



Collège des universitaires
de Maladies
Infectieuses et Tropicales

WEBINAIRE DES « Maladies Infectieuses et Tropicales » Octobre 2025 Séminaire n° 1 – Thématiques 9, 12, 14, 16 et 19

Infections virales respiratoires chez les immunodéprimés (hors SARS-CoV-2)

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Département des Maladies infectieuses et tropicales, CHU de Lyon, France



Université Claude Bernard Lyon 1

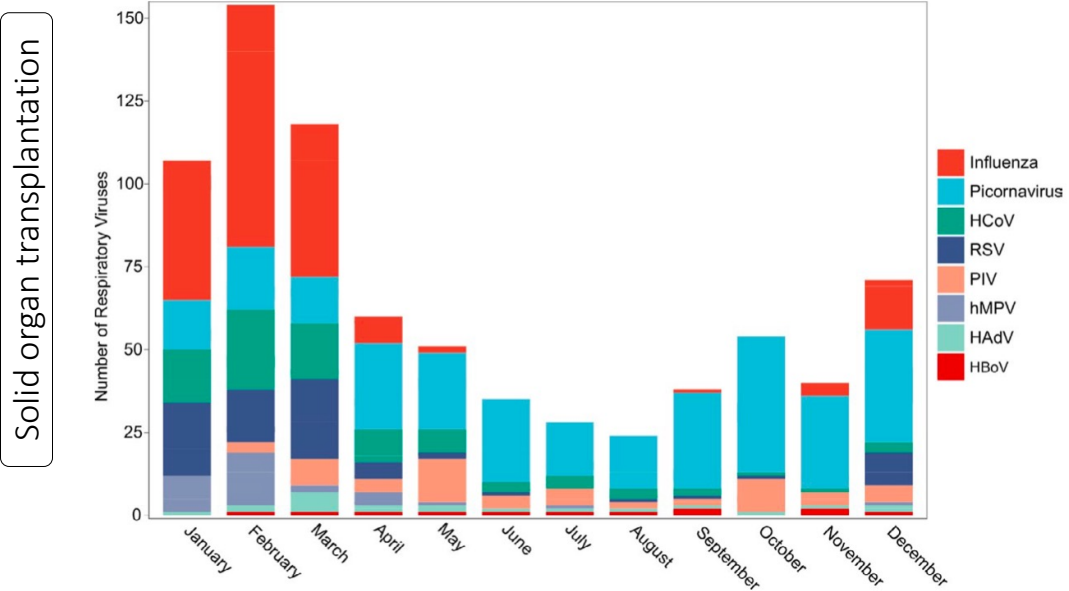
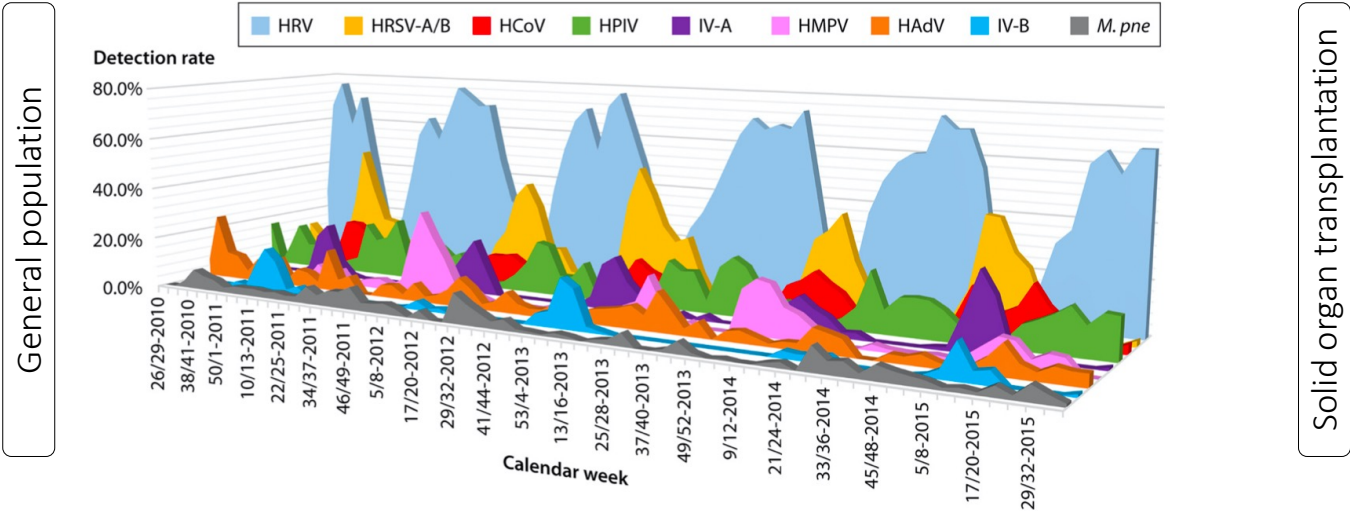


Déclaration de liens d'intérêt avec les industriels de santé
en rapport avec le thème de la présentation (loi du 04/03/2002) :

- Intervenant : ADER Florence
 - Titre : Infections respiratoires virales chez les immunodéprimés

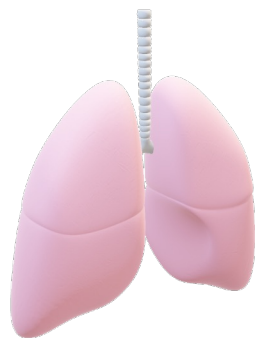
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| • Consultant ou membre d'un conseil scientifique | NON |
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| • Prise en charge de frais de voyage, d'hébergement
ou d'inscription à des congrès ou autres manifestations | NON |
| • Investigateur principal d'une recherche ou d'une étude clinique | NON |

Community-acquired respiratory viruses (CARV)



Seasonality	
Fall ---- > winter	Influenza virus (IV) A/B, HRSV, Metapneumovirus (HMPV)
Spring, summer --- > fall	Picornavirus/Rhinovirus (HRV), CoV, Parainfluenza virus (HPIV)

Ison MG, Hirsch HH. Clin Microbiol Rev 2019. doi: 10.1128/CMR.00042-19
Jain S,; CDC EPIC Study Team. N Engl J Med. 2015. doi: 10.1056/NEJMoa1500245
Mombelli M, et al; Swiss Transplant Cohort Study. Am J Transplant. 2021. doi: 10.1111/ajt.16383.



Lung Tx: overall post-transplant survival 6.2 y

Highest impact

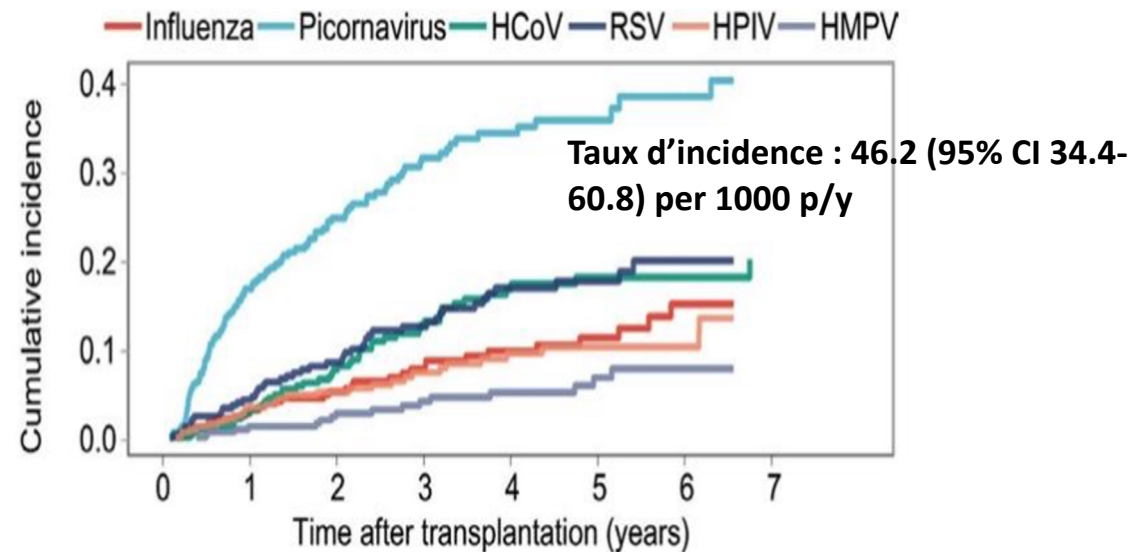
**Allo-HSCT
Lung Tx**

Other SOTs

COPD-bronchiectasis
Auto-inflammatory diseases

Lowest impact

Children < 5 a



Allograft rejection

**Bronchiolitis obliterans
& chronic lung allograft dysfunction**



Allo-HSCT, n= 426 – 1070 CARV episodes
 Lower RTD progression rate = 26%
 All-cause mortality rate at day 100 = 5%

Highest
impact

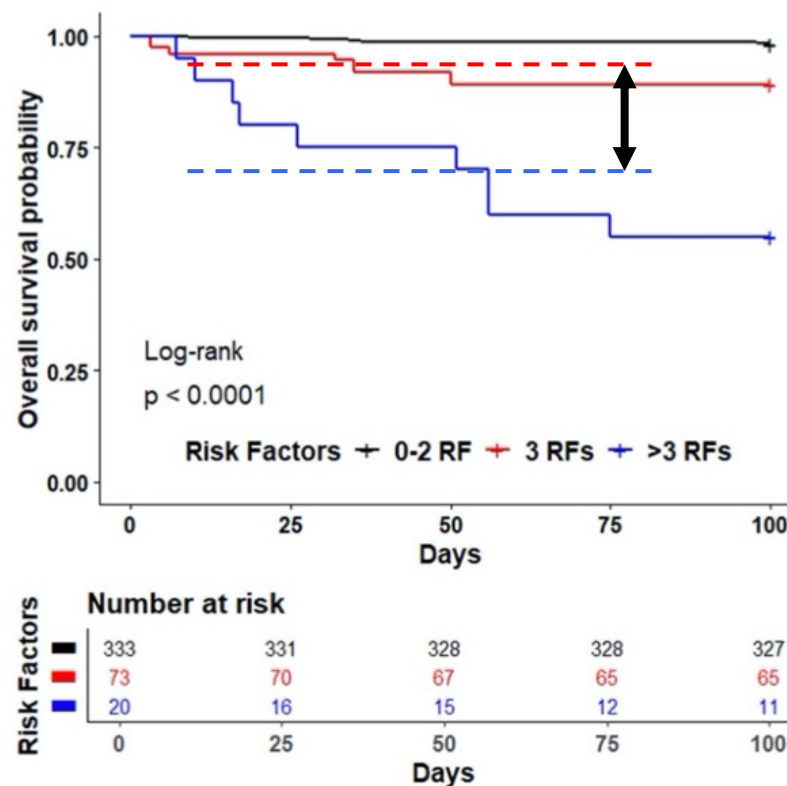
Allo-HSCT
Lung Tx

Other SOTs

COPD-bronchiectasis
 Auto-inflammatory
 diseases

Lowest
impact

Children < 5 a



Overall survival probability at day 100
 after CARV detection in allo-HSCT
 recipients with lower RT disease
 according to risk factors :

- Donor/recipient HLA mismatch
- CST use
- GvHD
- ALC < 0.1
- Neutropenia
- Age ≥ 40y



Highest
impact

Allo-HSCT
Lung Tx

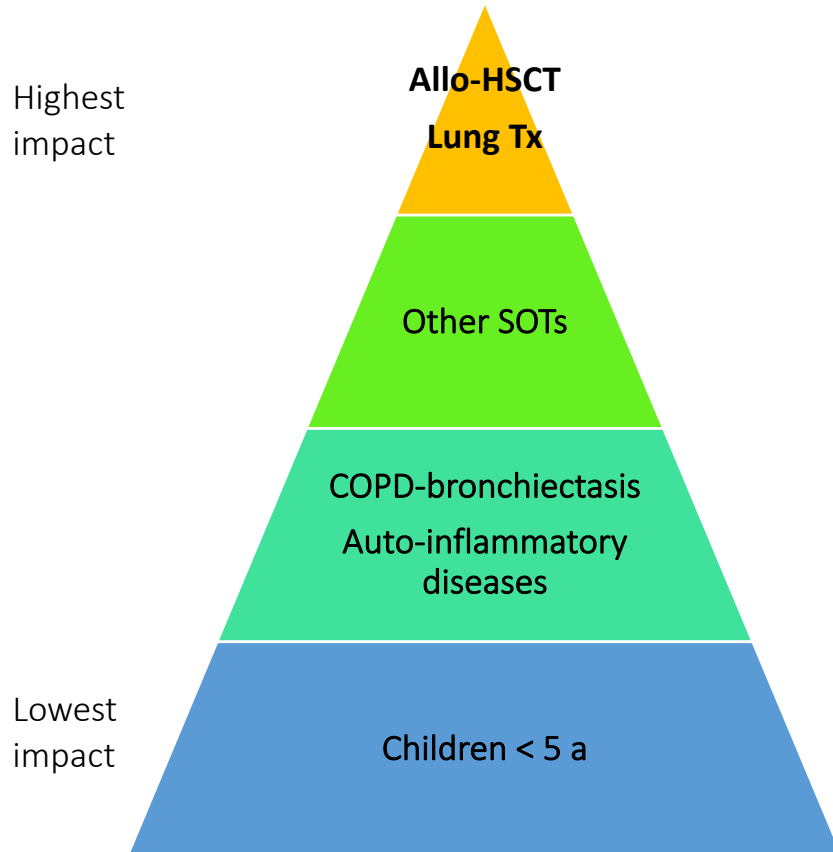
Other SOTs

COPD-bronchiectasis
Auto-inflammatory
diseases

Lowest
impact

Children < 5 a

→ Key factors influencing net immune status



At transplantation

Age (threshold 40 yr)

Multiple transplants

End-organ disease

Malnutrition

Conditioning

Graft source

Related vs. unrelated (HLA mismatch)

Receipt of lympho-depleting agents



Highest
impact

Allo-HSCT
Lung Tx

Other SOTs

COPD-bronchiectasis
Auto-inflammatory
diseases

Lowest
impact

Children < 5 a



Post-transplantation

Time from transplantation (< 6 m.)

Age and malnutrition

IS regimen <---> anti-donor/graft immunity

Hypogammaglobulinemia (HSCT)

Slow/poor immune reconstitution



Allo-HSCT with CARV (RSV, PIV, MTPv and Influenza A/B)
at risk for progression from upper RTI to lower RTD

Highest
impact

Allo-HSCT
Lung Tx

Other SOTs

COPD-bronchiectasis
Auto-inflammatory
diseases

Lowest
impact

Children < 5 a

Allo-HSCT – Immunodeficiency Scoring Index

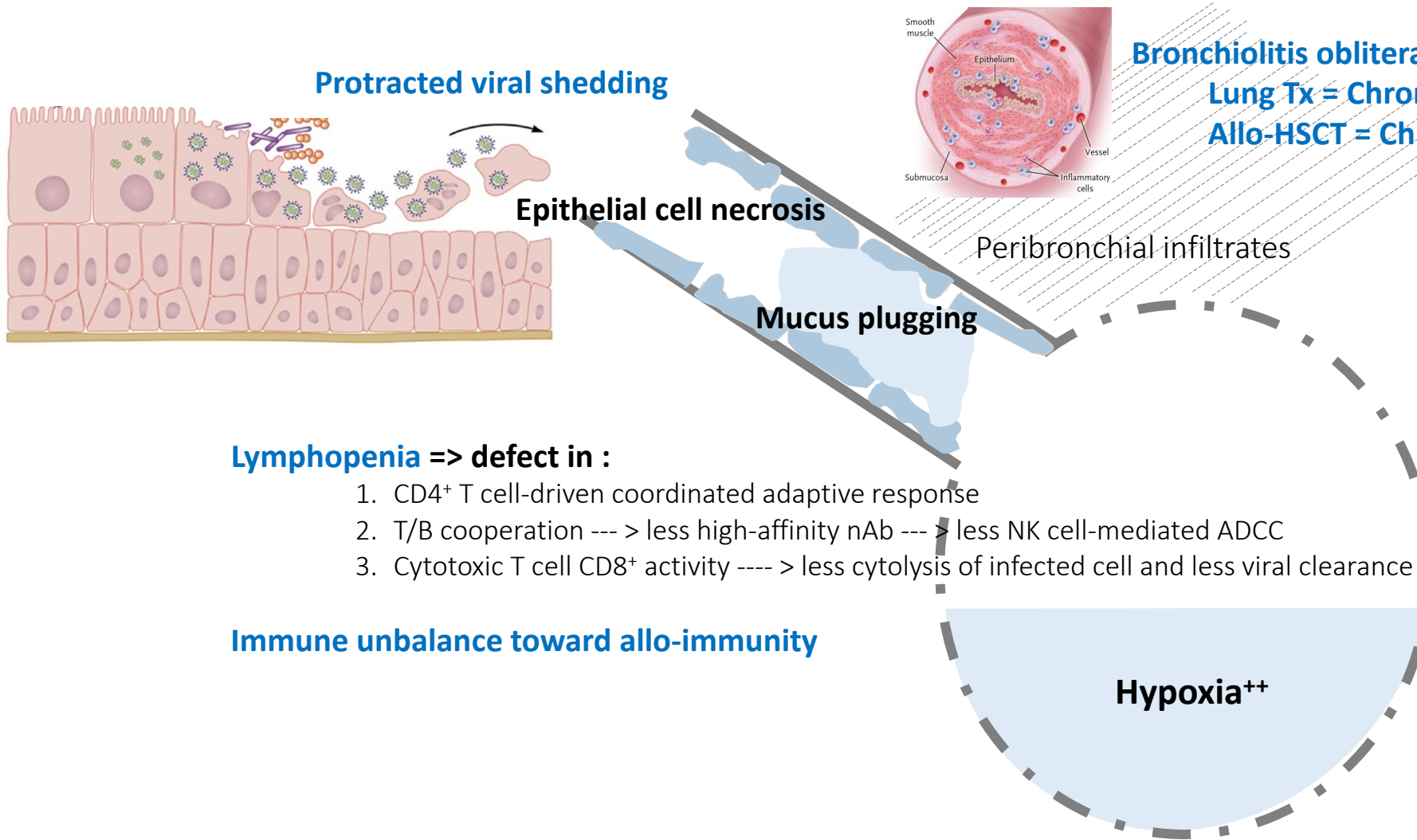
Criterion or parameter

Neutropenia, $<0.5 \times 10^9$ /L	3
Lymphopenia, $<0.2 \times 10^9$ /L	3
Myeloablative conditioning	1
Pre-engraftment or allo-HCT < 1 month	1
GvHD (acute/chronic)	1
Corticosteroids	1
Age, > 40 yr	2
Maximal	12

Stratification

Low risk	0-2
Moderate risk	3-6
High risk	7-12

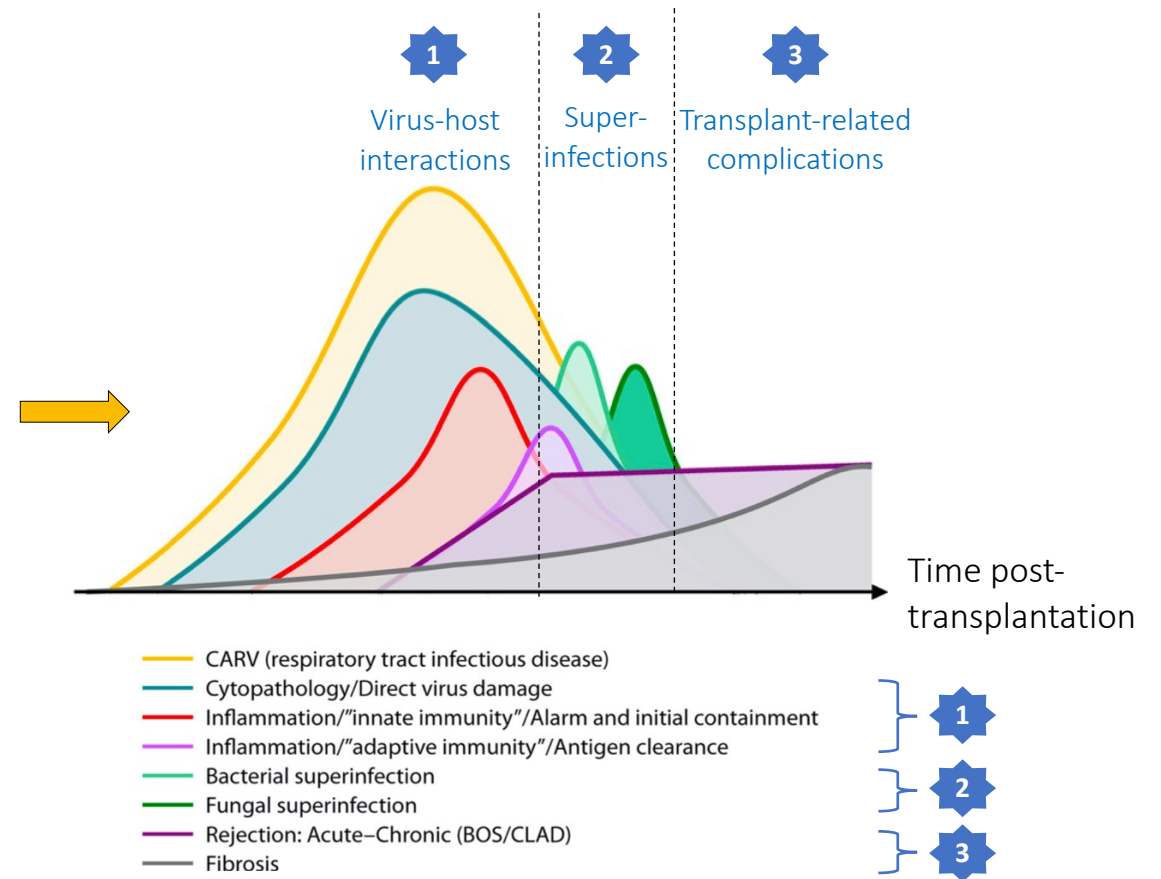
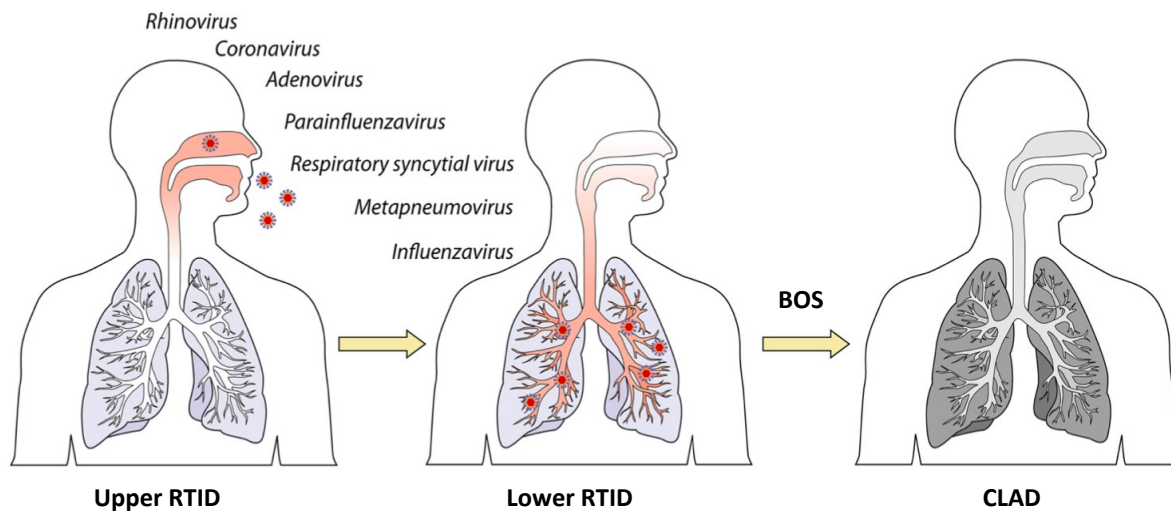
+ multiple transplants



Lymphopenia => defect in :

1. CD4⁺ T cell-driven coordinated adaptive response
2. T/B cooperation --- > less high-affinity nAb --- > less NK cell-mediated ADCC
3. Cytotoxic T cell CD8⁺ activity ---- > less cytotoxicity of infected cell and less viral clearance

Immune unbalance toward allo-immunity

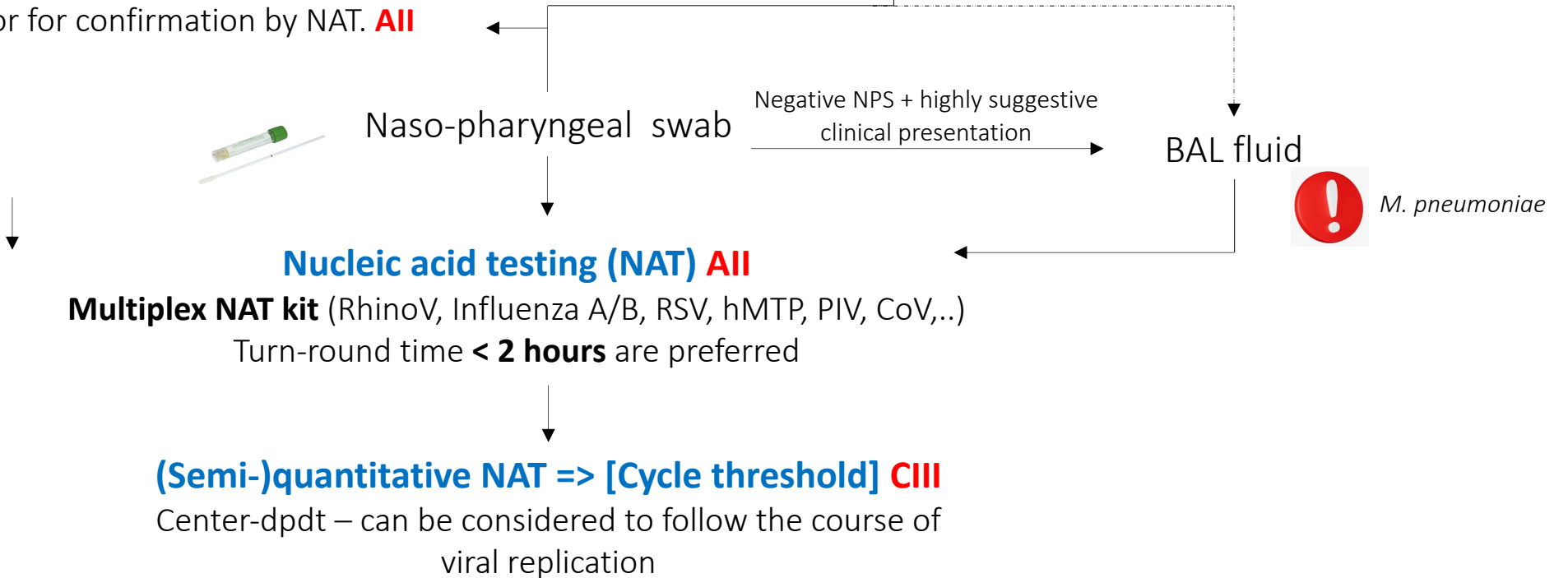


Diagnosis work up

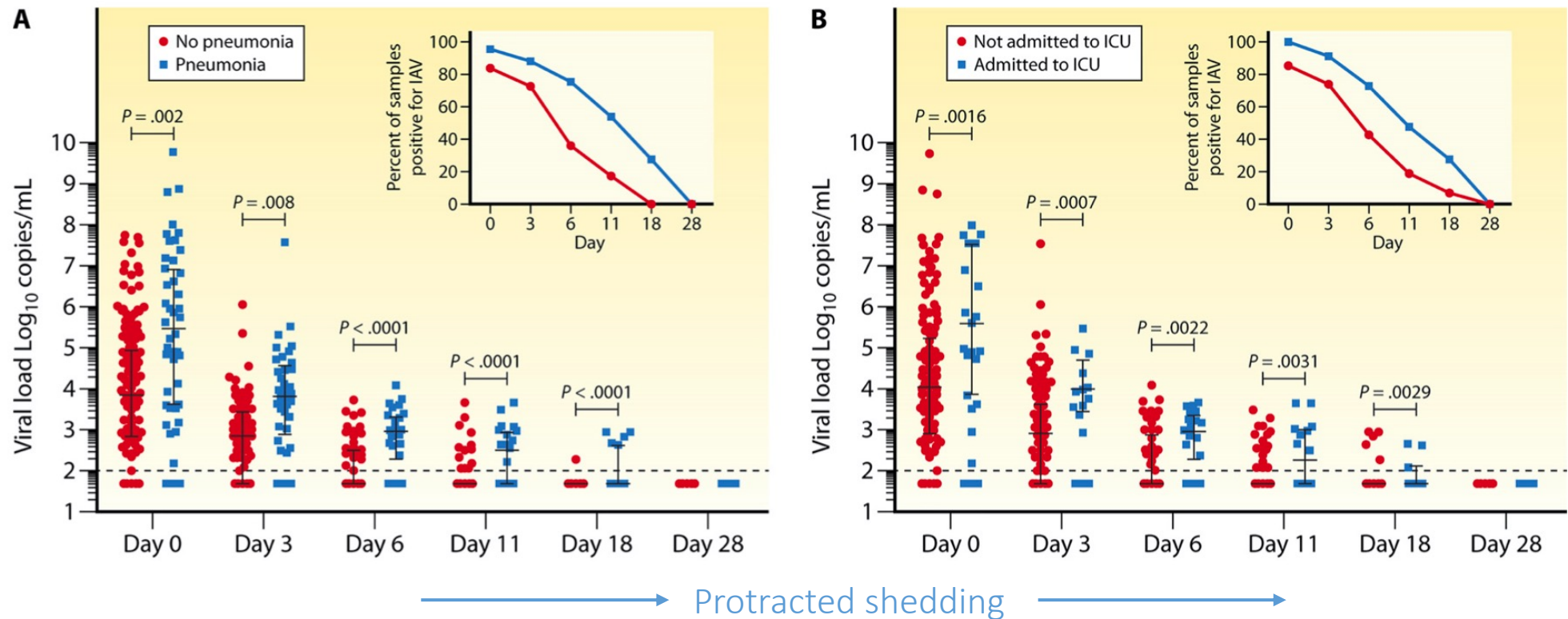


Direct antigen detection (DAD) = lower sensitivity compared to CARV-NAT and reduced specificity in low prevalence setting, but if used for rapid (self-) testing, the result should be discussed with referent physician to evaluate the consequences for care including the need of early antivirals or for confirmation by NAT. **AII**

ENT symptoms/cough/fever



5 consecutive **influenza** seasons
n=616 transplant recipients infected with influenza
SOT, n=477; HSCT recipients, n=139

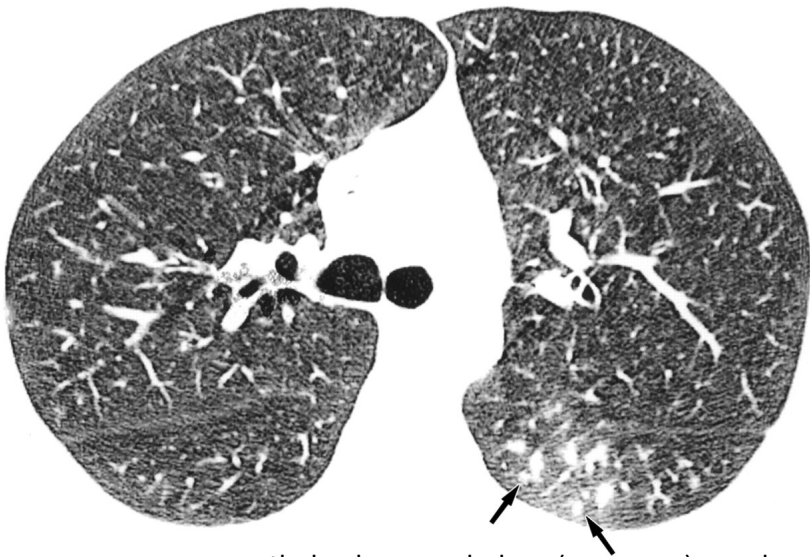


Imagery work up ----- > [HR] CT scan

Patches of **ground glass opacities**

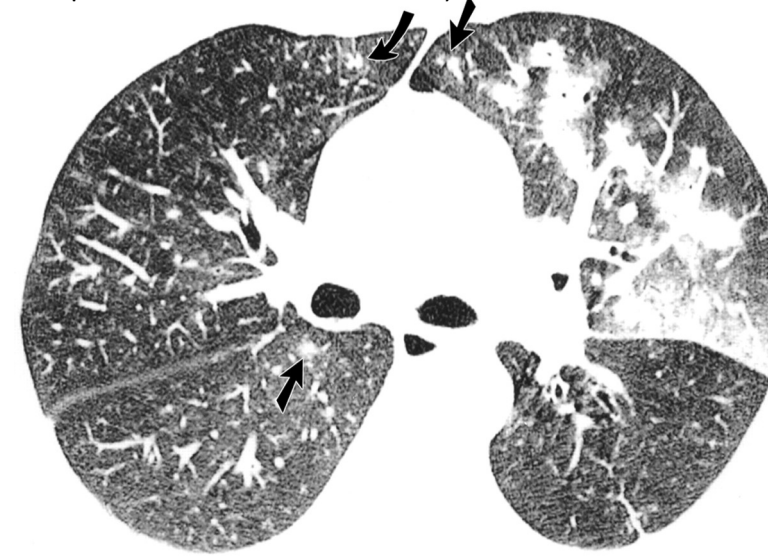
Airway inflammatory changes such as **tree-in-bud opacities** (20-50%), **bronchial wall thickening** (30-70%), **centrilobular nodules** (35-60%) and **peribronchiolar consolidation** (~ 50%) are associated with CARV LRTD.

Multifocal consolidation is commonly found in cases of CARV LRTD but is **non-specific**.



Centrilobular nodules (arrows) and adjacent ground-glass opacities

Centrilobular branching nodular opacities
(tree-in-bud pattern, curved arrow)

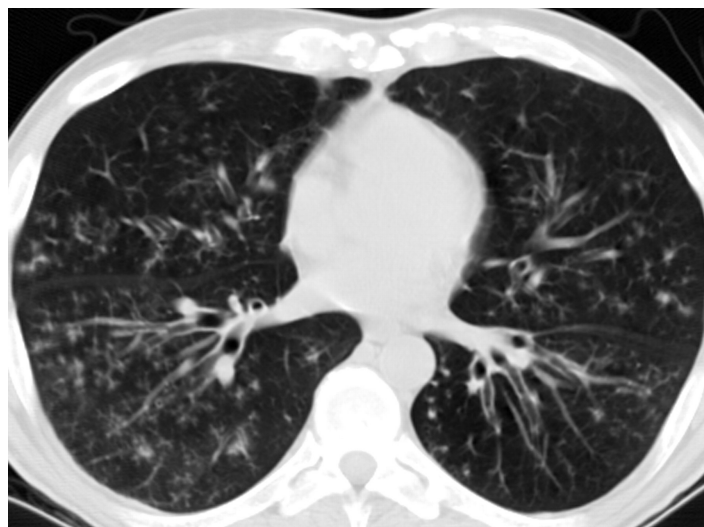


Centrilobular nodules (straight arrows)

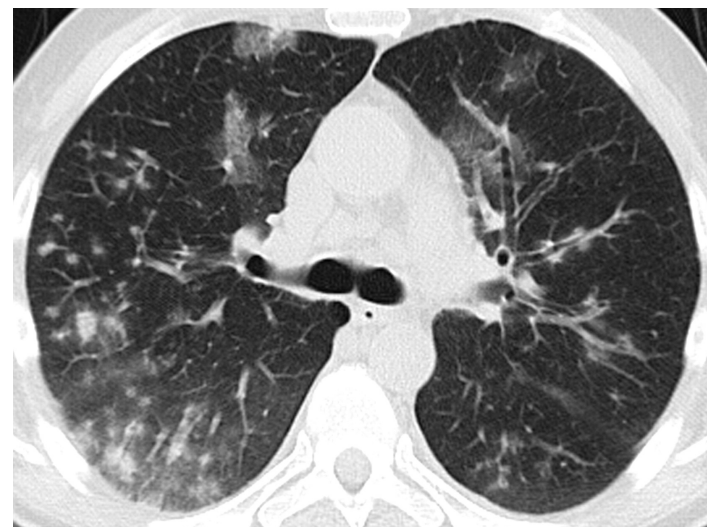
Ground-glass opacities and dense focal areas of consolidation



Lung Tx – RSV LRTD

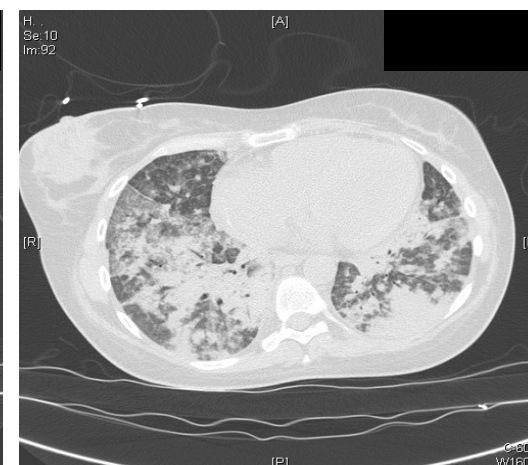
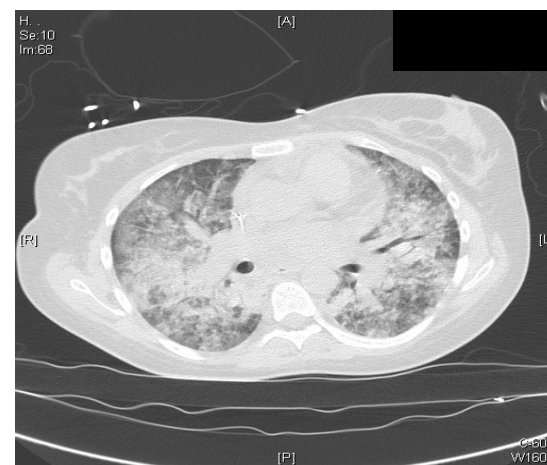
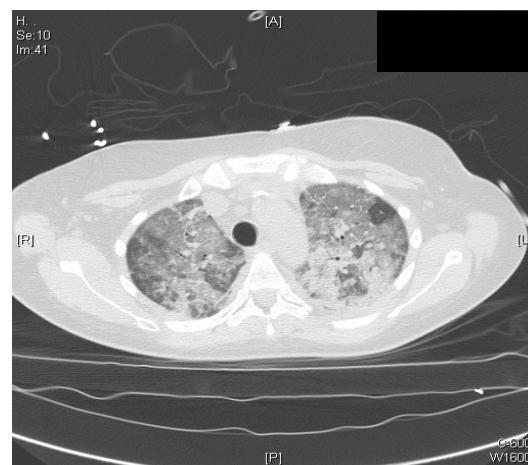
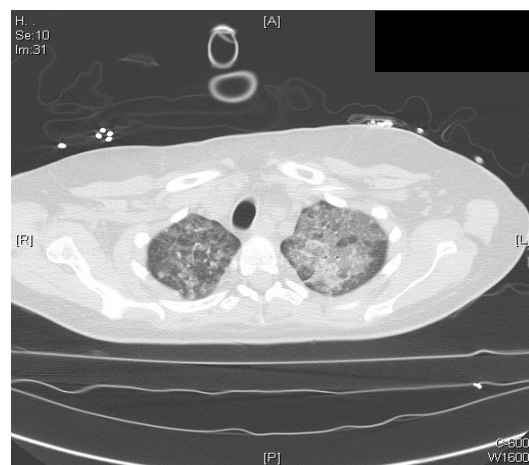


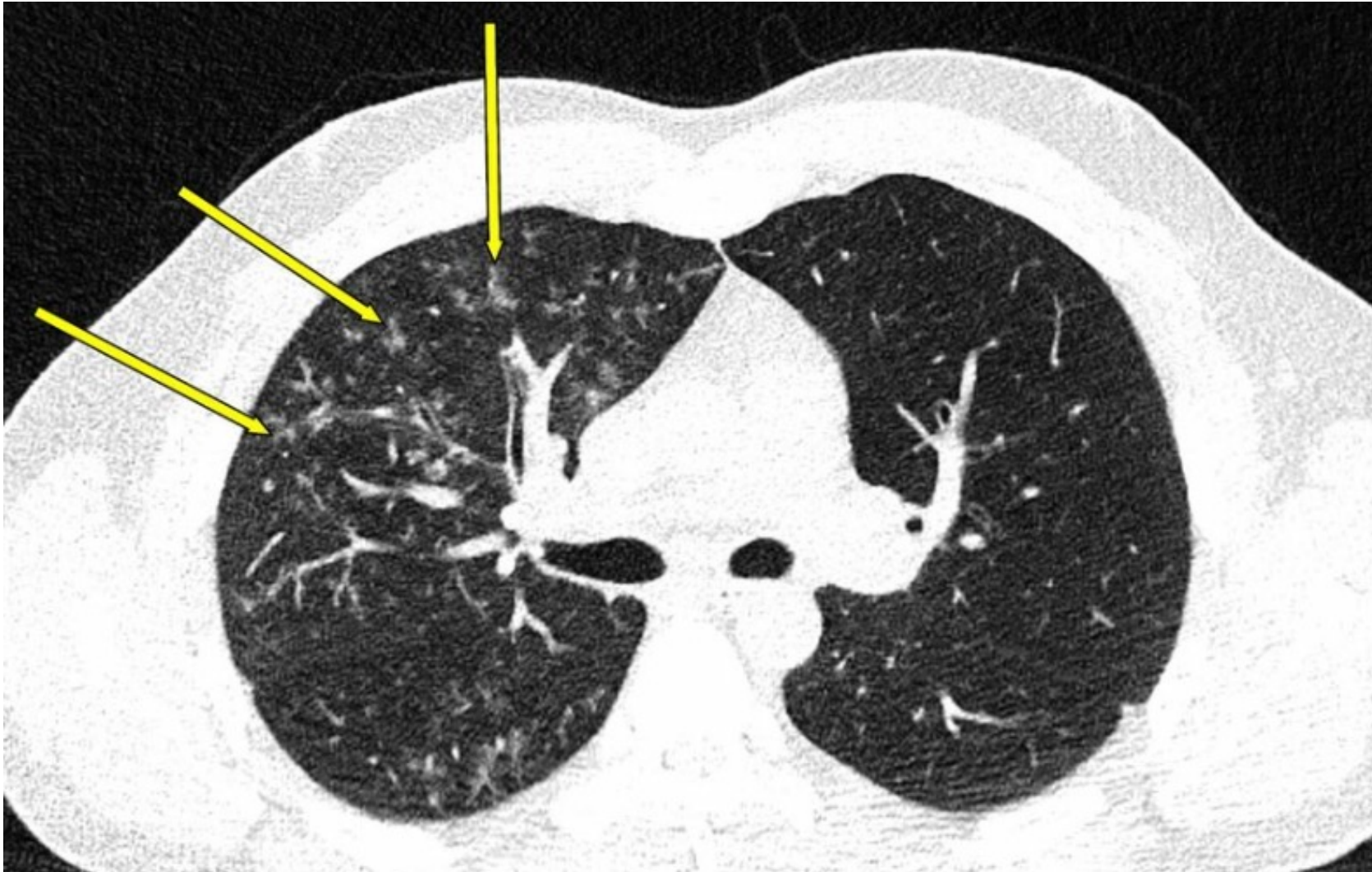
Allo-HSCT – Influenza LRTD



Allo-HSCT – RSV LRTD

Allo-HSCT day 10 post-transplantation – RSV ARDS





Upper respiratory tract infection (URTI)

- detection of respiratory virus in a respiratory sample
- AND
- at least one of: new onset of cough, or sore throat, or shortness of breath, or coryza, or fever, or nasal congestion
- AND
- clinician judgement that the illness was due to the infection
- AND
- **NO** criteria for LRTD

Lower respiratory tract disease (LRTD)

- detection of respiratory virus in a respiratory sample
- AND
- at least one of: new onset of cough, sore throat, shortness of breath, coryza, or fever
- AND
- clinician judgement that the illness was due to the infection
- AND
- at least one of:
 - hypoxia** defined as oxygen saturation <90% or need for supplemental oxygen,
 - or **radiologic infiltrate(s)**,
 - or detection of **respiratory virus in a LRT** sample

Upper respiratory tract infection (RTI) at
high-risk of progression to lower RT
disease (20-30%)

Determinants of decision making

Type of transplantation [Allo-HSCT, lung Tx]

Time after transplantation

IS regimen

GvHD/acute-chronic rejection

Lymphopenia/neutropenia



Timing of decision⁺⁺⁺

Treat **ALL** lower RT diseases

DIRECT-ACTING
ANTIVIRALS

?

IMMUNOGLOBULINS

?

CORTICOSTEROIDS

?

VIRUS-SPÉCIFIC mAbs



Data on adjuvant treatments: IV Igs or corticosteroids ?

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DOI: 10.1111/tid.14142

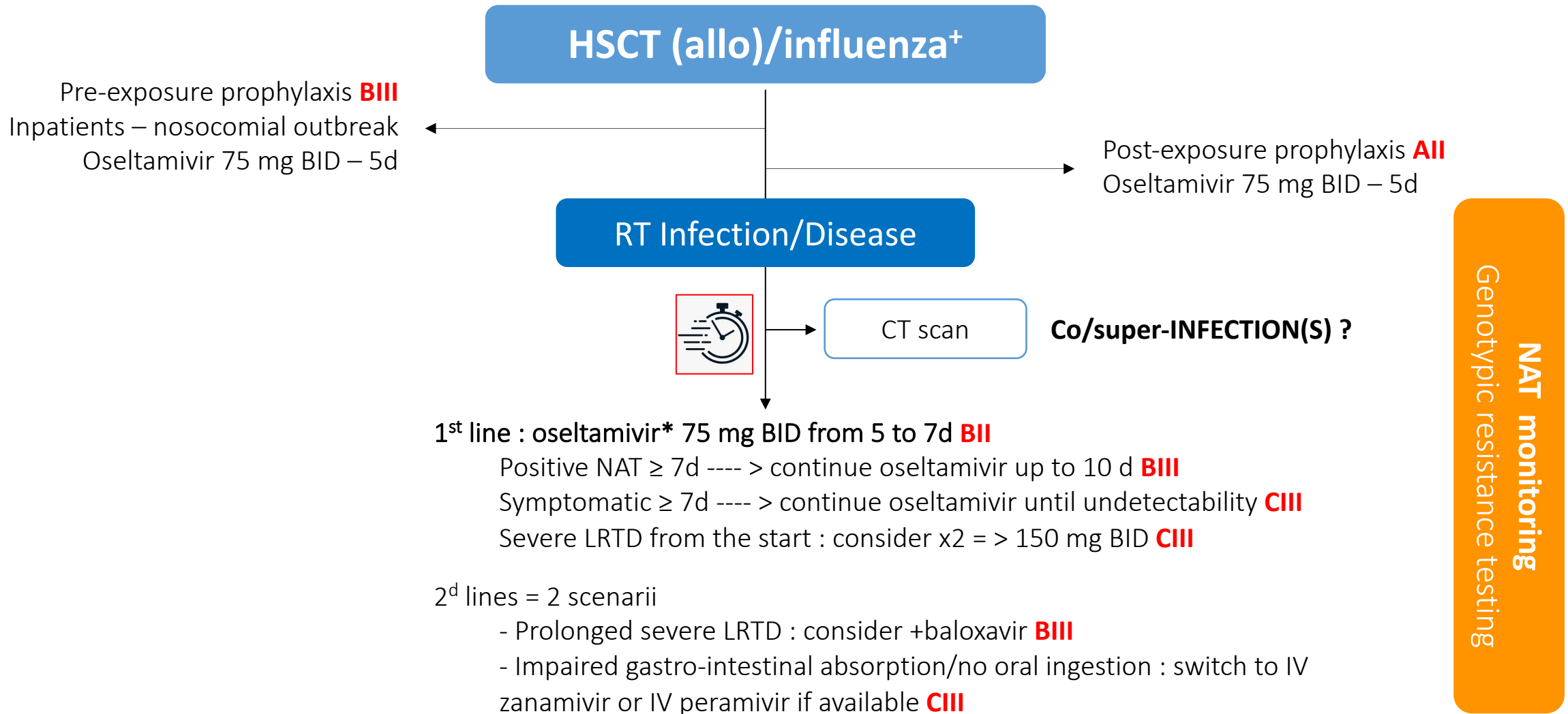
EDITORIAL



The role of systemic steroids in lung transplant recipients with community-acquired respiratory viruses: Time for a moratorium, or not?

*Courtesy of Dr Lorena van den Bogaart
Hospices Civils de Lyon*

Influenza : therapeutic algorithm



* Full dose oseltamivir 75 BID > 40 kgs

Inactivated Influenza Vaccine (IIV)

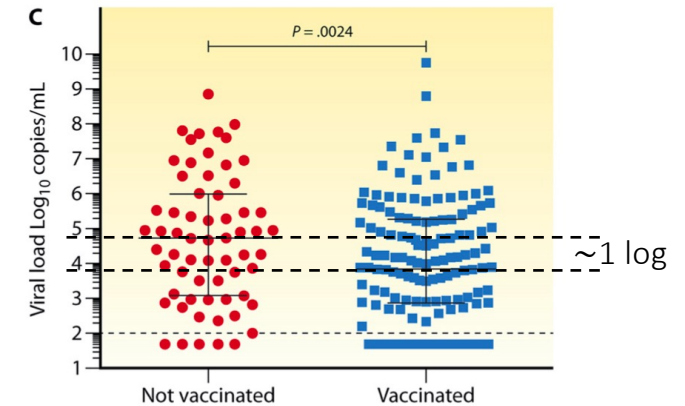
Risk Factor	No.	Pneumonia (n = 134)	No Pneumonia (n = 472)	P Value (Univariate)	Multivariate OR (95% CI)	P Value (Multivariate)
Influenza vaccination in the same season	543	63/119 (52.9)	306/416 (73.6)	<.001	0.34 (.21–.55)	<.001

Annual seasonal **IIV** is recommended to be given at the beginning of influenza season for all patients at **3 to 6 months** post-transplant. **AII**

Vaccination should be continued on a yearly basis. **AII**
+ vaccinations of **household individuals**

High-dose trivalent IIV-A/B is recommended for **allogeneic** HSCT-patients. **AII**

A **2nd dose after 4 weeks** may have a benefit **BIII** and should be considered in patients with **severe GvHD**, **low lymphocyte counts**, or during a prolonged **community outbreak**.



Kumar et al. Clin Infect Dis. 2018 doi: 10.1093/cid/ciy294

Ison MG, Hirsch HH. Clin Microbiol Rev 2019. doi: 10.1128/CMR.00042-19

Adapted from ECIL10 Sept 2024 update of 2019 guidelines <https://www.ecil-leukaemia.com/en/resources/resources-ecil>
von Lilienfeld-Toal M et al. Lancet Infect Dis 2025. 2025 Aug 27:S1473-3099(25)00365-2. doi: 10.1016/S1473-3099(25)00365-2.

STOP Flu Trial

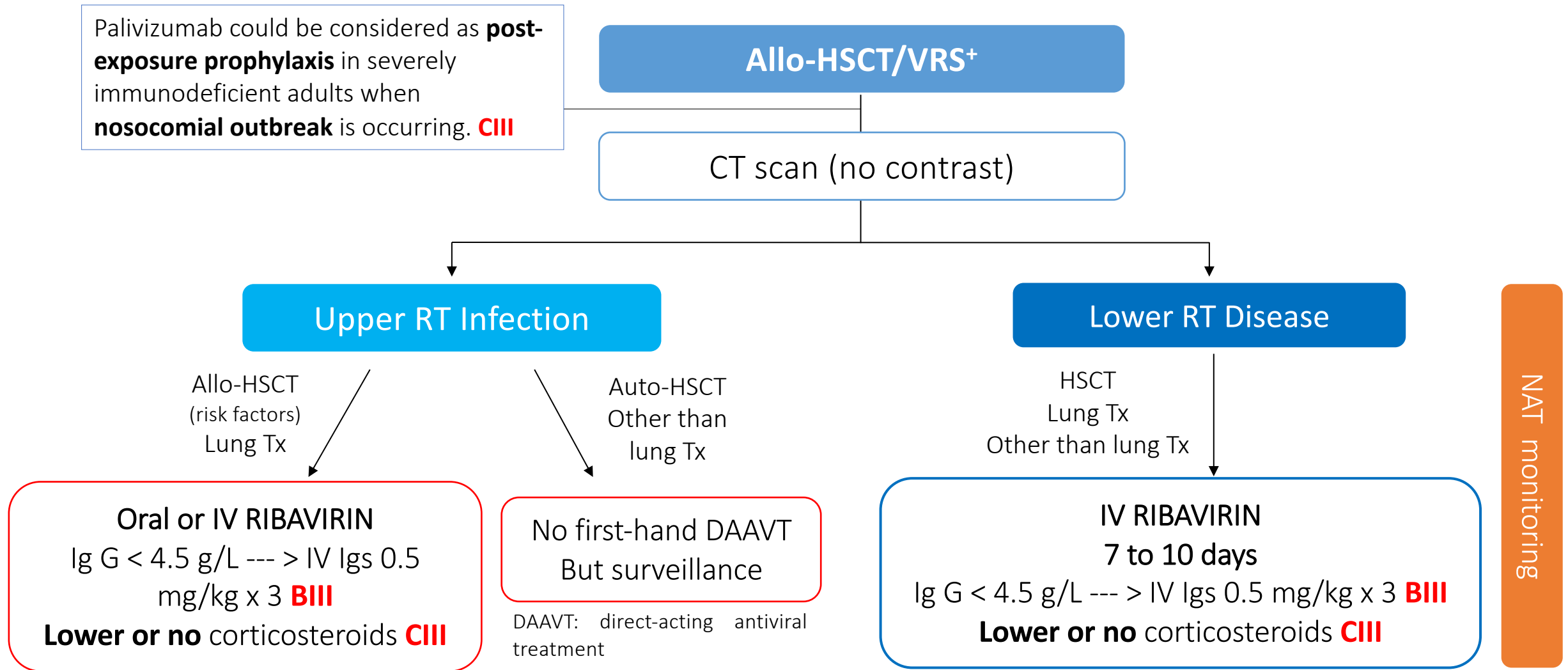
Target population = **SOT**

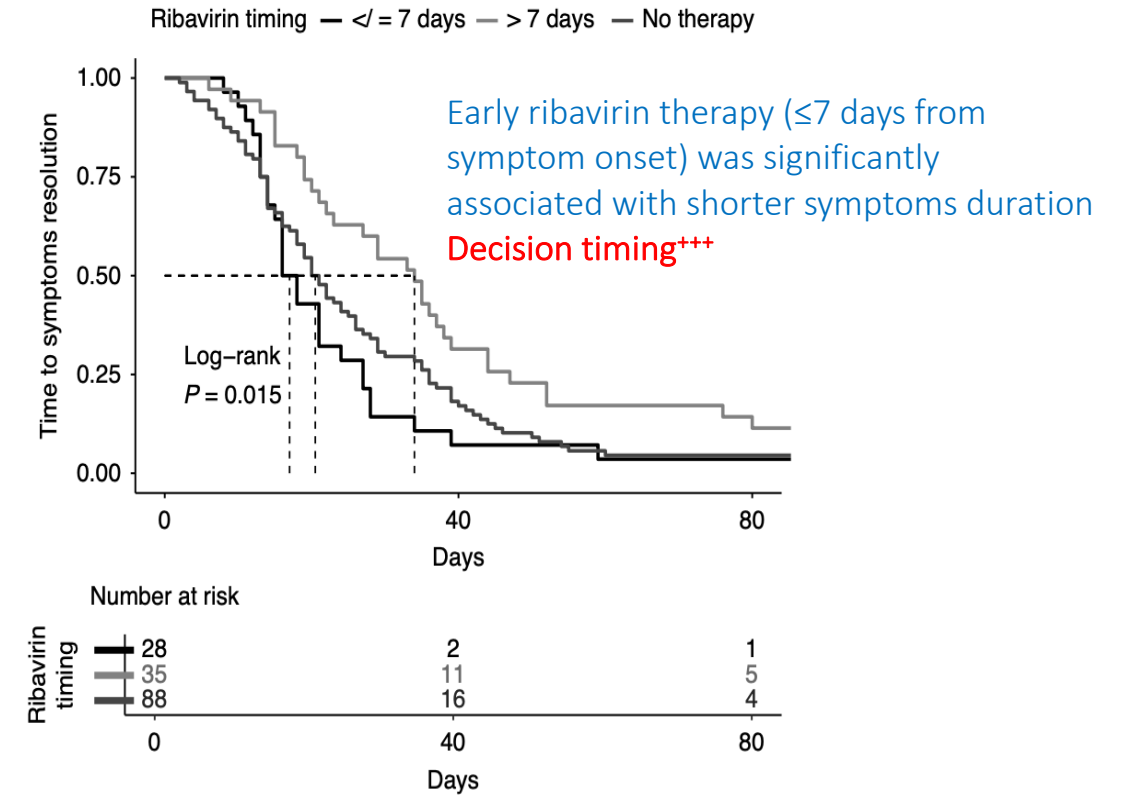
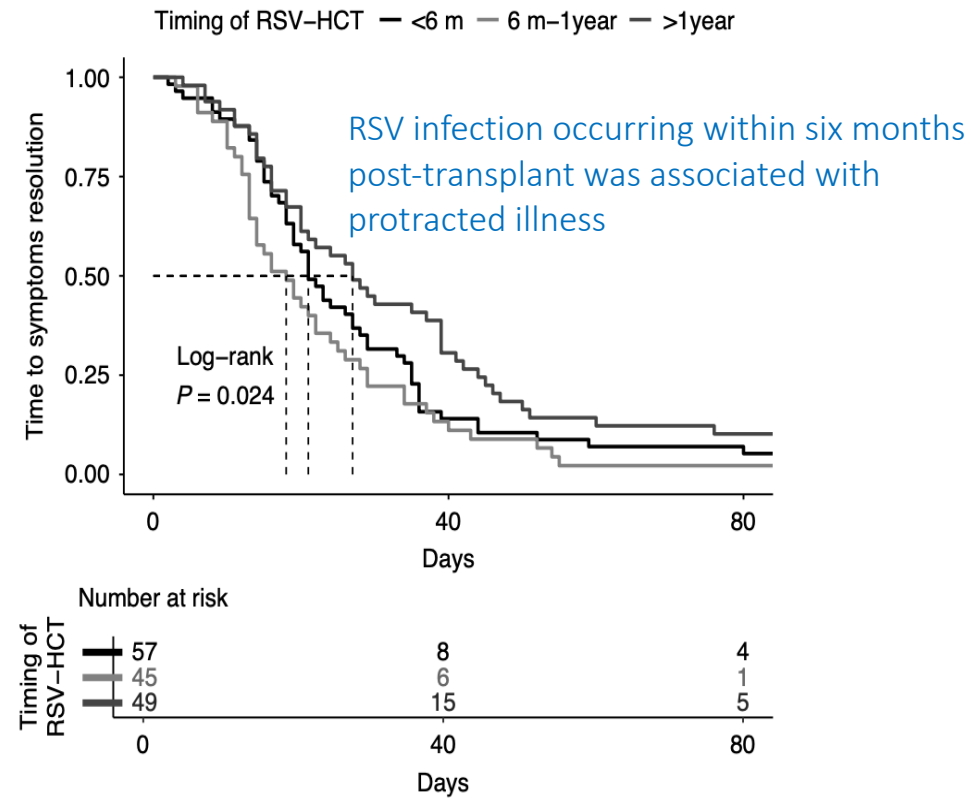
High-dose vs MF59-adjuvanted vs standard influenza vaccine – 1:1:1

Primary outcome : **vaccine response rate at day 28** = > proportion of seroconversion for at least 1 viral strain (at least 4-fold increase of HAI titer from baseline)

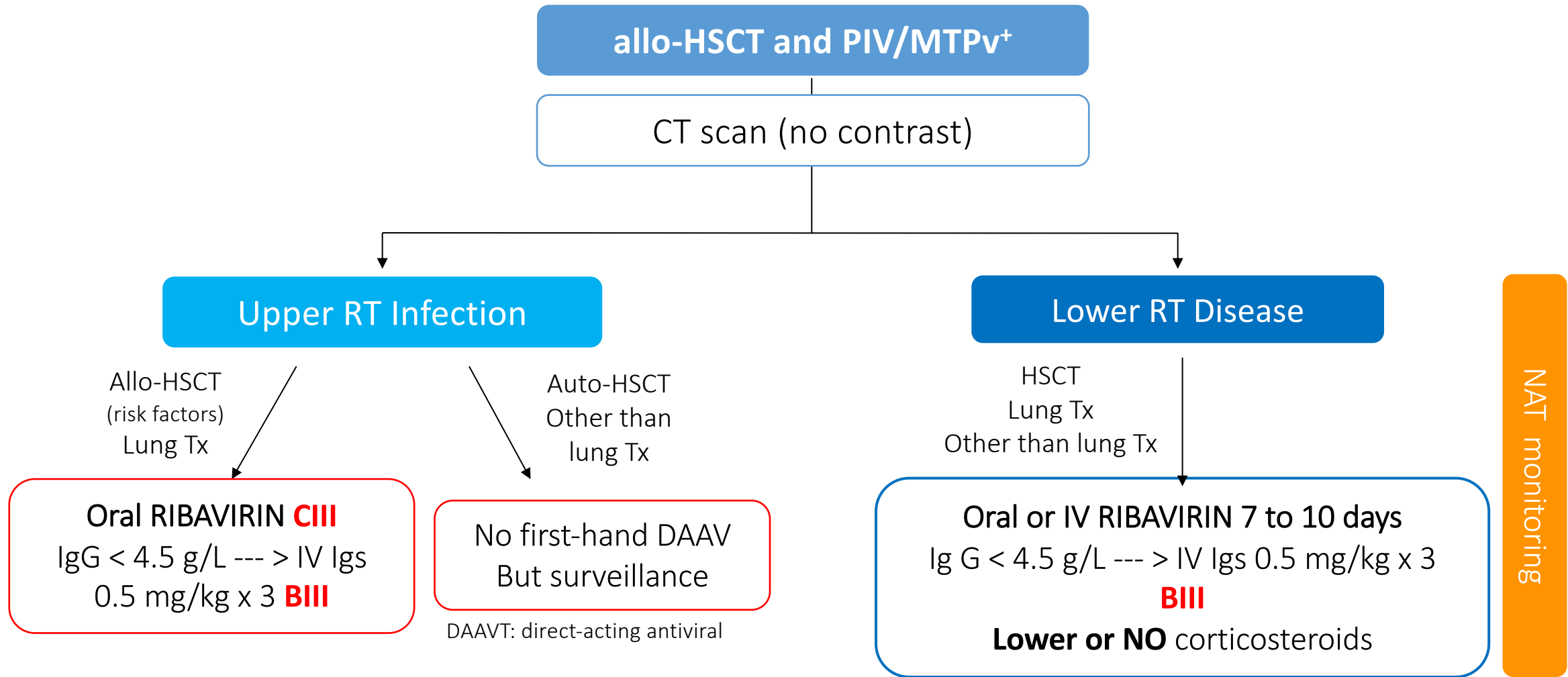
	Vaccine Response Rate	Risk Difference	<i>P</i> Value
High-dose and MF59-adjuvanted versus standard vaccine ^a	63% (251/400) versus 42% (84/198)	0.20 (97.5% CI, .12–1)	<.001
High-dose versus standard vaccine ^a	66% (129/195) versus 42% (84/198)	0.24 (95% CI, .16–1)	<.001
MF59-adjuvanted versus standard vaccine ^b	60% (122/205) versus 42% (84/198)	0.17 (97.5% CI, .08–1)	<.001
High-dose versus MF59-adjuvanted vaccine ^b	66% (129/195) versus 60% (122/205)	0.07 (95% CI, –.01 to 1)	.085

RSV : therapeutic algorithm





PIV and hMPV : therapeutic algorithm



For patients at high risk for progression to, or who have been diagnosed with, RSV-LRTID, adjunct treatment could be considered with at least three doses of intravenous immunoglobulin at 0·5 g/kg bodyweight within 1–2 weeks of diagnosis	BIII
For patients testing positive for RSV and hypogammaglobulinaemia (<4·5 g/L) , treatment with at least three doses of intravenous immunoglobulin at 0·5 g/kg bodyweight administered within 1–2 weeks of diagnosis could be considered	BIII
Use of corticosteroids at more than 1 mg/kg per day at diagnosis of RSV-LRTID has been associated with disease progression and mortality ; thus, reducing corticosteroid administration to less than 1 mg/kg of bodyweight can be considered if feasible	CIII

Ribavirin (RBV): 1972 !! Guanosine analogue

Bio-availability **45-65%**

Ingestion with **fat meal** : bio-availability optimization **x 1.5**

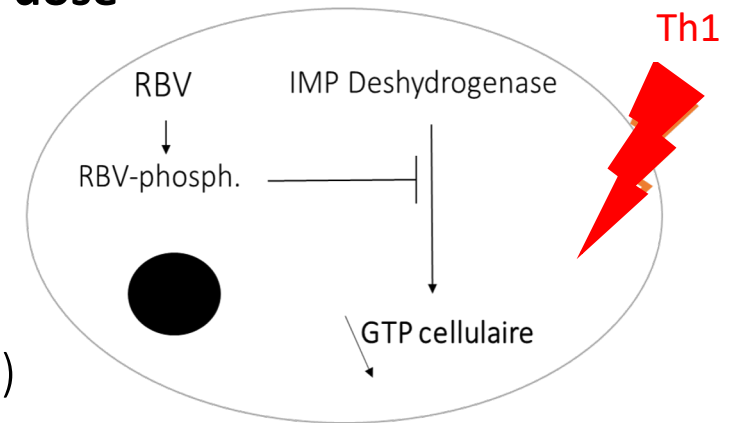
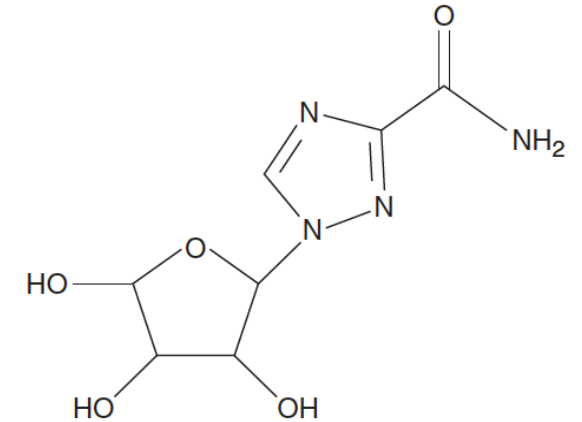
Important but slow **tissular diffusion index**, CNS included

Long half-life = **150h** (1 dose) up to **300h** (cumulative doses)---- > **loading dose**

Drug clearance dpdt on :

- **weight** (adaptation dose/weight)
- **renal function**

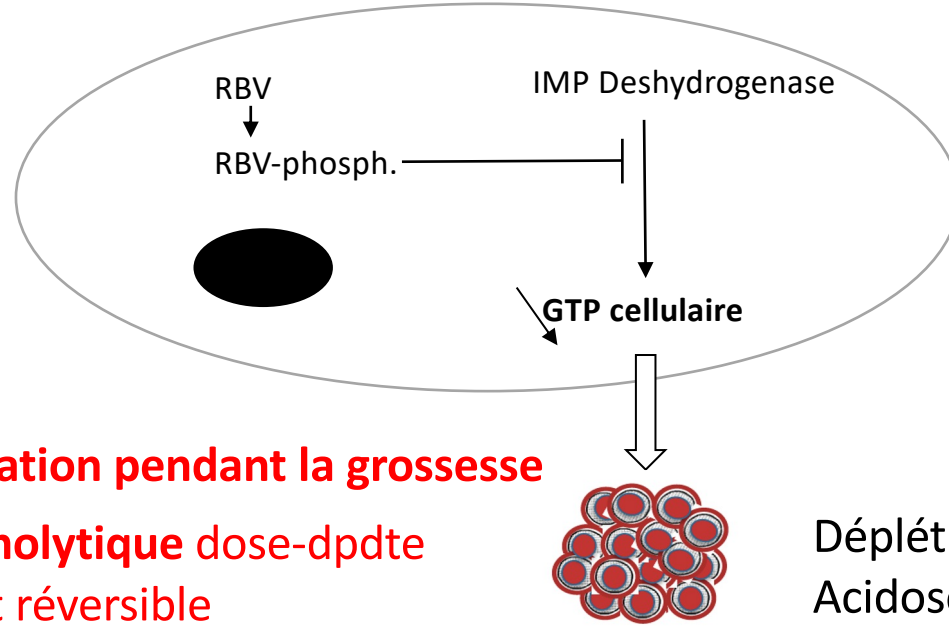
No hepatic metabolization = no dose adaptation (end-stage liver diseases)



Use of systemic ribavirin for RTI/D with RSV, PIV, and MPV

Treatment course	Description
Oral or intravenous ribavirin maximal dosing at 10 mg/kg body weight every 8 h for adults	Day 1: start with 600 mg loading dose, then 200 mg every 8 h Day 2: 400 mg every 8 h Day 3: Increase the dose to a maximum of 10 mg/kg body weight every 8 h In case of adverse events, decrease dose or discontinue ribavirin
Oral or intravenous administration according renal function	Dose for a creatinine clearance of 30 to 50 ml/min: a maximum of 200 mg every 8 h For a creatinine clearance of 10 to 30 ml/min, no dose recommendation can be given ^b

^bSome experts use 200 mg once daily under close clinical and laboratory monitoring

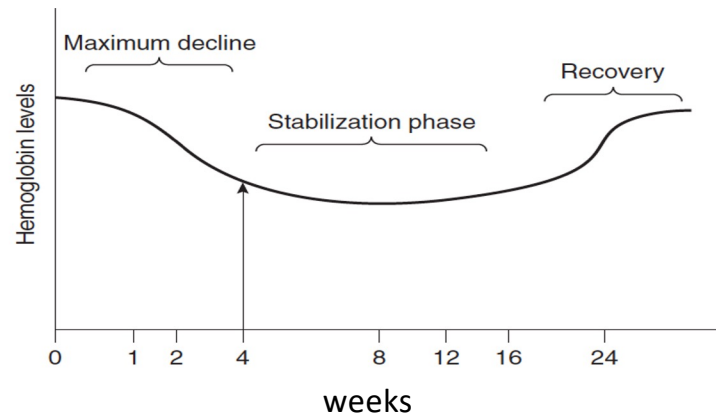


Anemia (11-35%)
Hemolytic anemia (10-13%)
 Neutropenia (8-40%)
 Lymphopenia (14%)
MOSTLY IF >14 days



Contre-indication pendant la grossesse
Anémie hémolytique dose-dépendante et réversible

Déplétion GTP et ATP
 Acidose lactique



Prophylactic anti-RSV mAbs in high-risk adult transplant recipients ?



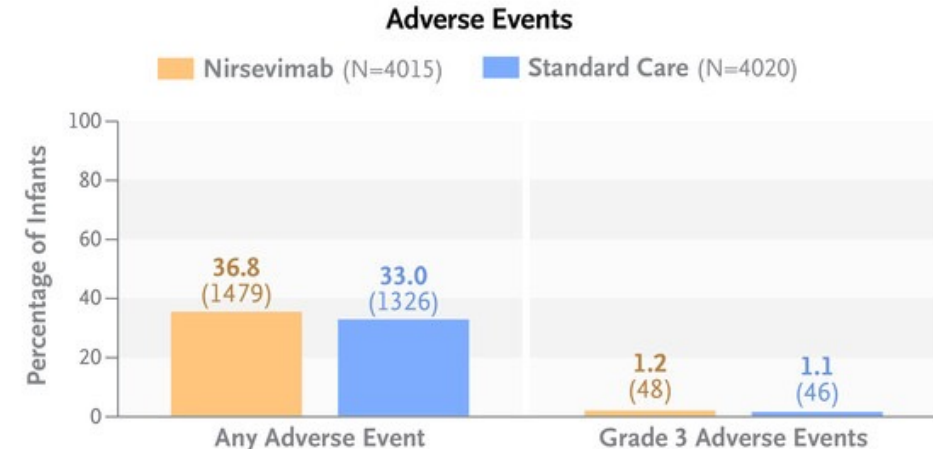
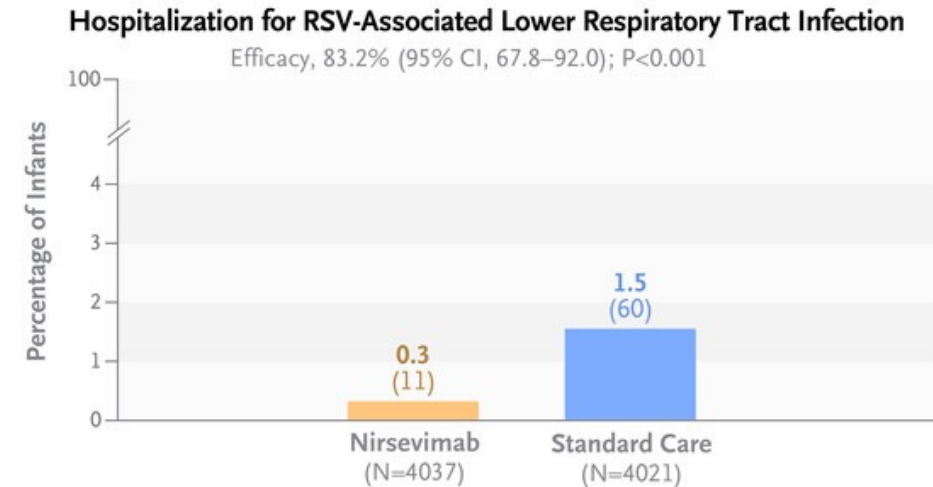
Randomized Controlled Trial > N Engl J Med. 2023 Dec 28;389(26):2425-2435.

doi: 10.1056/NEJMoa2309189.

Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants

Simon B Drysdale¹, Katrina Cathie¹, Florence Flamein¹, Markus Knuf¹, Andrea M Collins¹, Helen C Hill¹, Friedrich Kaiser¹, Robert Cohen¹, Didier Pinquier¹, Christian T Felter¹, Natalya C Vassilouthis¹, Jing Jin¹, Mathieu Bangert¹, Karine Mari¹, Rapi Nteene¹, Sophie Wague¹, Michelle Roberts¹, Pierre Tissières¹, Simon Royal¹, Saul N Faust¹; HARMONIE Study Group

Phase III, open label RCT
1:1 nirsevimab vs SoC



International phase III RCT vs placebo, ≥60y, exclusion criteria = immunocompromised

ORIGINAL ARTICLE

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

A. Papi, M.G. Ison, J.M. Langley, D.-G. Lee, I. Leroux-Roels, F. Martinon-Torres, T.F. Schwarz, R.N. van Zyl-Smit, L. Campora, N. Dezutter, N. de Schrevel, L. Fissette, M.-P. David, M. Van der Wielen, L. Kostanyan, and V. Hulstrøm, for the AReSVi-006 Study Group*

RSVPreF3 OA (adj.) n = 24,966

n LRTD VRS+

47 (2S+ ou 3 S+)

Vaccine efficacy

82.6%

ORIGINAL ARTICLE

Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults

E.E. Walsh, G. Pérez Marc, A.M. Zareba, A.R. Falsey, Q. Jiang, M. Patton, F.P. Polack, C. Llapur, P.A. Doreski, K. Ilangovan, M. Råmet, Y. Fukushima, N. Hussen, L.J. Bont, J. Cardona, E. DeHaan, G. Castillo Villa, M. Ingilizova, D. Eiras, T. Mikati, R.N. Shah, K. Schneider, D. Cooper, K. Koury, M.-M. Lino, A.S. Anderson, K.U. Jansen, K.A. Swanson, A. Gurtman, W.C. Gruber, and B. Schmoele-Thoma, for the RENOIR Clinical Trial Group*

RSVpreF (biv.) n = 34,284

44 (2S+)/16 (3S+)

66.7% (2S+)/85.7% (3S+)

ORIGINAL ARTICLE

Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults

E. Wilson, J. Goswami, A.H. Baqui, P.A. Doreski, G. Perez-Marc, K. Zaman, J. Monroy, C.J.A. Duncan, M. Ujije, M. Råmet, L. Pérez-Breva, A.R. Falsey, E.E. Walsh, R. Dhar, L. Wilson, J. Du, P. Ghaswalla, A. Kapoor, L. Lan, S. Mehta, R. Mithani, C.A. Panozzo, A.K. Simorellis, B.J. Kuter, F. Schödel, W. Huang, C. Reuter, K. Slobod, S.K. Stoszek, C.A. Shaw, J.M. Miller, R. Das, and G.L. Chen, for the ConquerRSV Study Group*

mRNA-1345 n = 35,541

64 (2S+)/20 (3S+)

83.7% (2S+) / 82.4% (3S+)

Papi A, et al; AReSVi-006 Study Group. N Engl J Med. 2023 doi: 10.1056/NEJMoa2209604
Walsh EE, et al; RENOIR Clinical Trial Group. N Engl J Med. 2023 doi: 10.1056/NEJMoa2213836
Wilson E, et al; ConquerRSV Study Group. N Engl J Med. 2023 doi: 10.1056/NEJMoa2307079

RSV vaccines

Nom, Fabricant	RSVpreF3-AS01, GSK	RSVpreF, Pfizer Inc	mRNA-1345, Moderna
Type de vaccin	Protéique recombinant, avec adjuvant AS01E 1 dose	protéique recombinant, bivalent (A et B), sans adjuvant 1 dose	ARNm
AMM FDA	50-59 ans « à risque » ≥60 ans 	18-59 ans « à risque » ≥60 ans 	≥60 ans 
AMM EMA	50-59 ans « à risque » ≥60 ans 	≥18 ans 	≥60 ans 
Disponible en France	≥ 65 ans « à risque » ≥ 75 ans Femme enceinte 32-36 SA 		
Remboursement			
Prix	libre ≈200€	196,10€	

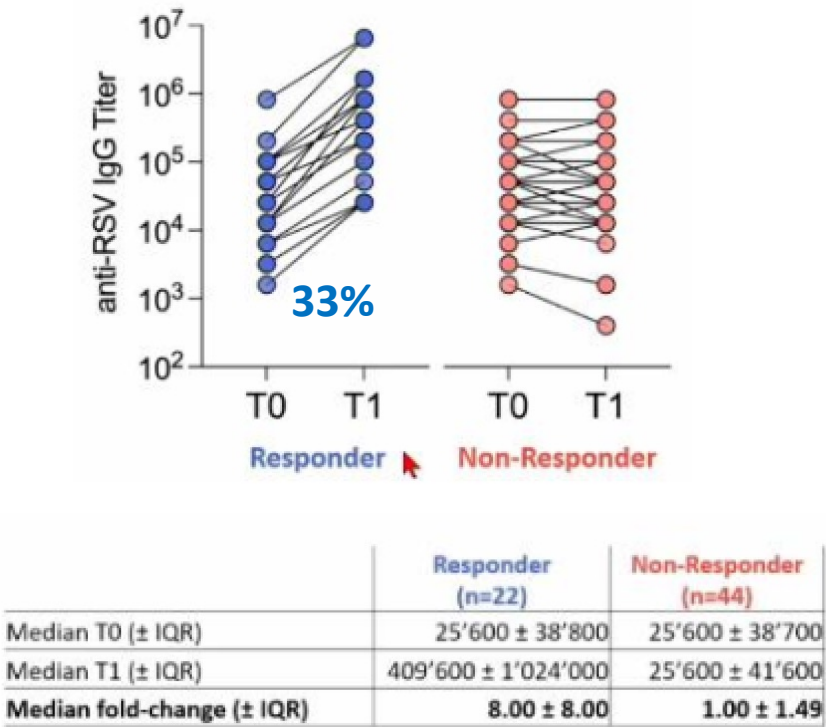
J. Lötscher, ESCMID Global 2025

Prospective, single-center Bâle
n = 112 allo-HSCT > 3 months. Median age 62y
Status = 50% IS drug, 50% GvHD
Single dose RSVpré-F3 (Arexsvy®) 53% within 12 months

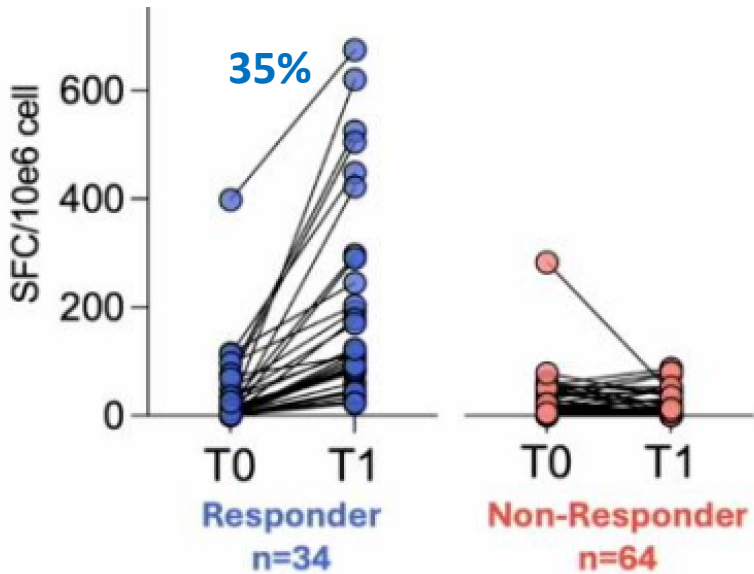


Risk factors for unresponsiveness:
GvHD
IS therapy
Delayed immune cellular recovery

Humoral response
(x4 anti-RSV pre-F IgG titers)
n = 66



Cellular response
(Anti-F ELISPOT)
n = 98



Prevention⁺⁺⁺/Education ---- > what have we learned from the COVID-19 pandemics (??)

Allo-HSCT/lung Tx

Frequency : RhinoV

Severity : influenza/RSV

Co/super-infections

Proactive decision-making: risk factors + NAT + CT scan

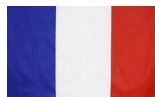
Neuraminidase inhibitor/oseltamivir

Guanosine analogue/ribavirin

Influenza vaccine⁺⁺⁺

RSV vaccine ? ----- >RSVaxID

Prophylactic mAbs ?



PHRC N 2025

RSVaxID: immunogenicity and safety of two respiratory syncytial virus vaccine strategies in lung and allogeneic haematopoietic stem cell transplant recipients: a phase 2 trial
PI: Dr. Anne CONRAD