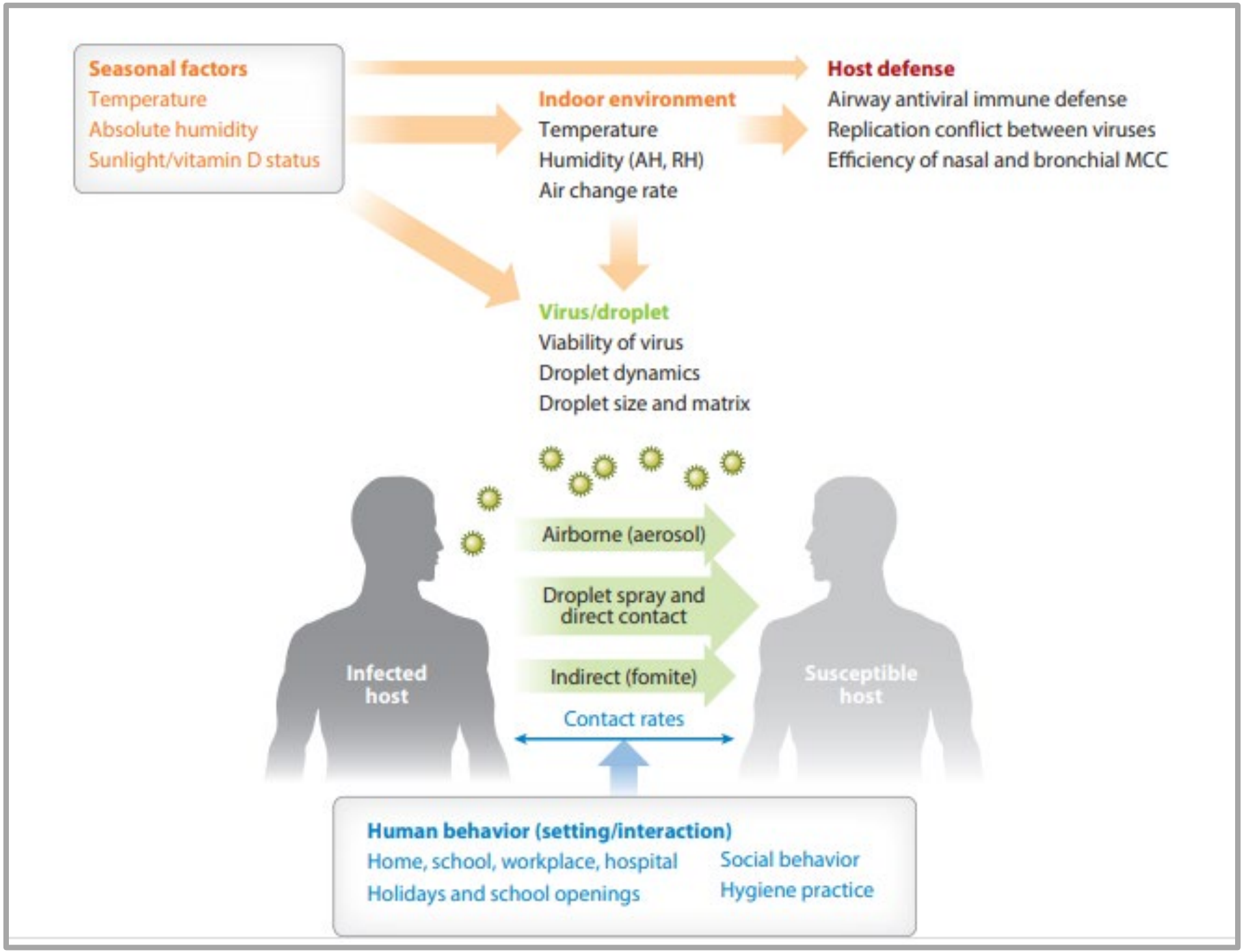
Virus	Family	Genome	Diversity	Distribution (%)
Rhinovirus	Picornaviridae	RNA	A, B, C, >100 types	21–62 %
Coronavirus	Coronaviridae	RNA	OC43, E229, HKU1, NL63	13–29 %
Influenza virus	Orthomyxoviridae	RNA	A, B, C / H3N2, H1N1pdm	2-16 %
Respiratory syncytial virus	Paramyxoviridae	RNA	A and B	6–20 %
Parainfluenza virus	Paramyxoviridae	RNA	1, 2, 3 and 4	3–18 %
Metapneumovirus	Paramyxoviridae	RNA	A1, A2, B1, B2	4–7 %
Adenovirus	Adenoviridae	DNA	7 species, > 50 serotypes	1–25 %

Ison et al. Clin Microbiol Rev. 2019

Seasonality in SOT follows that of general population

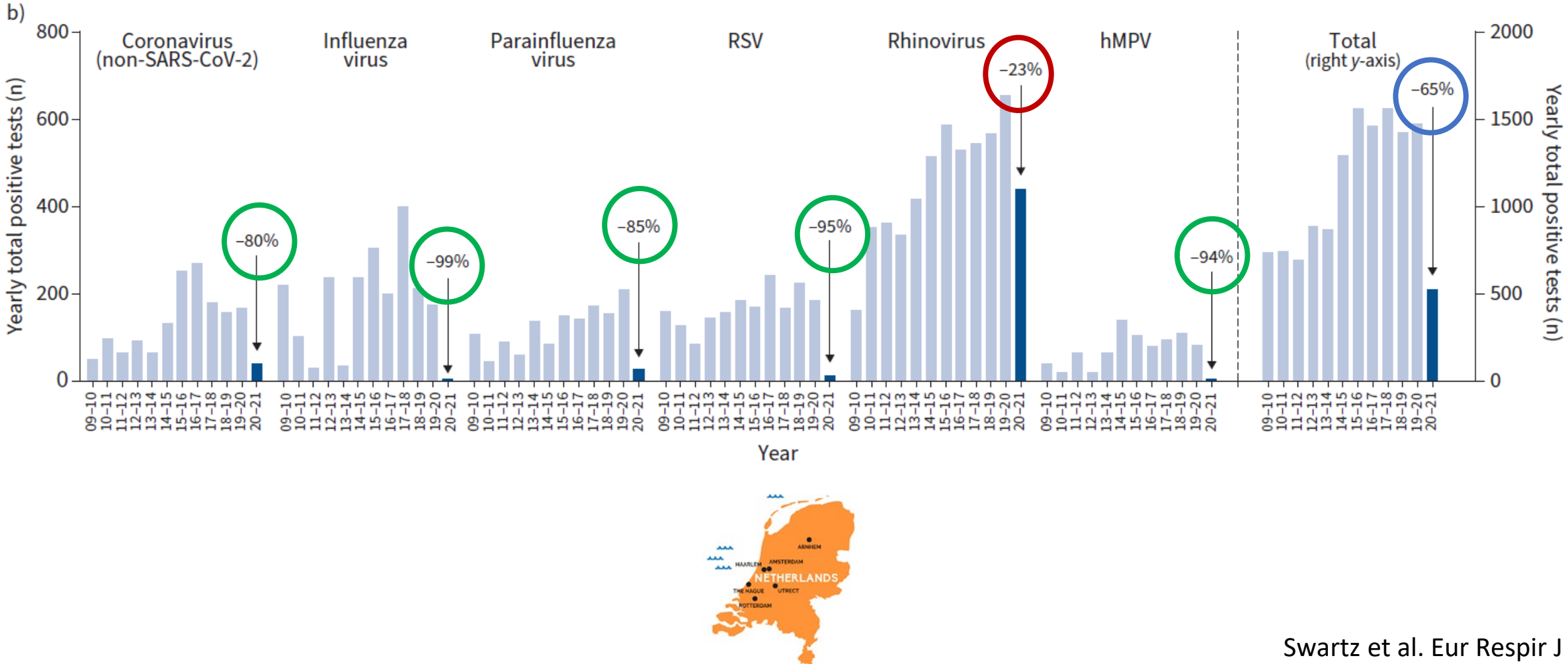


Peghin et al. American Journal of Transplantation 2017
Mombelli et al. Am J Transplant. 2021


Seasonal factors
Temperature
Absolute humidity
Sunlight/vitamin D status
Indoor environment
Temperature
Humidity (AH, RH)
Air change rate
Host defense
Airway antiviral immune defense
Replication conflict between viruses
Efficiency of nasal and bronchial MCC
Virus/droplet
Viability of virus
Droplet dynamics
Droplet size and matrix
Airborne (aerosol)
Droplet spray and direct contact
Indirect (fomite)
Contact rates
Infected host
Susceptible host
Human behavior (setting/interaction)
Home, school, workplace, hospital
Holidays and school openings
Social behavior
Hygiene practice

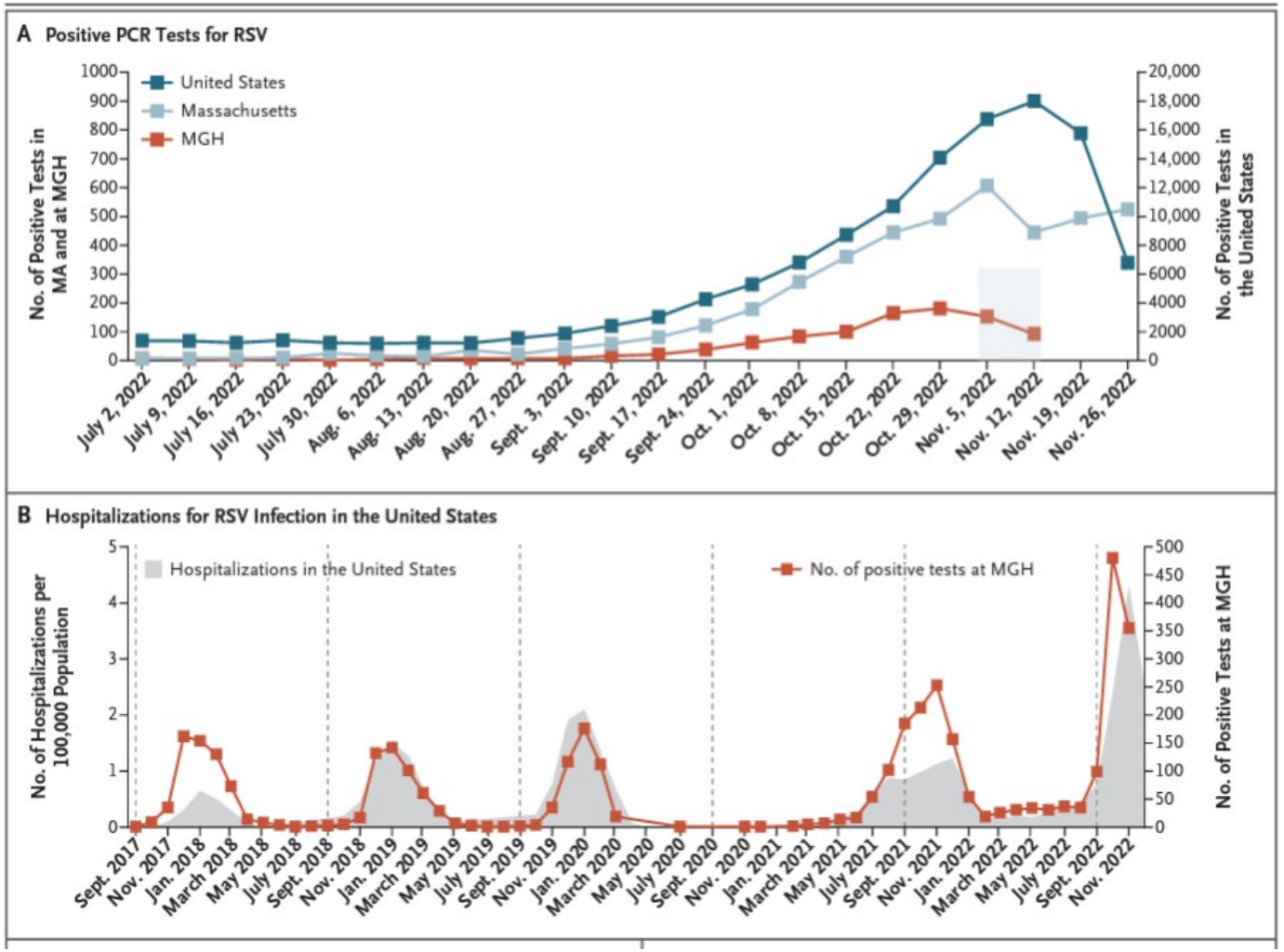
COVID-19 social distancing and strong reduction in RVs circulation

change in incidence in 2020–2021



Swartz et al. Eur Respir J 2022

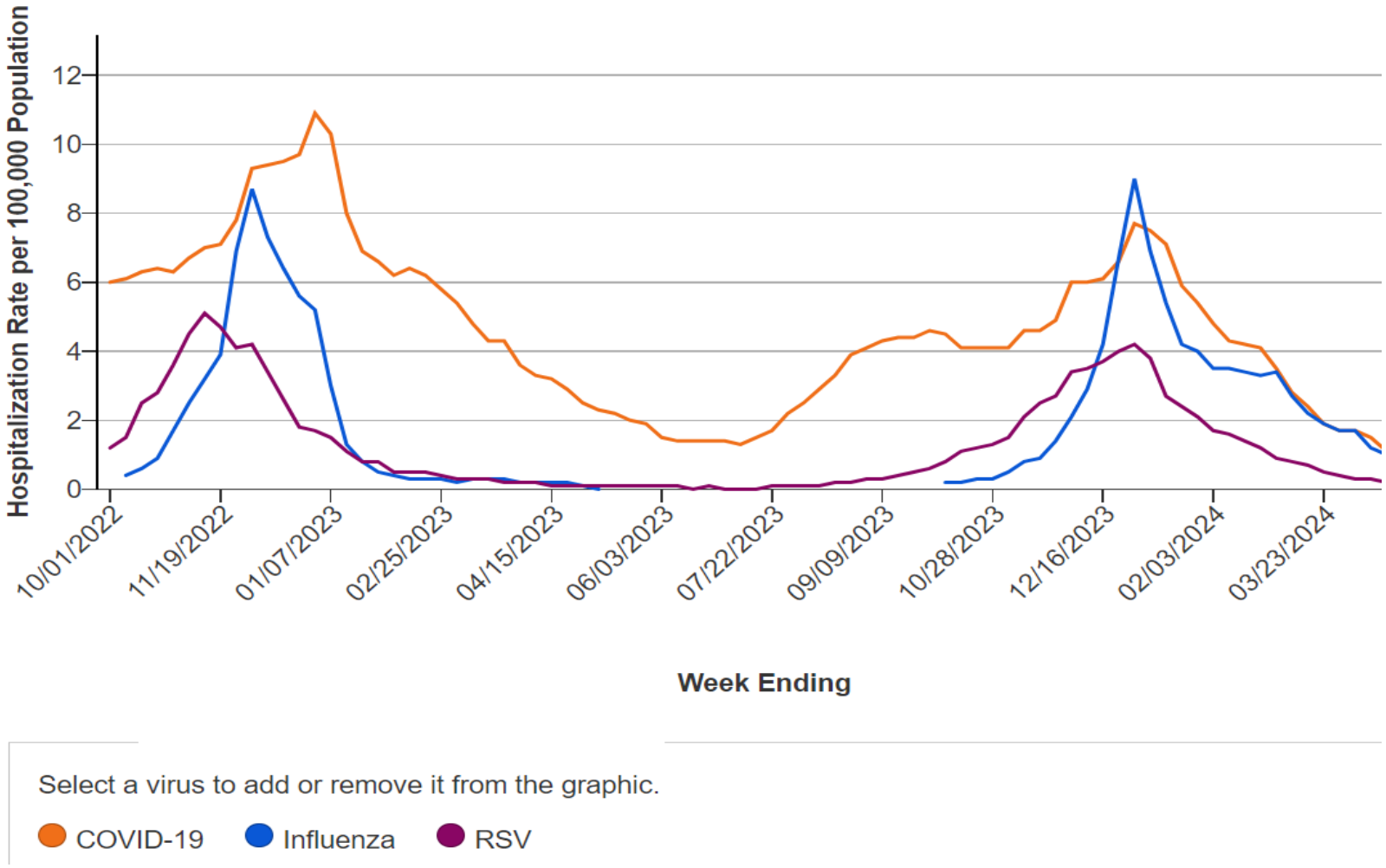
‘A “tripledemic”’of SARS-CoV-2,Influenza and RSV infections in the 2022/2023 winter season



Adams et al. N Engl J Med. 2023

SARS-CoV-2,Influenza and RSV infections in the 2023/24 winter

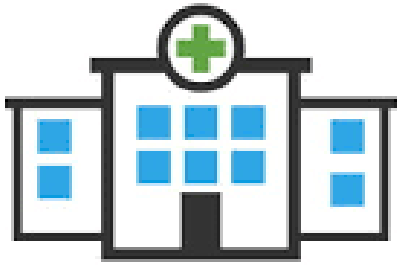
Hospitalizations and deaths were below last season



www.cdc.gov

Respiratory viruses: community acquired or nosocomial acquired ?

- RV as a cause of HAP (≈ 32%) and VAP (≈ 5.1%)
- Viral etiology: Influenza (27%); Rhinovirus (27%) ; RSV (17%)
- **Majority of nosocomial RV in the immunocompromised (≈ 45-60%, ≈ SOT 35%)**



Zildeberg et al. Viruses 2023

Luyt et al. Semin Respir Crit Care Med 2022

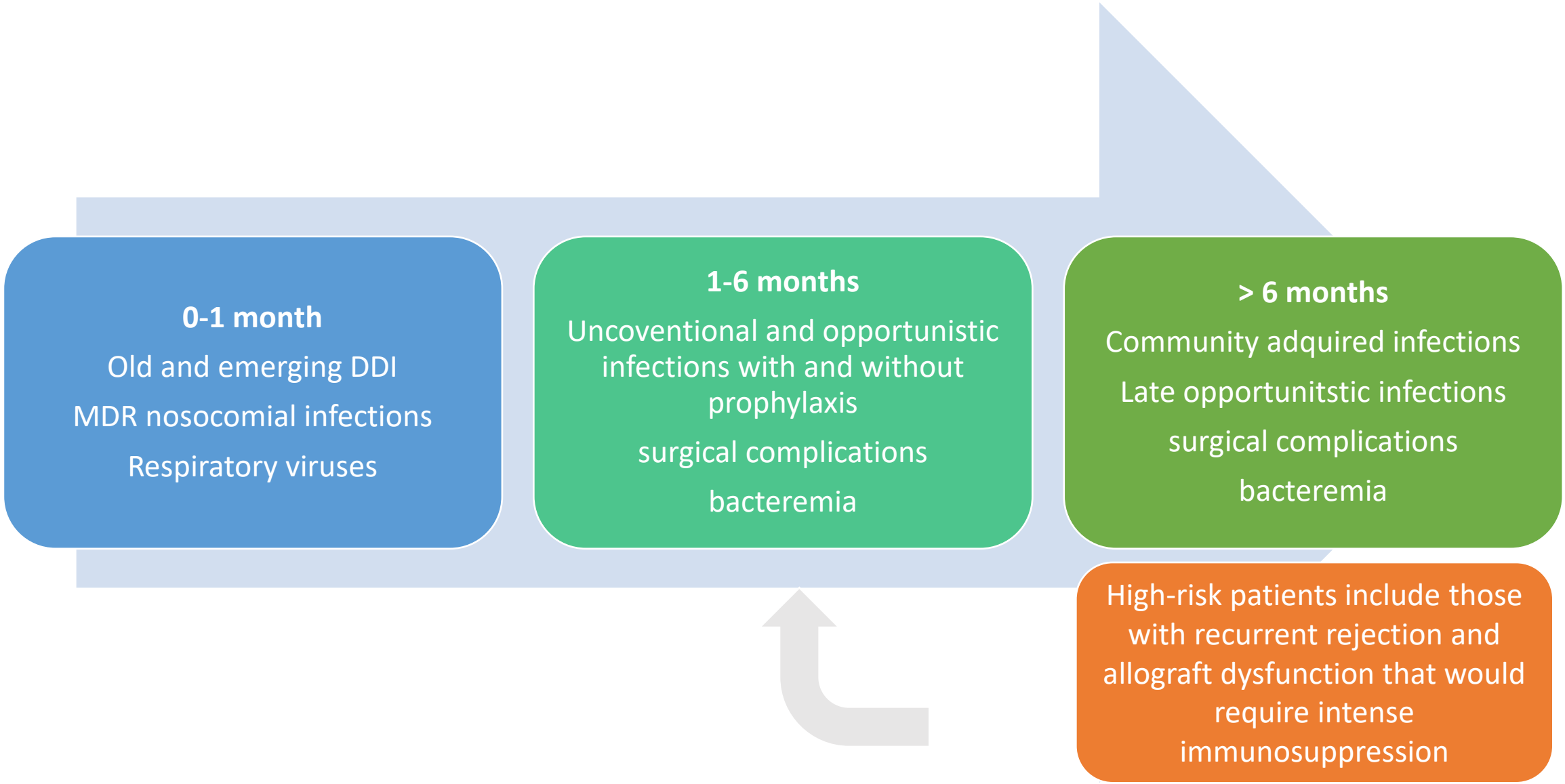
Nosocomial RV in SOT

- Hospital-acquired non-SARS-CoV-2 RV infections account for **6.8-7%** in SOT
- **Nosocomial acquisition in SOT as an independent risk factor for**
  - **progression to LRTI**
  - **increased length of stay**
  - **ICU admission**
- Risk for outbreaks of RV
- Importance of adequate infection control measures and vaccination

Peghin et al. American Journal of Transplantation 2017
Read et al. Lancet 2021
Mombelli et al. Am J Transplant. 2021

The timeline of post-transplant infections

three consecutive often overlapping periods after liver transplantation



Conclusions

- Despite advances in liver transplantation, morbidity and mortality due to infectious complications remains a major problem

- The risk of infection and types of infections differ based upon the time after transplantation, but changes in immunosuppressive agents over time and prophylaxis can alter the timeline of infections

- A better understanding of the common and important infectious complications is needed to improve quality of life and survival rate after liver transplantation.

Grazie


SITA
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