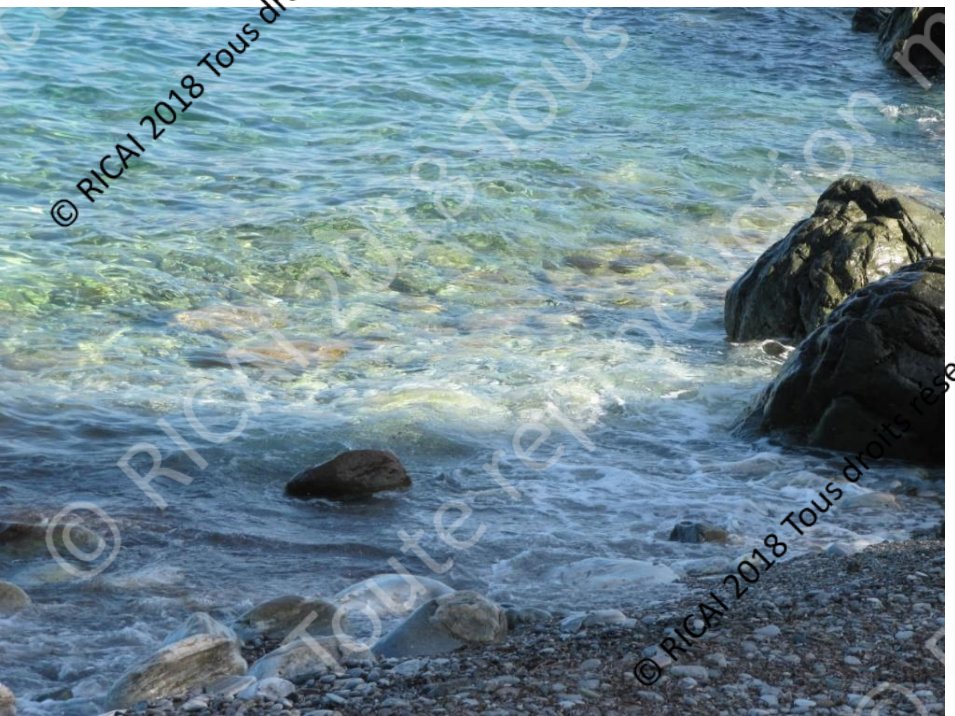
Infections à *Herpesviridae* en réanimation: mythe ou réalité ?



Laurent PAPAZIAN

Médecine Intensive-Réanimation

Hôpital Nord - Marseille

Conflits d'intérêts sur le sujet

- Industriel: aucun
- Institutionnel: PHRC 2011 étude PTH

Conflits d'intérêts sur d'autres sujets

- Faron, Air Liquide Santé, GSK, Covidien, Janssen, Orion, Johnson & Johnson, Peninsula Pharma

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Why???

- Viruses = emerging infectious diseases in ICU
- Many publications in MV patients
- Microbiological diagnosis

- Are herpesviruses pathogenics in ICU patients?
- Do HSV and CMV have the same pathogenicity?

Herpesviridae

- Normal population: 60-95%: *herpesviridae*

Simmons JID 2002

- Recognized as a pulmonary pathogen since 1949

Morgan and Finland Am J Med Sci 49

- Reactivation >>> primary infection/reinfection

HSV-1 and ARDS

- **Bronchial cytology**
  - ARDS (46): 30%
  - Mechanical ventilation (no ARDS): 0%

Tuxen et *al.* ARRD 82

- **Autopsies (n=16) in burns**
  - Herpetic viral inclusions: 0
  - IHC: 81 %

Byers et *al.* Eur Respir J 96

- **Autopsies**
  - HSV by IHC
    - Interstitial pneumonia: 46 %
    - Controls: 52 %
  - HSV by HE
    - Interstitial pneumonia: 18 %
    - Controls: 0 %

Oda *et al.* Hum Pathol 94

Anesthesiology
1996; 84:280–7

Cytomegalovirus

An Unexpected Cause of Ventilator-associated Pneumonia

Laurent Papazian, M.D., Alain Fraisse, M.D.,† Louise Garbe, M.D.,‡ Christine Zandotti, M.D.,§ Pascal Thomas, M.D.,‖ Pierre Saux, M.D.,* Gilles Perrin, M.D.,* François Gouin, M.D.#*

- **Retrospective study** (n = 2,795)
- **ARDS** and ventilation of more than 7 days + histology
- **Exclusion criteria**: leukemia, AIDS, steroids, chimiotherapy
- **Autopsies (n = 60), OLB (n = 26)**

  25 histologically-proven CMV pneumonia
- CMV sole pathogen in 88%

Herpes simplex virus (HSV)

- Recognized as a pulmonary pathogen since 1949
- HSV-1 and HSV-2
- Primary infections: asymptomatic
- Latent infection of neuronal cells
  - Trigeminal ganglia
  - Superior cervical ganglia
  - **Vagal ganglia**

Morgan and Finland Am J Med Sci 49

Reactivation of HSV-1

Oropharynx as the main source

- 64 patients who had multiple samples
  - Oropharynx
  - BAL
- HSV-1 isolates from the lung genetically indistinguishable from strains isolated from the oral cavity
- Also true when the microsatellite haplotypes of serial isolates were examined
- Isolation of HSV-1 in BAL always associated with or preceded by the isolation of HSV-1 from the oral cavity
- Lack of evidence for a close genetic relationship among the different HSV-1 strains (no nosocomial transmission)

Deback *et al.* J Clin Virol 2010

CMV reactivation

- Lung is a major site of CMV latency and recurrence

Balthesen *et al.* J Virol 93

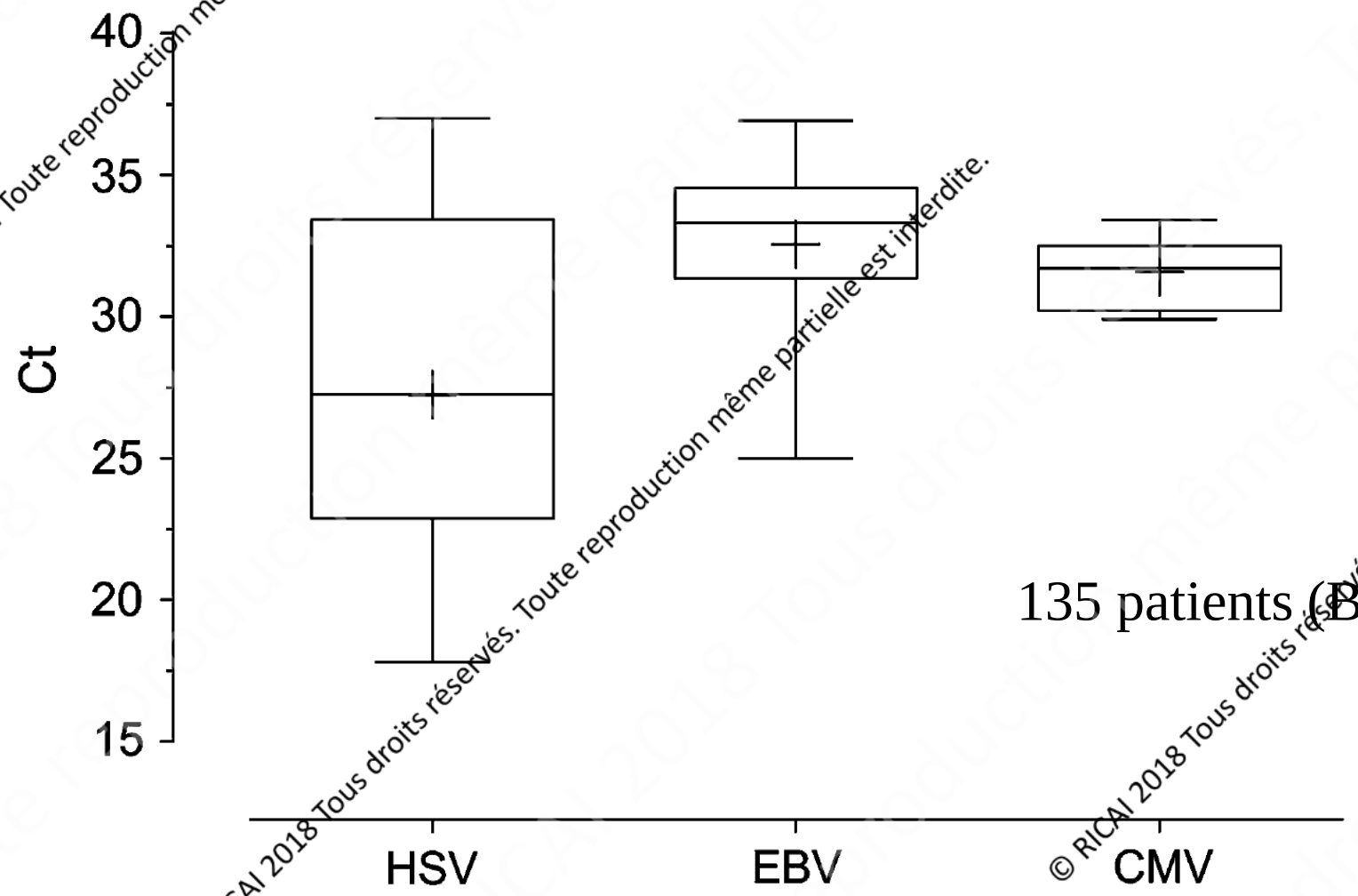
- CMV is carried in myeloid lineage progenitor cells in the BM and is maintained in the cells as they divide down the myeloid lineage into 0.01 % of peripheral mononuclear cells

- CMV reactivates when blood monocytes differentiate into macrophages into tissues under the influence of cytokines

Sissons *et al.* J Infect 2002

Other *herpesviridae*

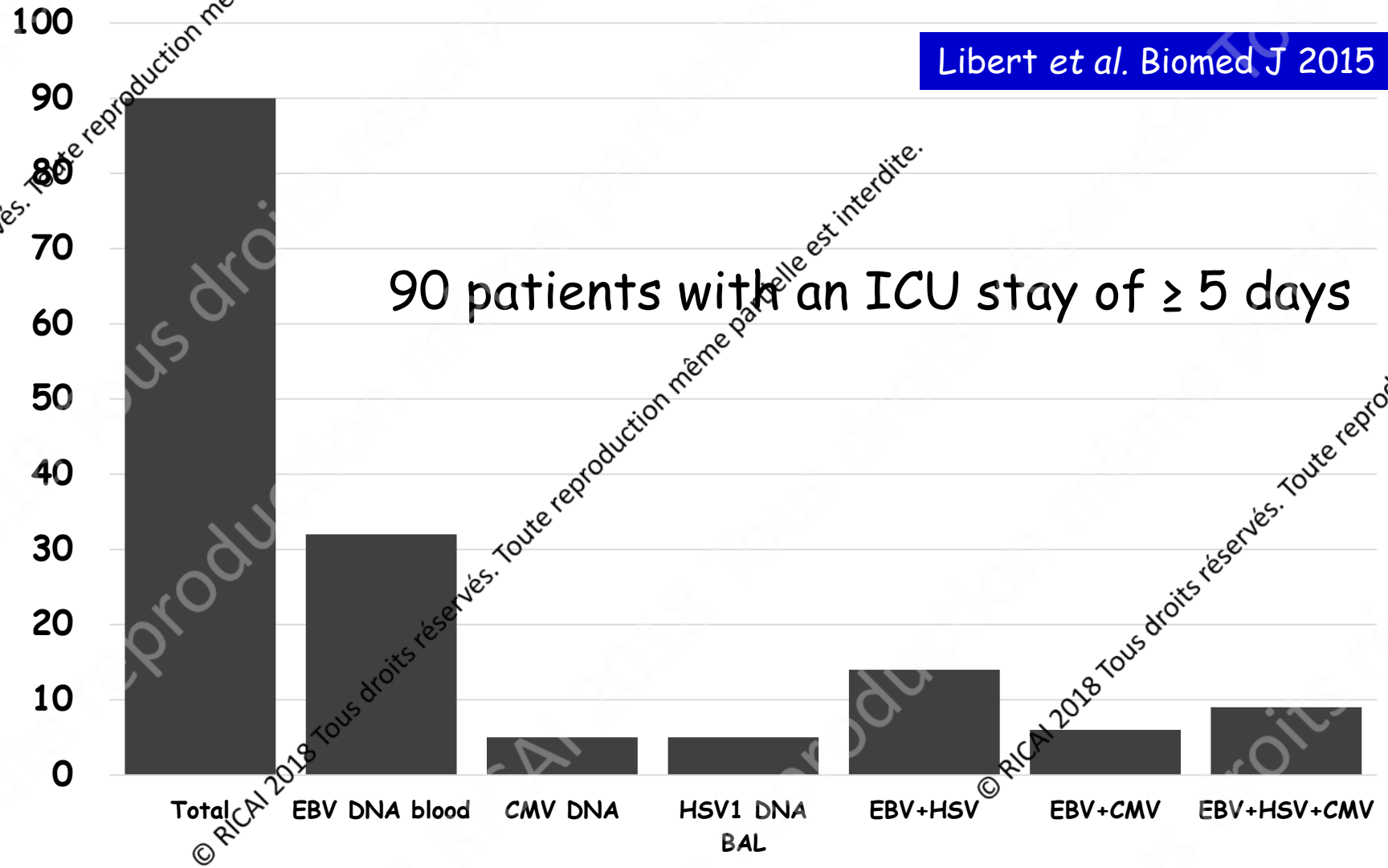
Detection of herpesvirus DNA in BAL samples of ICU patients

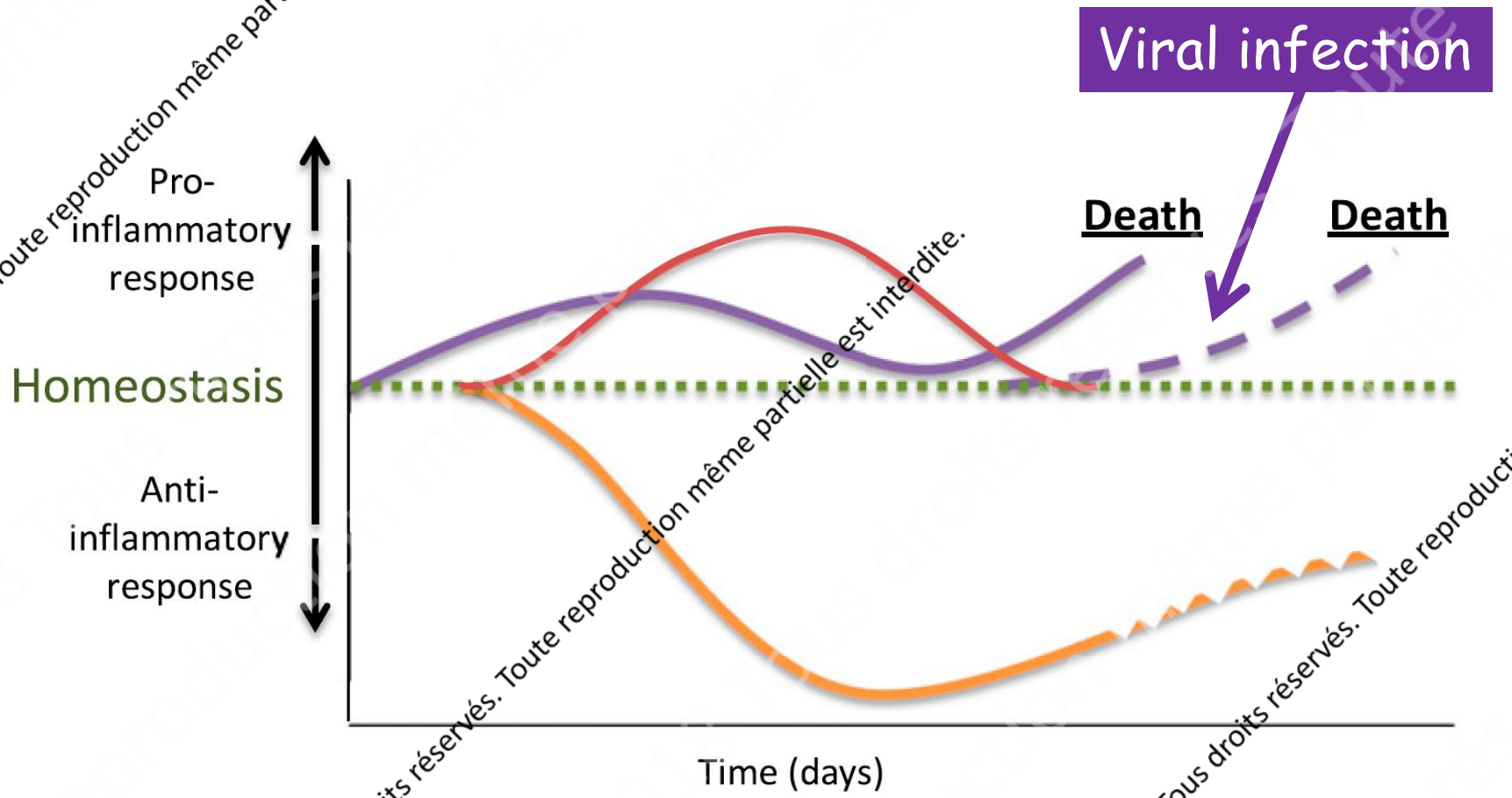


135 patients (BAL)

Friedrichs *et al.* Med Microbiol Immunol 2013

Multiple viral reactivations in ICU immunocompetent patients





Leentjens *et al.* AJRCCM 2013

HSV-1 shedding incidence in ventilated patients

- **Throat swabs and tracheal aspirates (PCR)**
  - 393 patients
  - HSV-1: 27%
  - Correlation age or APACHE II – HSV-1 shedding

Ong *et al.* J Med Virol 2004

- **Tracheal aspirates and blood (culture)**
  - 95 patients
  - HSV-1: 23%

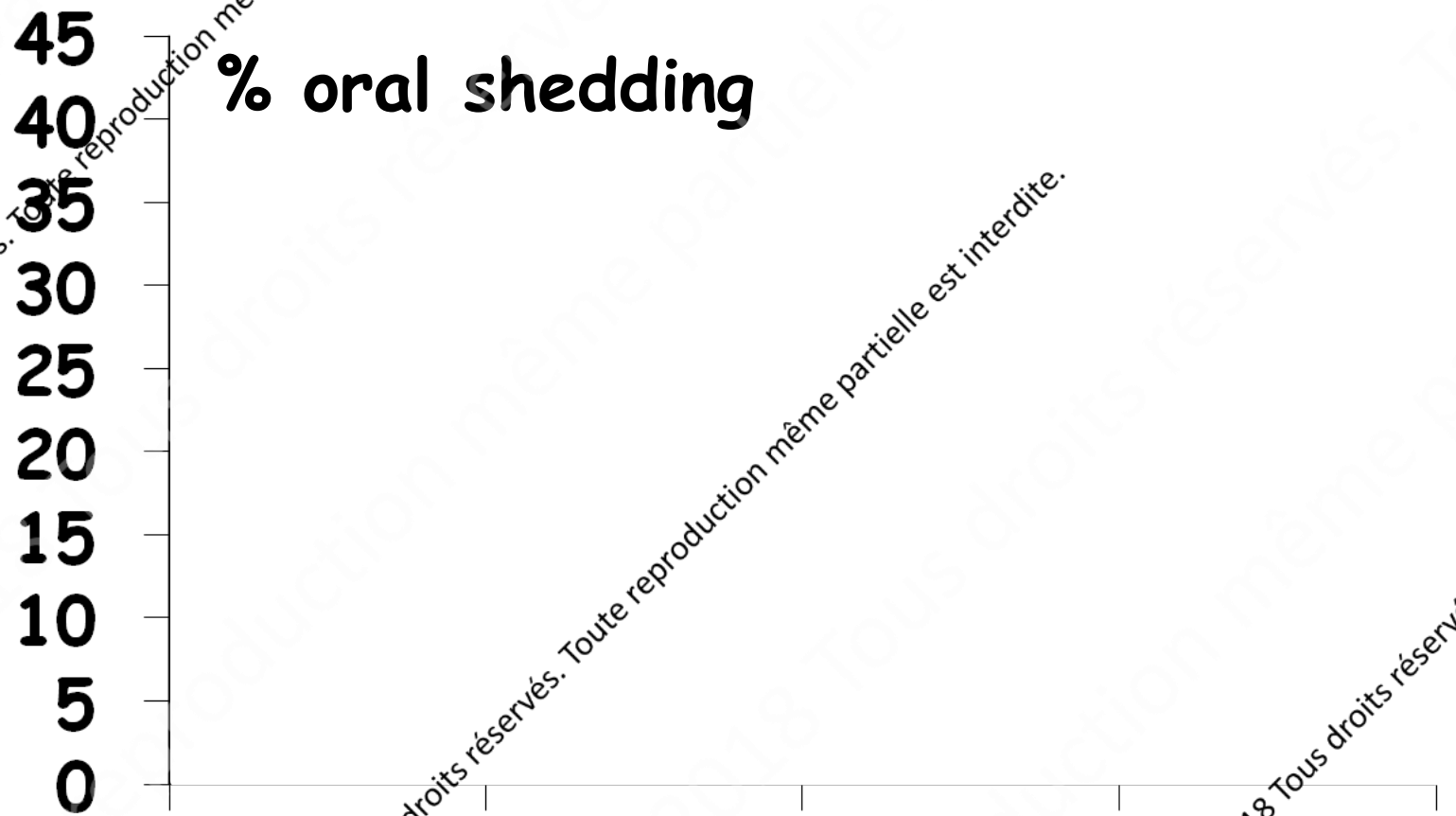
Cook *et al.* Crit Care Med 2003

- **Throat swabs (culture)**
  - 617 patients
  - HSV-1: 21%

Bruynseels *et al.* The Lancet 2003

HSV and nonimmunocompromised patients

Porteous et al. Crit Care Med 84

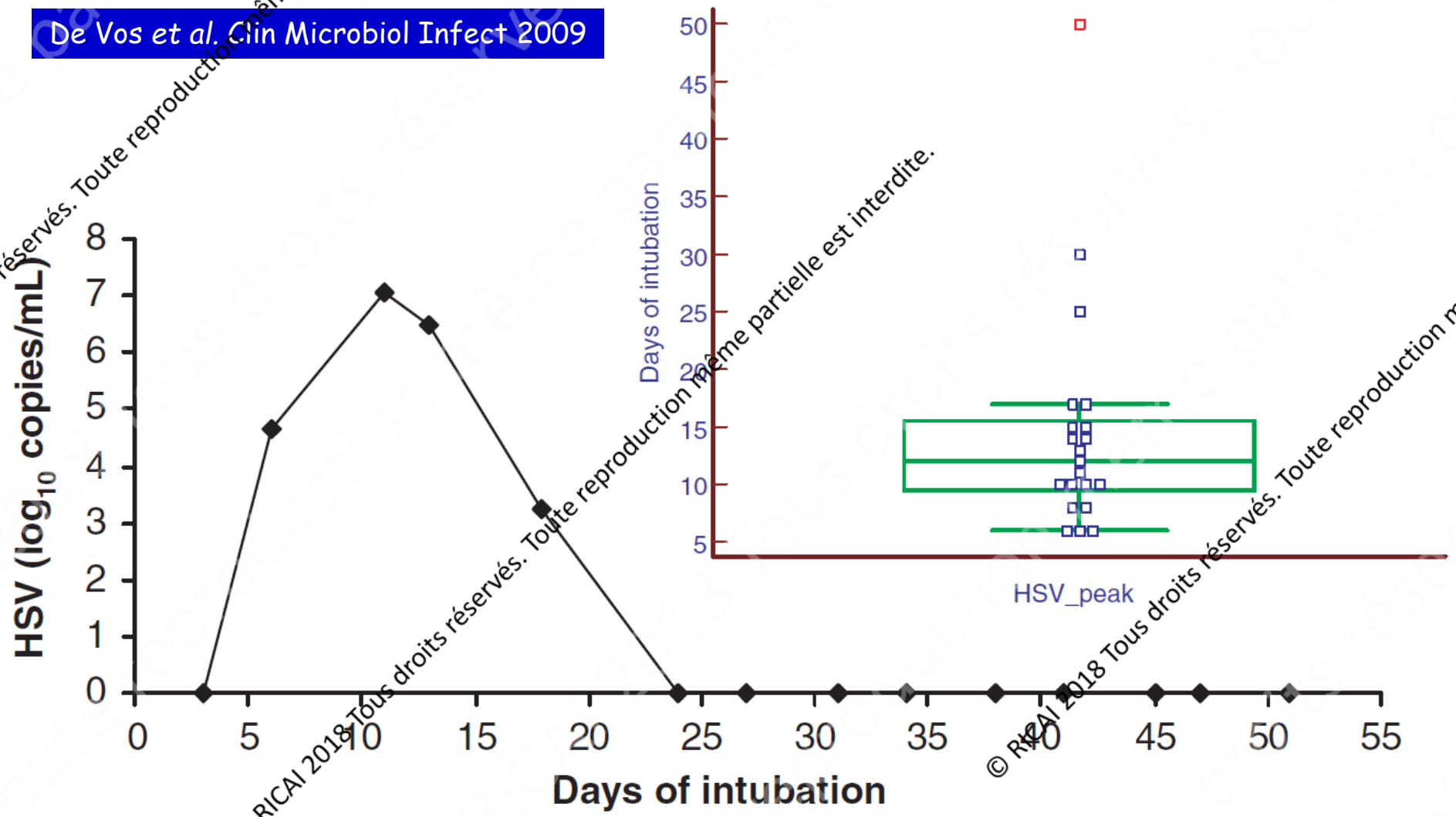


HSV kinetic pattern

Tracheal aspirates

- 21 MV patients

De Vos *et al.* Clin Microbiol Infect 2009

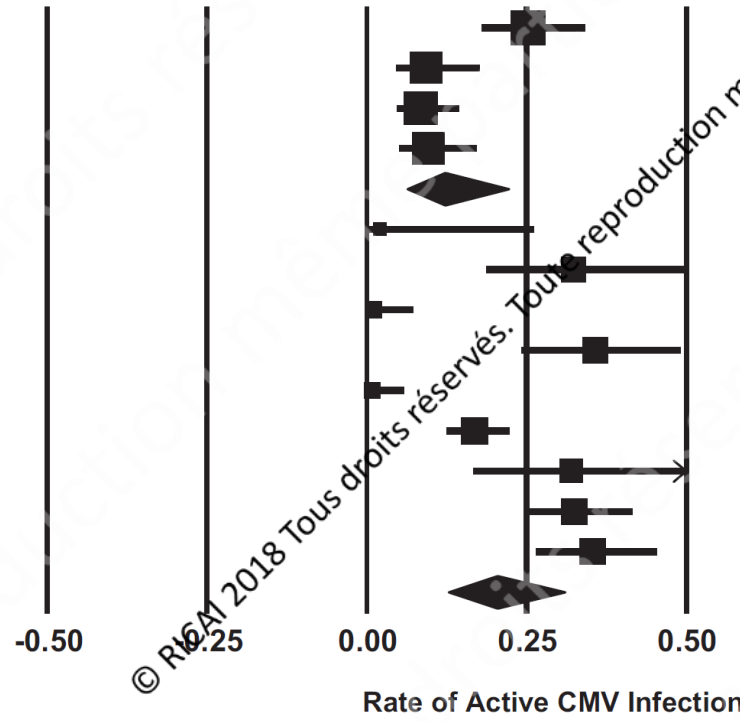


Incidence of active CMV infection

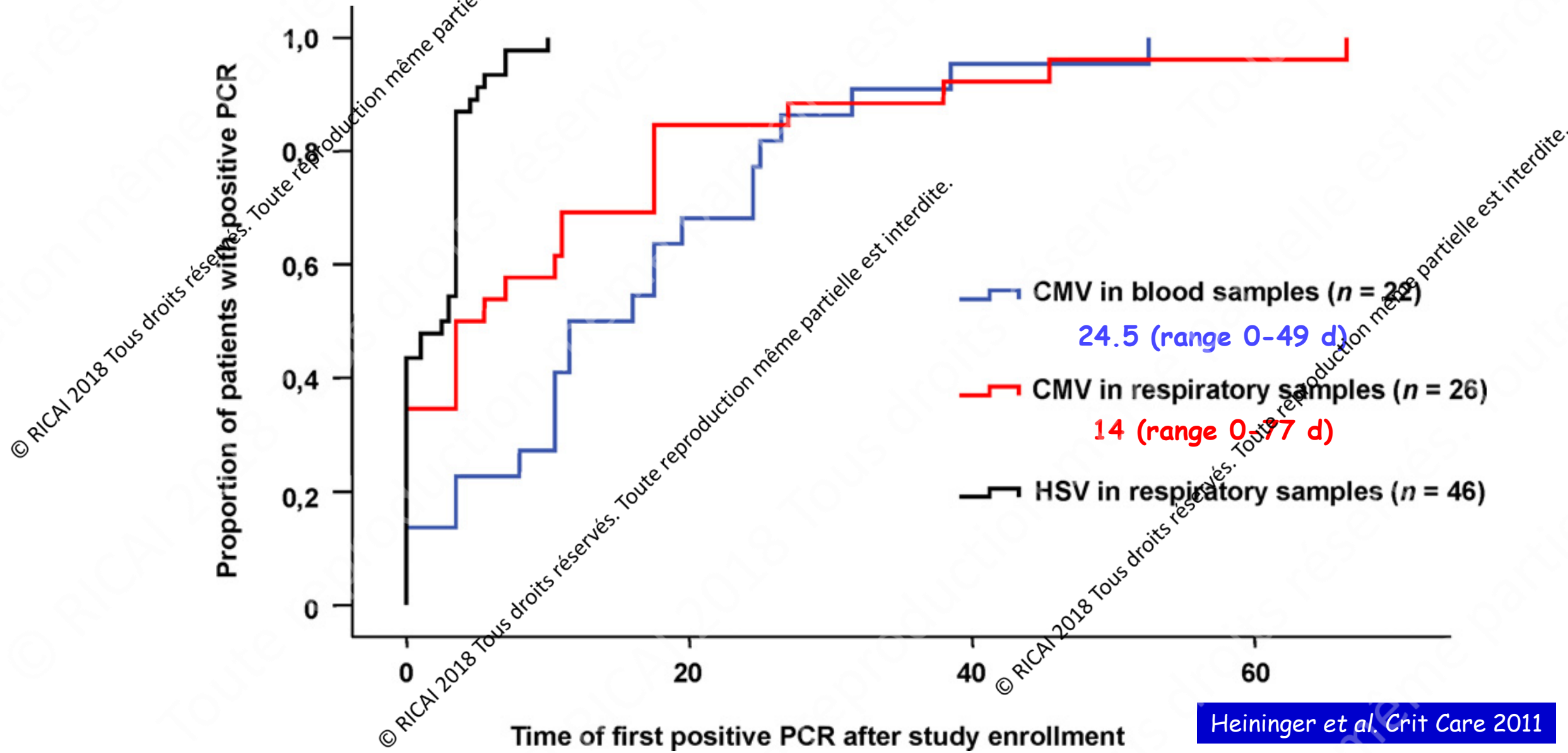
Kalil & Florescu Crit Care Med 2009

Active CMV* Infection Rate by Diagnostic Method

Group by CMV Diagnostic Method	Study name	Event rate	Lower limit	Upper limit	Total
Viral Culture	Domart Y 1990	0.25	0.18	0.34	29 / 115
Viral Culture	Papazian L 1996	0.09	0.05	0.18	8 / 86
Viral Culture	Cook CH 1998	0.08	0.05	0.14	12 / 142
Viral Culture	Cook C 2003	0.10	0.05	0.17	10 / 104
Viral Culture		0.12	0.06	0.22	59 / 447
Viral DNA or Antigen	Stephan F 1996	0.02	0.00	0.26	1 / 24
Viral DNA or Antigen	Kutza A 1998	0.32	0.19	0.50	11 / 34
Viral DNA or Antigen	Desachy A 2001	0.01	0.00	0.07	1 / 96
Viral DNA or Antigen	Heininger A 2001	0.36	0.24	0.49	20 / 56
Viral DNA or Antigen	Razonable R 2002	0.01	0.00	0.06	1 / 120
Viral DNA or Antigen	Jaber S 2006	0.17	0.13	0.22	40 / 237
Viral DNA or Antigen	von Muller L 2006	0.32	0.17	0.52	8 / 25
Viral DNA or Antigen	Limaye A 2008	0.33	0.25	0.41	39 / 120
Viral DNA or Antigen	Zissmann M 2008	0.35	0.27	0.45	35 / 99
Viral DNA or Antigen		0.20	0.13	0.31	156 / 811

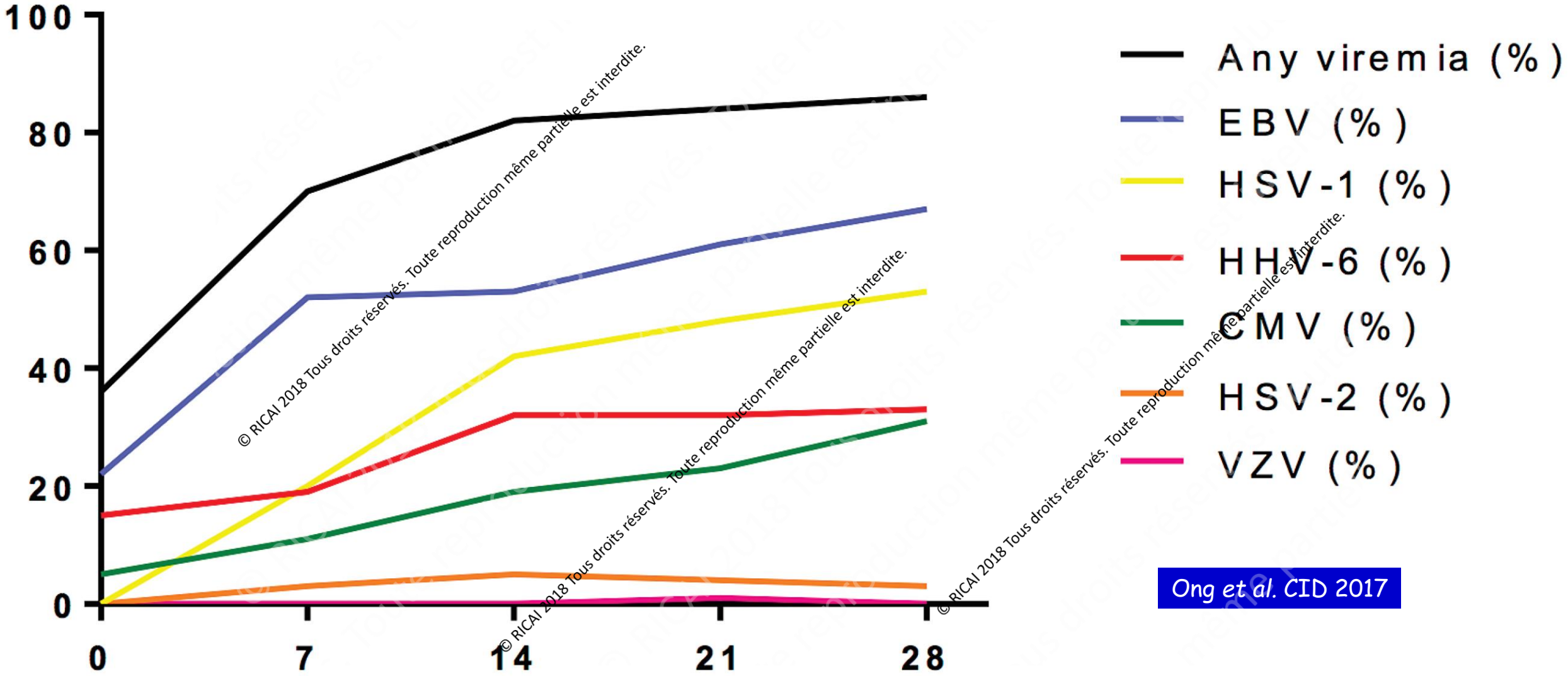


CMV and HSV PCR



Heininger *et al.* Crit Care 2011

Proportion of septic shock patients with viremia



Ong et al. CID 2017

Herpes Viremia

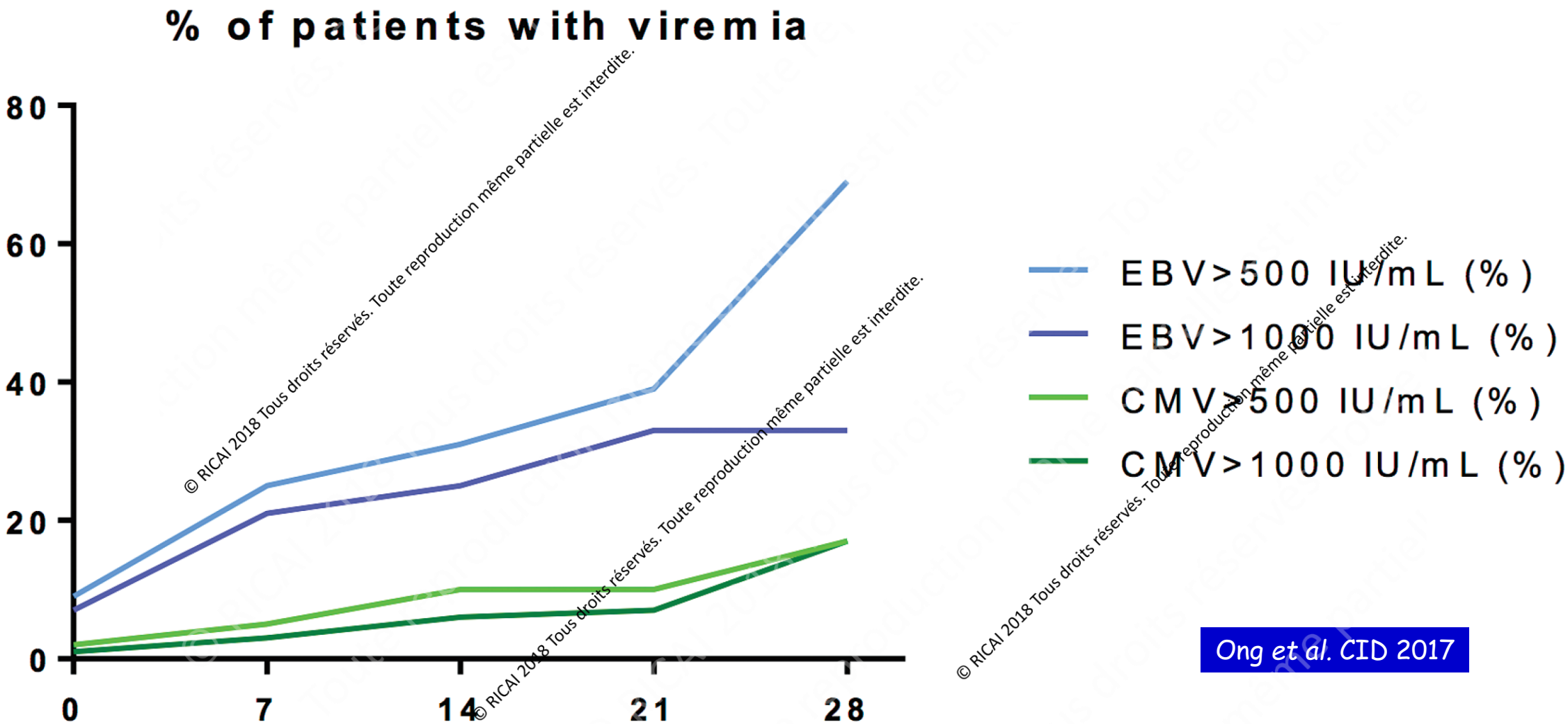
- 329 patients with septic shock and with an ICU admission longer than 4 days and without known prior immune deficiency or previous antiviral treatment

68%

Ong et al. CID 2017

Patient Characteristic	Ever Viremia (n = 223)	Never Viremia (n = 106)	*P* Value
Age (y)	65 (57–74)	66 (54–73)	.36
Male gender	146 (65)	62 (58)	.22
Non-European descent	28 (13)	11 (10)	.57
Body mass index (kg/m^2)	25 (22–28)	25 (22–29)	.60
Prior ICU admission	57 (26)	26 (25)	.84
Medical admission	153 (69)	71 (67)	.77
Charlson comorbidity index[a]	4.6 (0–11)	4.6 (0.0–10.6)	.73
Acute Physiology and Chronic Health Evaluation (APACHE) IV score[b]	85 (10–109)	82 (69–99)	.16
Plasma lactate[c]	3.8 (2.3–7.0)	2.8 (1.8–4.5)	<.01
C-reactive protein[d]	168 (83–280)	85 (27–207)	<.01
Source of infection			.01
Pulmonary	95 (43)	55 (52)	
Abdominal	76 (34)	19 (18)	
Other	52 (23)	32 (30)	

daily dose of ≥250 mg hydrocortisone or equivalent during the first 4 days in the ICU



Ong et al. CID 2017

What kind of patients ?

Variables	CMV Group (n = 40)
Surgical	24
Oesogastrectomy	3
Duodenopancreatectomy	2
Colonic surgery	7
Peritonitis	9
Miscellaneous	3
Medical	13
ARDS	4
Necrotizing pancreatitis	2
Digestive bleeding	3
Cirrhotic decompensation	3
Miscellaneous	1
Trauma	3
Cranial	1
Thoracic	1
Abdominal	1

Jaber *et al.* Chest 2005

HSV bronchopneumonitis

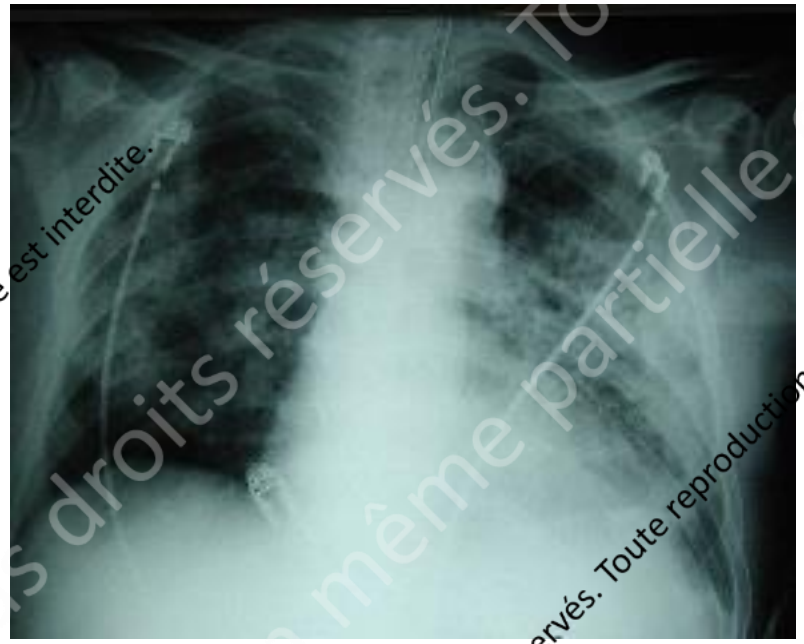
- All the following criteria
  - (1) clinical deterioration;
  - (2) HSV detection in the lower respiratory tract (PCR and/or culture);
  - and (3) HSV-specific nuclear inclusions in cells collected during BAL, endotracheal aspiration, and/or bronchial biopsy

Luyt *et al.* AJRCCM 2007

Clinical presentation

- t° = 36.6 ± 2.4 °C
- GB = 13.9 ± 5.8 G/l
- Weinberg = 5 (3-7)
- PaO2/FiO2 = 195 (139-277)

- Cholestasis
- ASAT, UI.L^{-1} = 30 (19-40)
- ALAT, UI.L^{-1} = 35 (20-99)



Other sites of CMV infection

- Colitis
  - From January 2000 to March 2013
    - Patients with a histopathological diagnosis of CMV colitis
    - 158 ICU beds
  - 14 cases
  - Mortality rate, 71.4%

Siciliano *et al.* Int J Infect Dis 2014

Chan *et al.* J Crit Care 2014

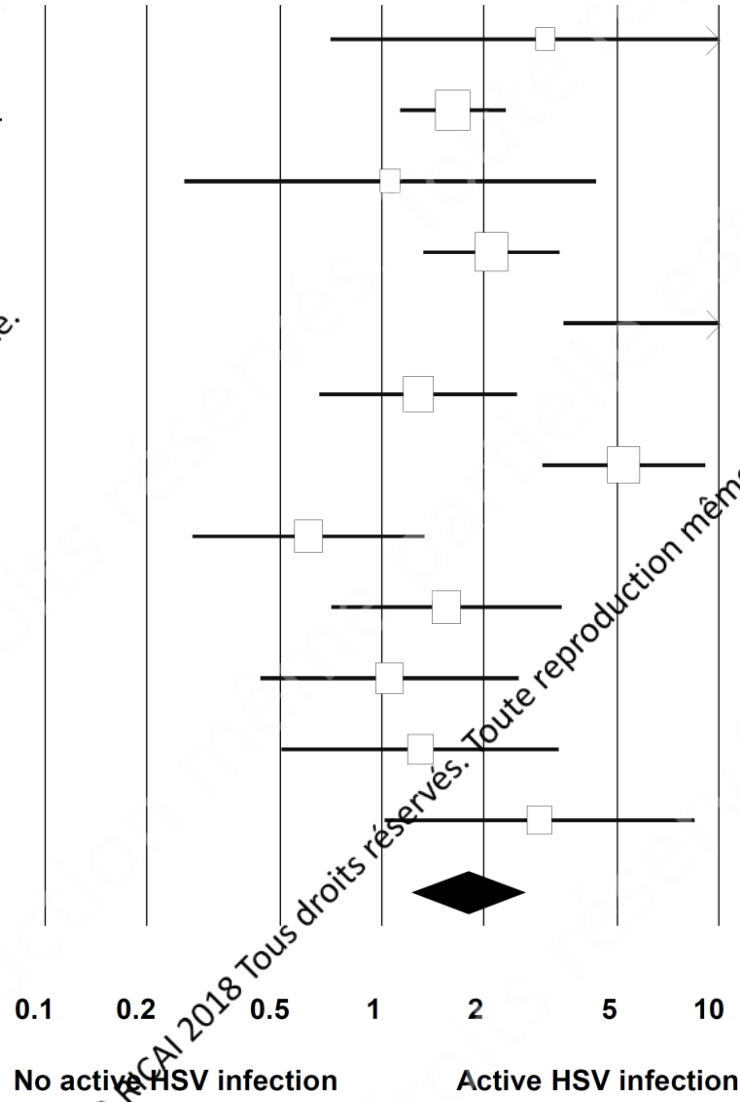
HSV and prognosis

Parameter	HSV Bronchopneumonitis: Yes ($n = 42$)	HSV Bronchopneumonitis: No ($n = 159$)	p Value
Total duration of MV, d	36.7 ± 27.5	30.0 ± 27.1	0.03
VAP episodes/patient, n	1.5 ± 1.0	1.1 ± 1.1	0.03
ICU length of stay, d	40.1 ± 27.8	32.1 ± 28.1	0.01
In-hospital mortality, n (%)	20 (48)	66 (42)	0.5

Luyt *et al.* AJRCCM 2007

Studies	Odds ratio	Lower limit	Upper limit	Z-value	P-value	HSV pos	HSV neg
						Deaths /Total	
Cook 1998	3.062	0.698	13.435	1.483	0.138	5/8	43/122
Bruynseels 2003	1.622	1.125	2.338	2.590	0.010	59/180	135/584
Cook 2003	1.050	0.257	4.343	0.077	0.939	3/11	22/84
Ong 2004	2.116	1.320	3.393	3.111	0.002	43/106	70/287
Engelmann 2007	66.176	3.436	1274.460	2.778	0.005	7/7	8/45
Luyt 2007	1.281	0.647	2.536	0.711	0.477	20/42	66/159
Linssen 2008	5.221	2.969	9.181	5.739	0.000	50/82	41/178
De Vos 2009	0.605	0.271	1.350	-1.227	0.220	13/65	19/40
Scheithauer 2010	1.552	0.701	3.433	1.084	0.278	23/51	18/52
Smith 2010	1.053	0.433	2.559	0.113	0.910	9/27	38/118
Bouza 2011	1.299	0.500	3.374	0.537	0.591	10/19	71/154
Coisel 2012	2.933	1.009	8.528	1.976	0.048	11/26	9/45
All studies	1.794	1.216	2.649	2.943	0.003		

$Z = 5.89$ $P = 0.0001$ $Q = 31.99$ $I^2 = 65.6\%$



HSV and ICU mortality

Coisel *et al.* PLOSone 2012

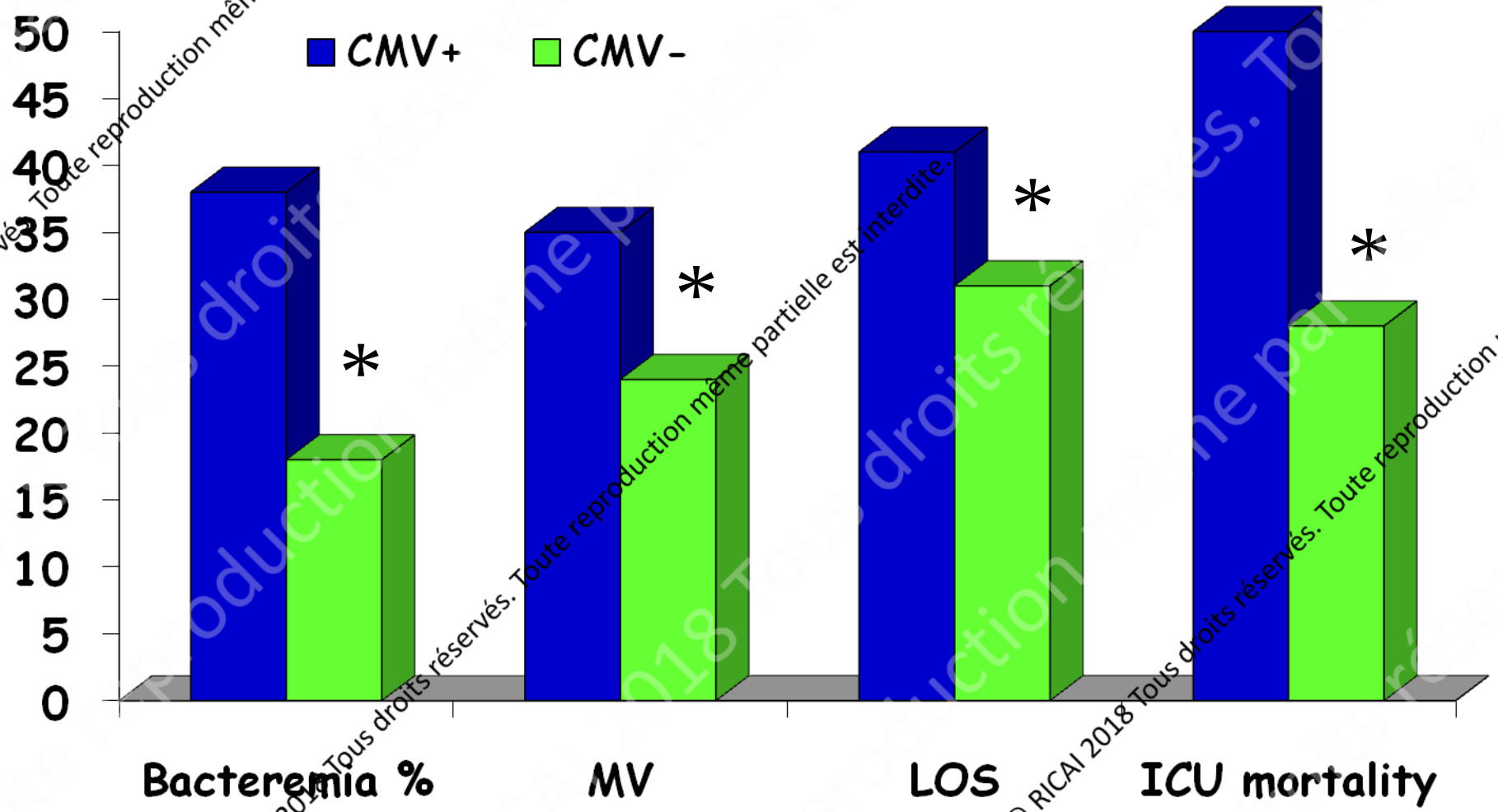
CMV: clinical significance?

- 237 patients: at least 1 positive antigenaemia
- Incidence: 40/237 (17%)

Variables	Exact Matched Pairs, No. (%)	Mean Difference	Maximal Difference
Gender equal	39/40 (97.5)		
Age (± 10), yr	40/40 (100)	5	10
SAPS II (± 7)	35/40 (87.5)	4	16
To ICU admission time (± 12), mo	35/40 (87.5)	9	29
Type of admission equal	35/40 (87.5)		

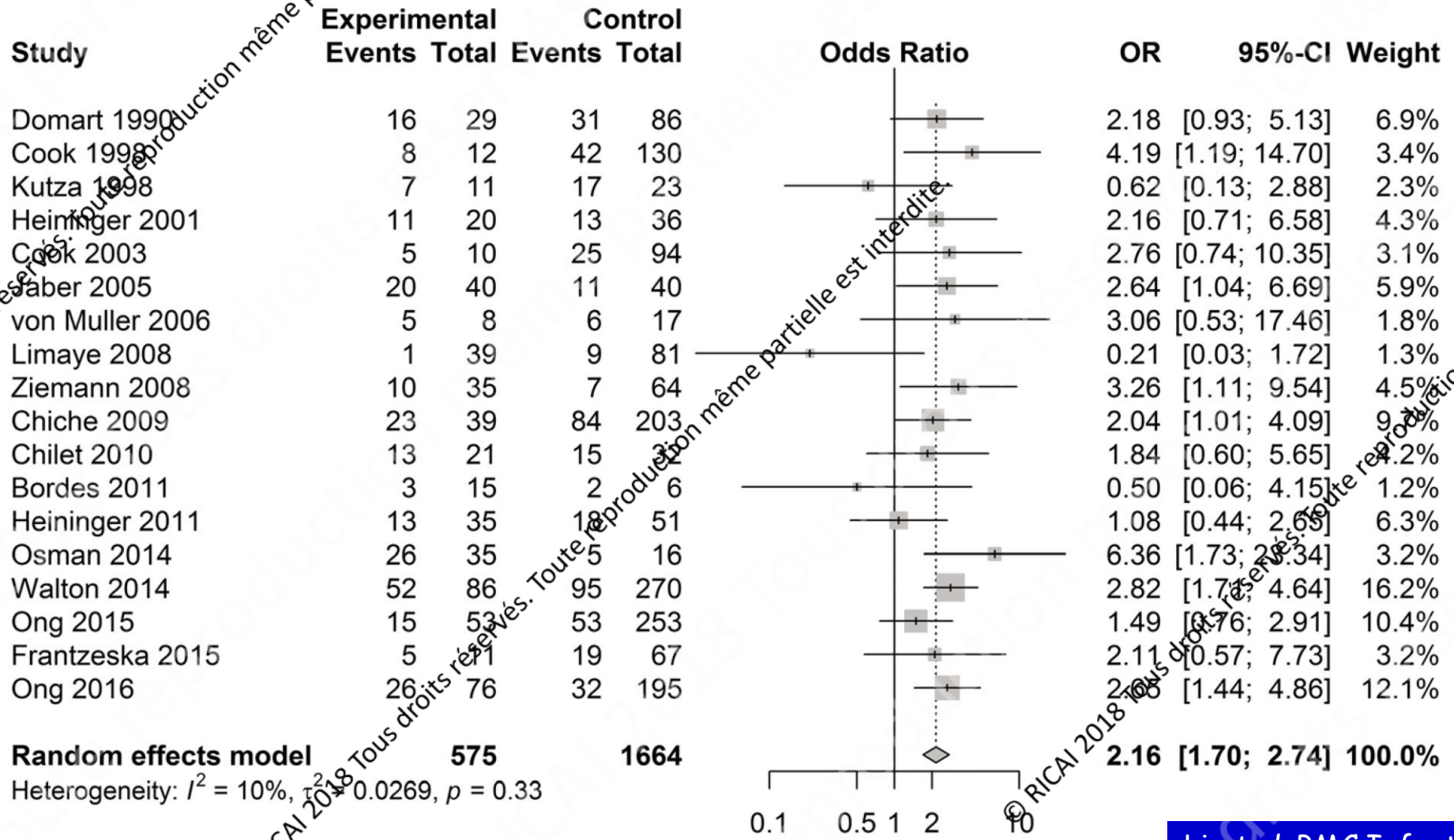
Jaber *et al.* Chest 2005

Morbidity - ICU mortality



Jaber *et al.* Chest 2005

All-cause mortality



Li *et al.* BMC Infect Dis 2018

Is anti-viral treatment active?

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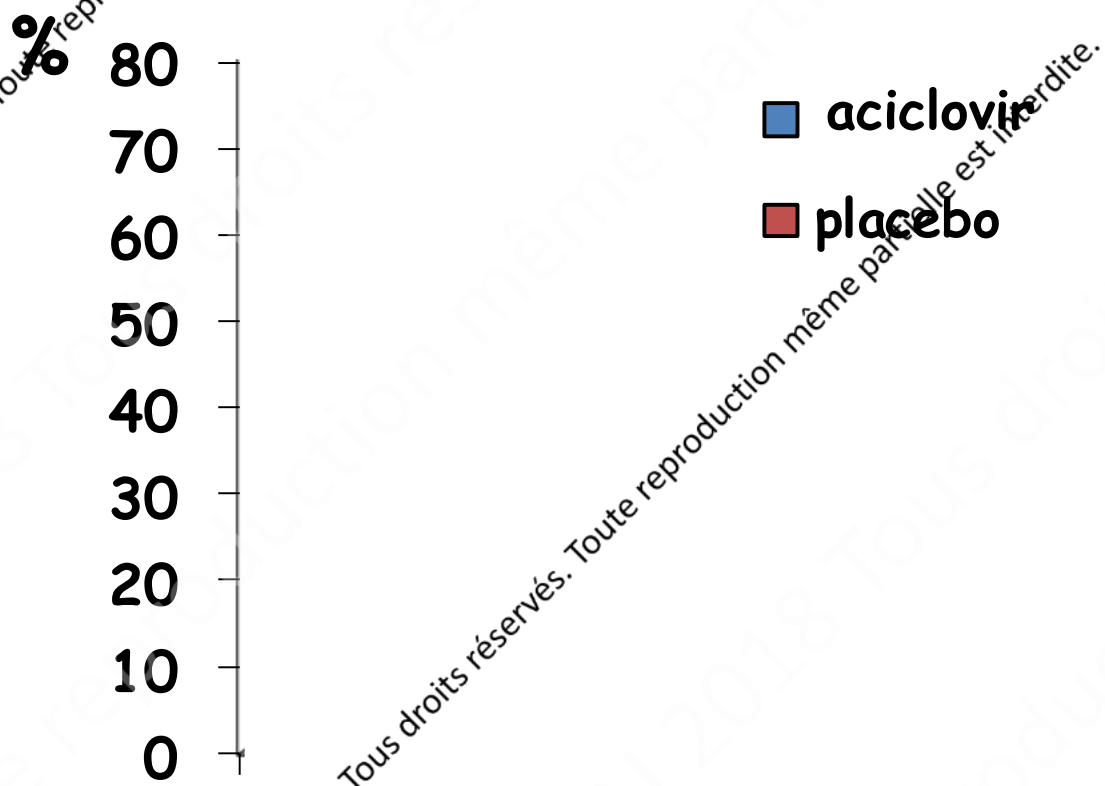
HSV and pathogenicity

- ARDS patients: double-blind randomized study aciclovir-placebo



Tuxen *et al.* ARRD 87

Acyclovir and HSV-1

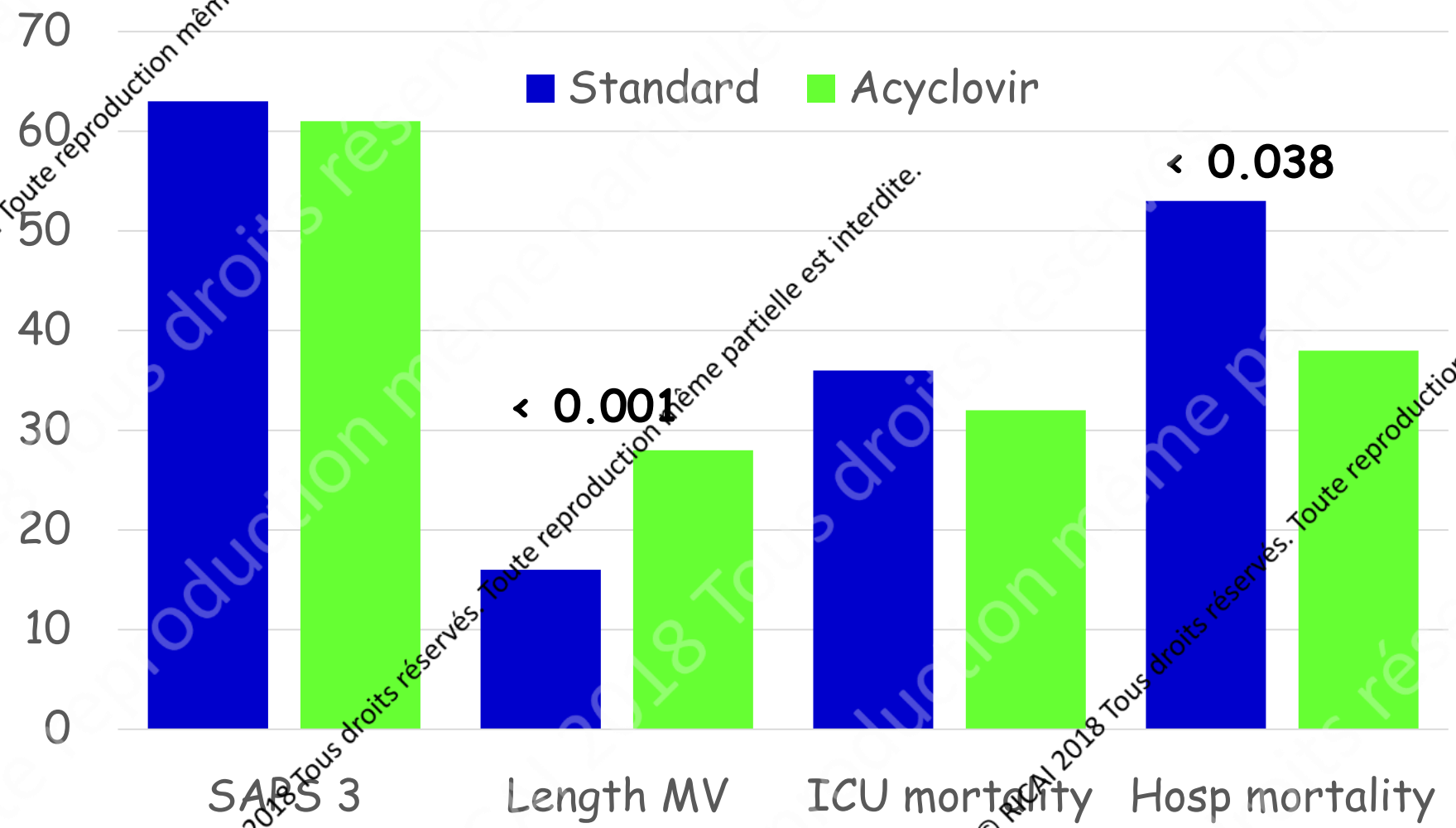
Traen *et al.* J Clin Virol 2014

- Retrospective 8-year study
  - all ICU patients for 10 days or longer with a positive HSV-1 culture in the respiratory tract (i.e., nasopharyngeal, ETA, bronchial aspirate, sputum, BAL)
  - compared patients who received acyclovir/standard treatment

	Acyclovir – (n = 106)	Acyclovir + (n = 106)	p
Patient characteristics			
Male gender	71.0 (67.0%)	70.0 (66.0%)	0.884
Age (years)	65.3 (18–88)	62.5 (20–84)	0.188
Weight (kg)	76.1 (47–103)	77.3 (40–120)	0.626
BMI (kg/m^2)	25.7 (17–41)	26.2 (14–40)	0.541
Mean risk factors on admission			
Immunosuppressant's use	0 (0.0%)	1 (0.9%)	0.316
Chronic steroid use	6 (5.7%)	2 (1.9%)	0.149
Diabetes mellitus	14 (13.2%)	20 (18.9%)	0.261
Chemotherapy	4 (3.8%)	2 (1.9%)	0.407
Radiotherapy	2 (1.9%)	2 (1.9%)	1
Chronic heart failure	4 (3.8%)	12 (11.3%)	0.038
Liver cirrhosis	5 (4.7%)	7 (6.6%)	0.552
COPD + asthma	12 (11.3%)	20 (18.9%)	0.125
Renal failure	11 (10.1%)	13 (12.3%)	0.587

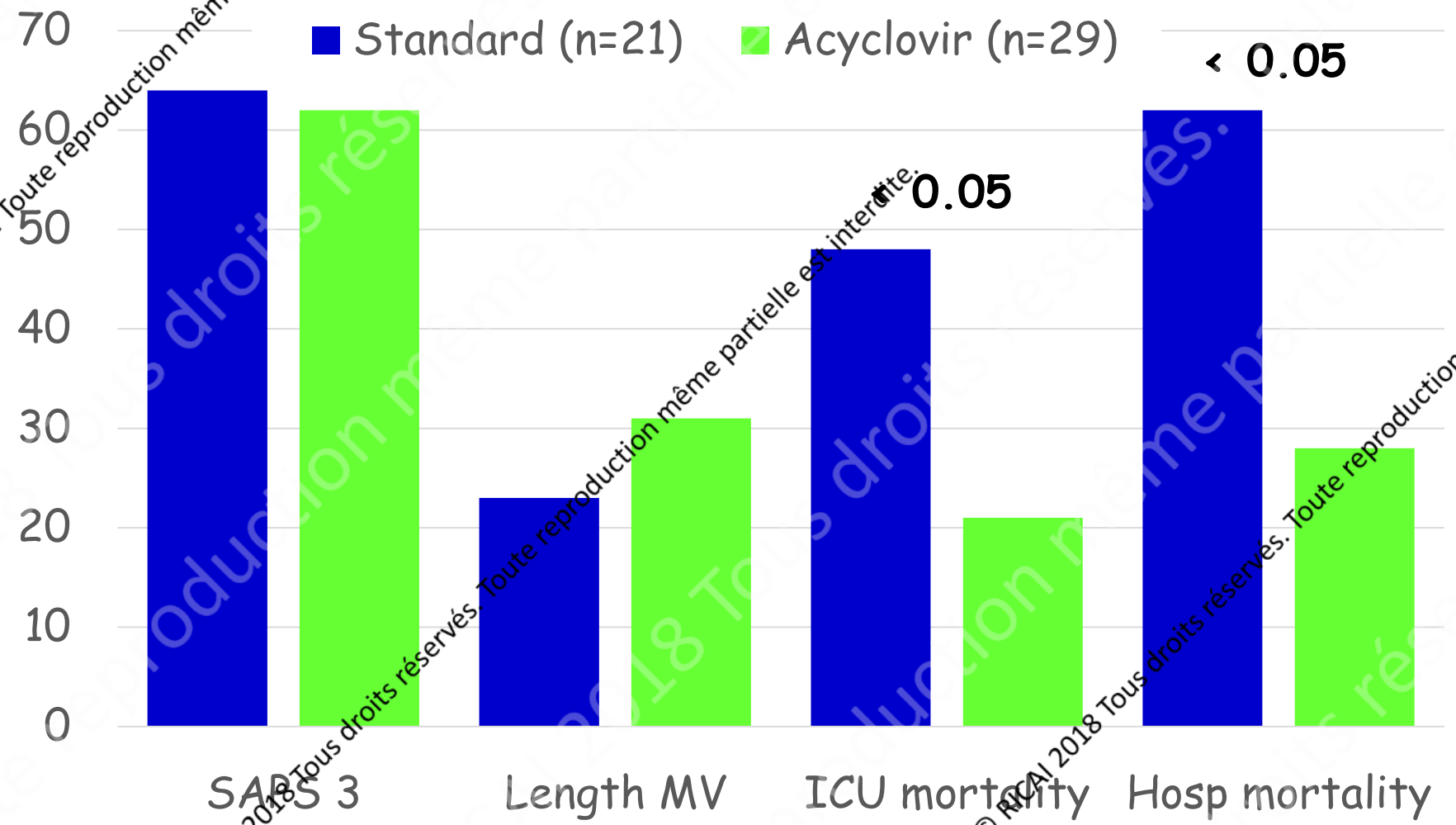
All patients

Traen *et al.* J Clin Virol 2014



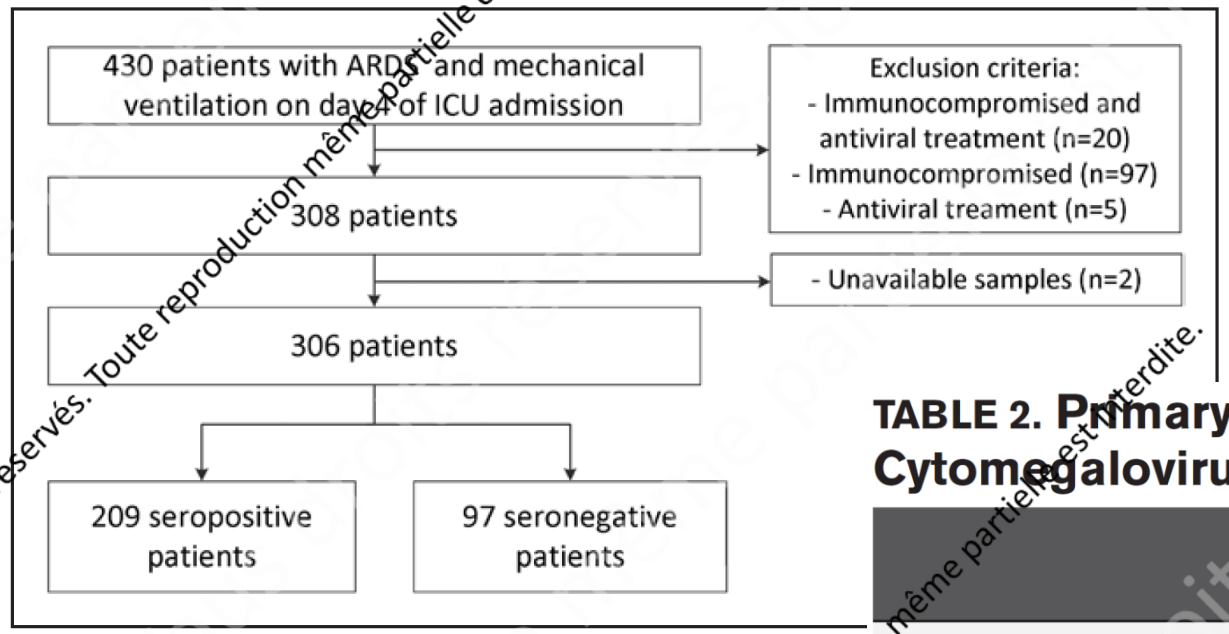
Only BAL positive patients

Traen *et al.* J Clin Virol 2014



When to treat?

Is the serologic status relevant?



Ong et al. CCM 2015

TABLE 2. Primary Outcome by Cytomegalovirus Serostatus

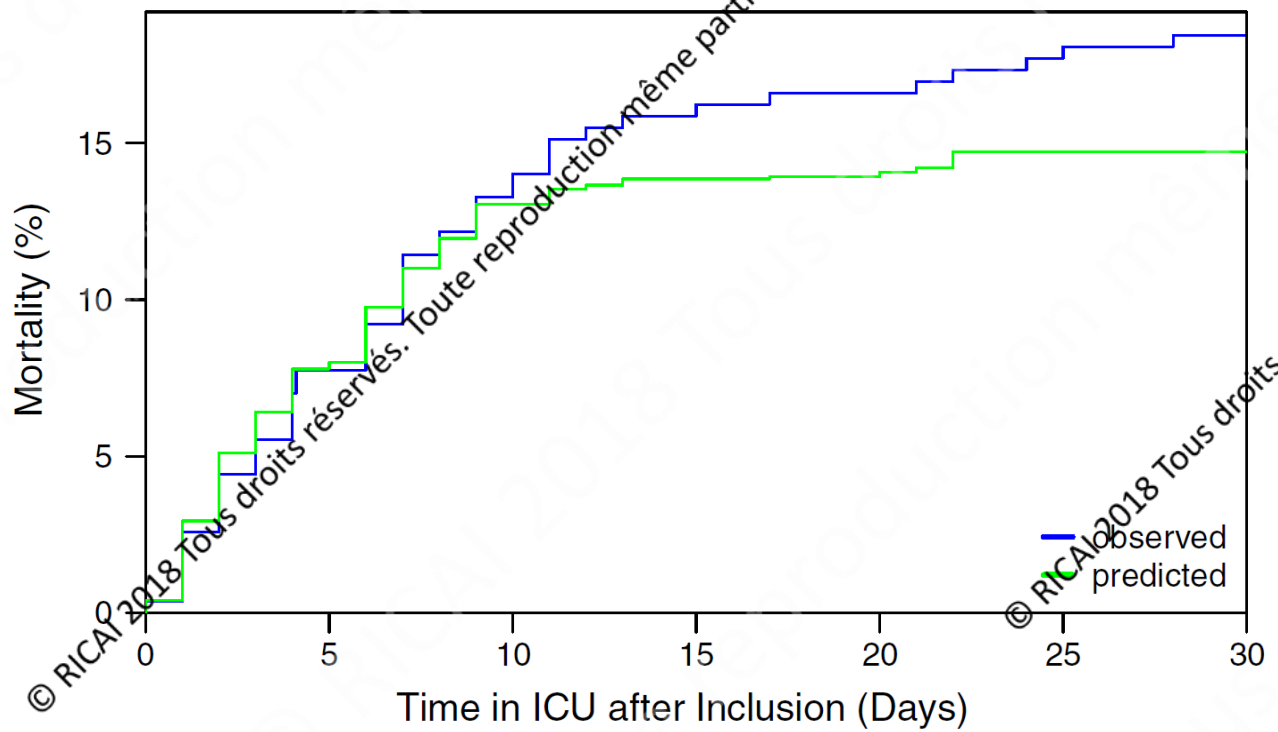
	Seronegative ($n = 97$)	Seropositive ($n = 209$)
Ventilator-free days[a]		
0[b]	28 (29)	72 (34)
1–18	36 (37)	63 (30)
19–24	33 (34)	74 (35)

- CMV reactivation 53 of 209 patients (26%)
- 28-day mortality was 28%
  - compared to 24% in seropositive patients without reactivation
  - and 16% (p=0.09) in seronegative patients

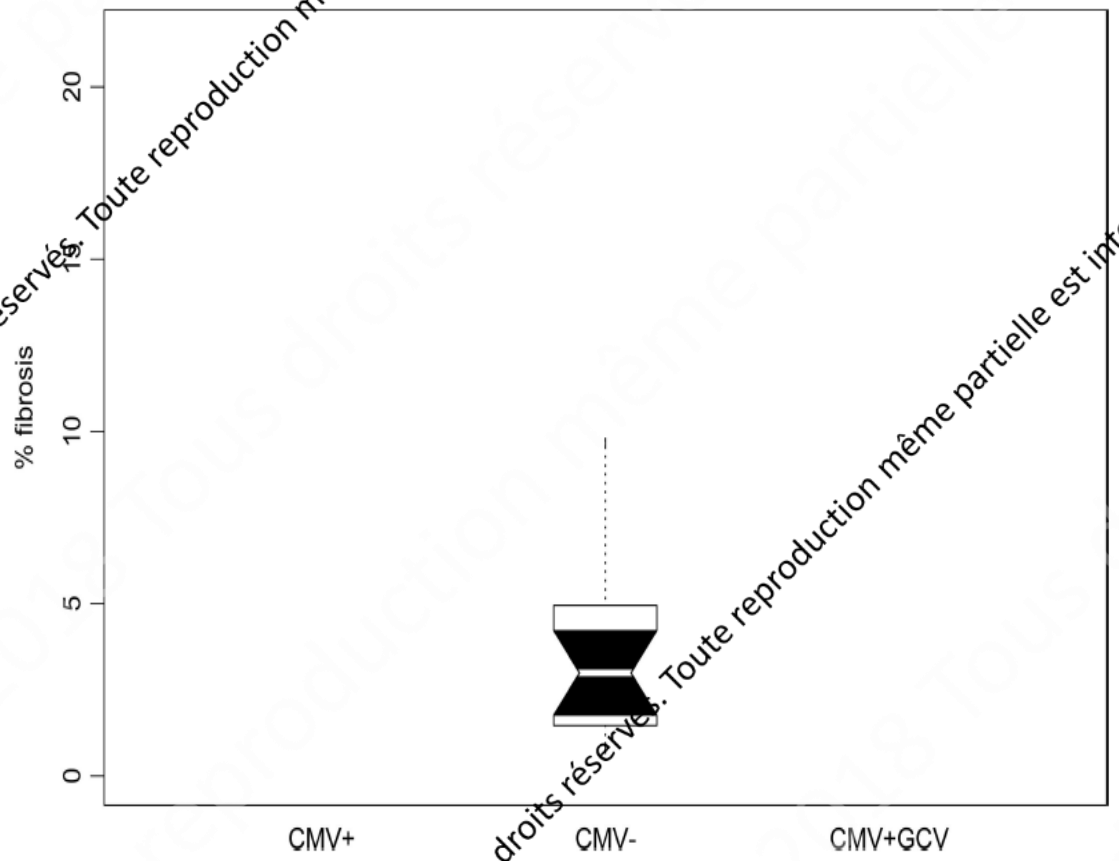
Mortality in seropositive ARDS patients presenting a reactivation

Ong *et al.* Intensive Care Med 2016

	Reactivation	Non-reactivation	*p* value
Death on ventilator before day 30[a]	23/74 (31)	29/197 (15)	<0.01
Death in ICU	26/76 (34)	32/195 (16)	<0.01
Death by day 90[b]	35/76 (46)	55/195 (28)	<0.01
Duration of mechanical ventilation (days)	15 (10–26)	8 (6–12)	<0.01
Length of stay in ICU (days)	16 (11–28)	9 (7–14)	<0.01



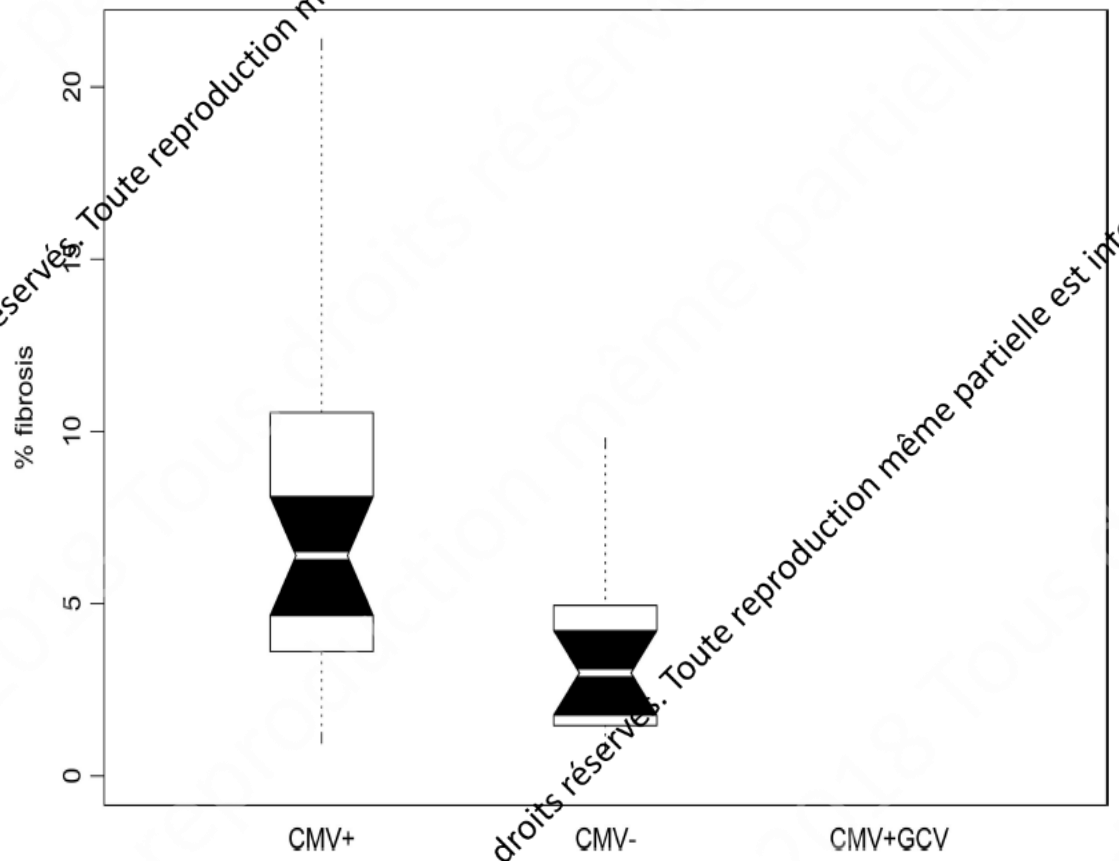
CMV and lung fibrosis



- Mice
- Peritonitis
- After 3 weeks
  - CMV -
  - Reactivation CMV
  - Reactivation CMV + Ganciclovir

Cook *et al.* Crit Care Med 2006

CMV and lung fibrosis



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Cook *et al.* Crit Care Med 2006

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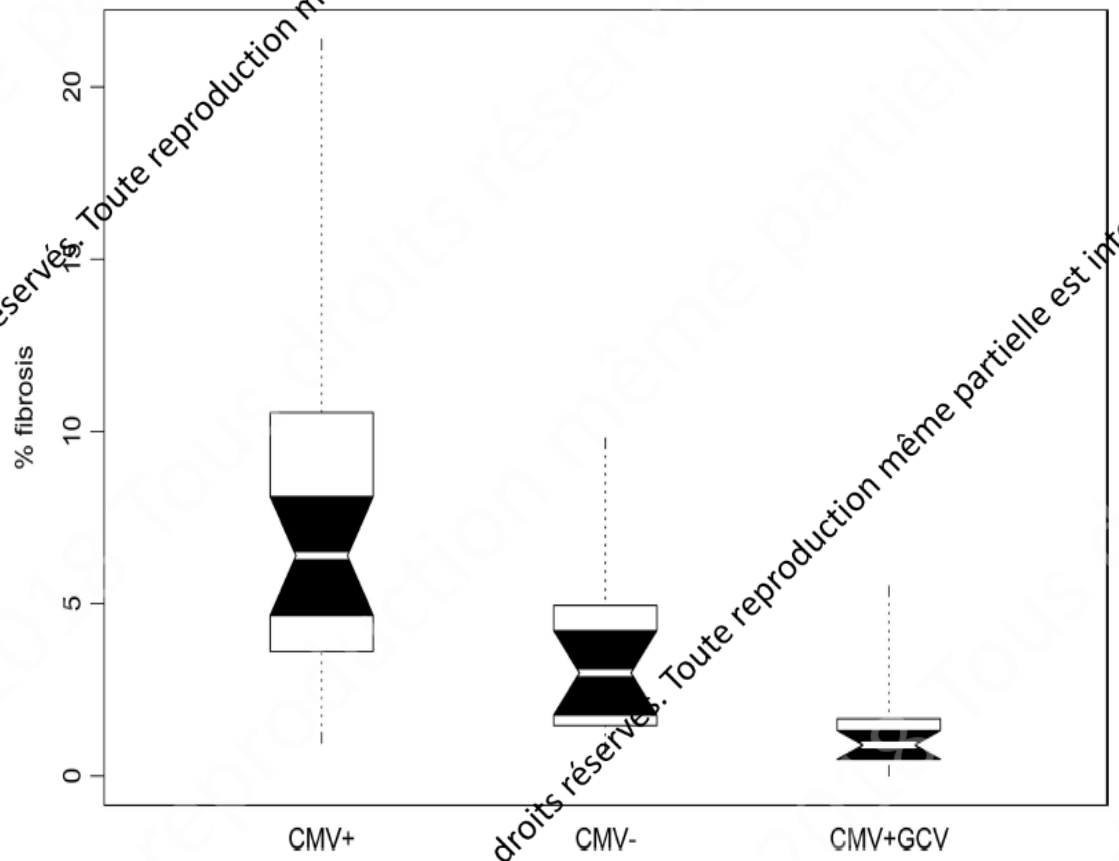


- Mice
- Peritonitis
- After 3 weeks
  - CMV -
  - Reactivation CMV
  - Reactivation CMV + Ganciclovir

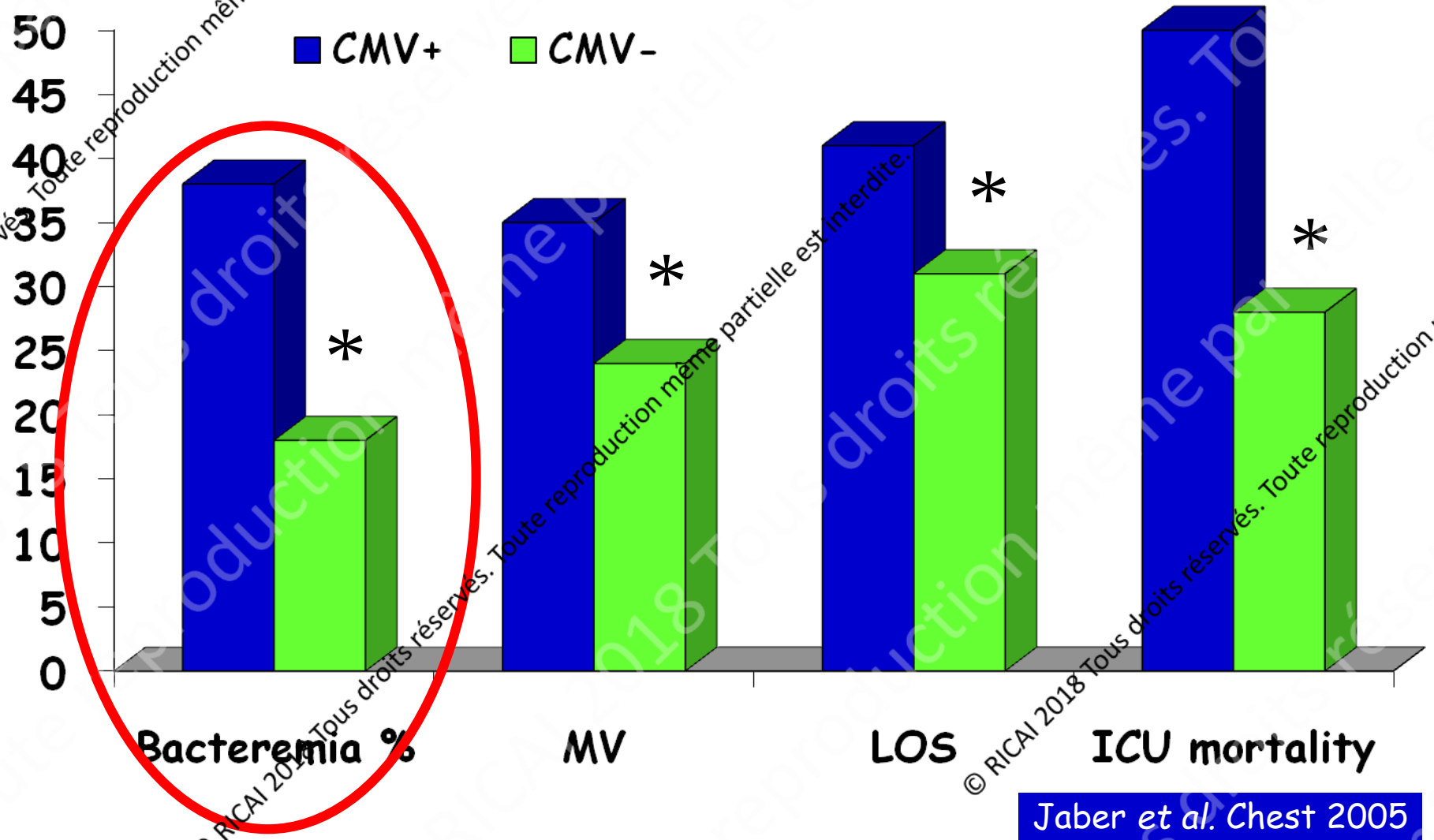
Cook *et al.* Crit Care Med 2006

CMV and bacterial infections

	CMV + (39)	CMV – (203)	
ICU death	21 (54)	76 (37)	0.08
Hospital death	23 (59)	84 (41)	0.06
VFD d28	0 (0–0)	2 (0–19)	<0.001
VFD d60	0 (0–23)	34 (0–51)	<0.001
≥ 1 VAP bact	22 (56)	47 (23)	<0.001
≥ 1 bacterial noso infection	27 (69)	68 (33)	<0.001
ARDS	17 (44)	59 (29)	0.11

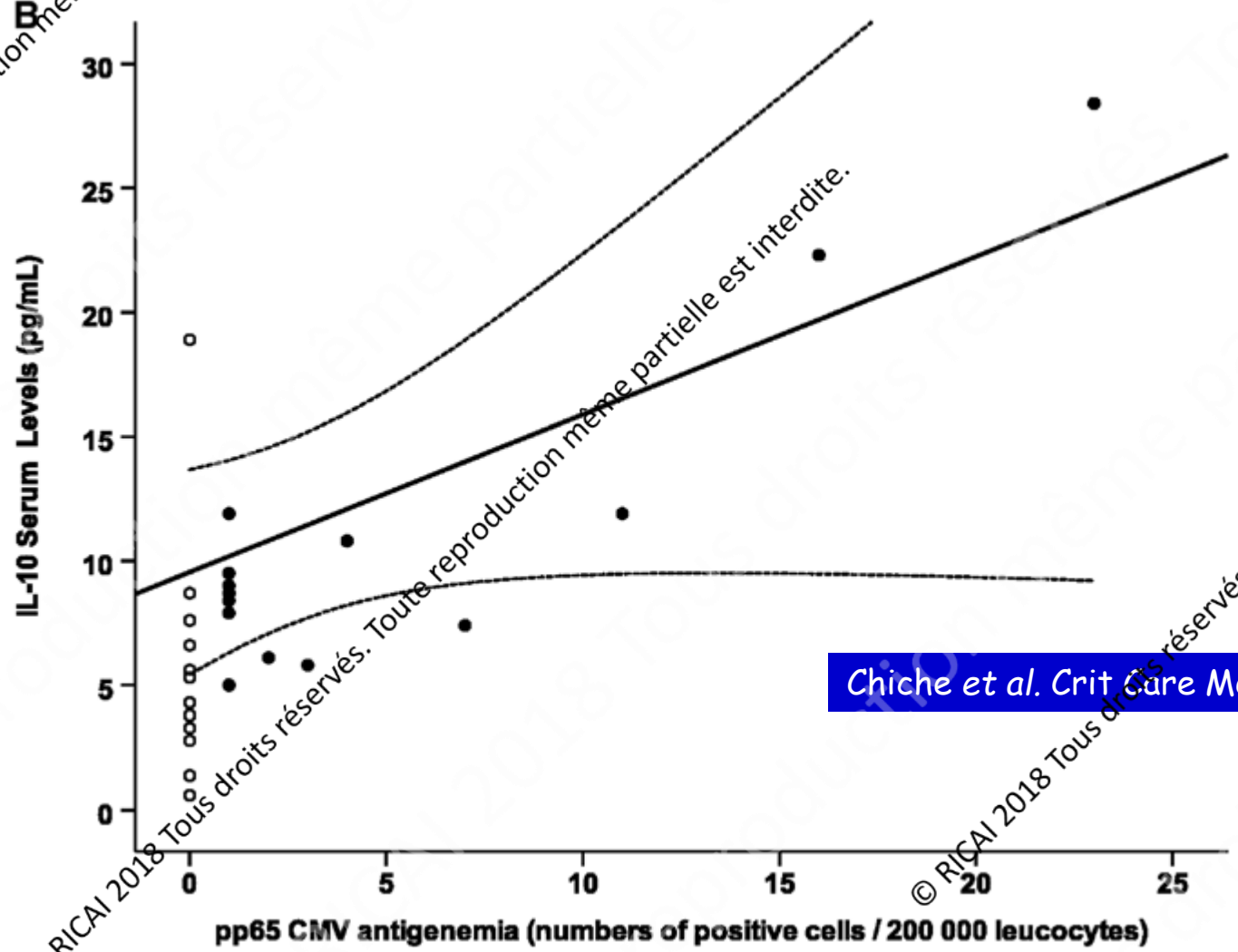
Chiche *et al.* CCM 2009

Morbidity - ICU mortality

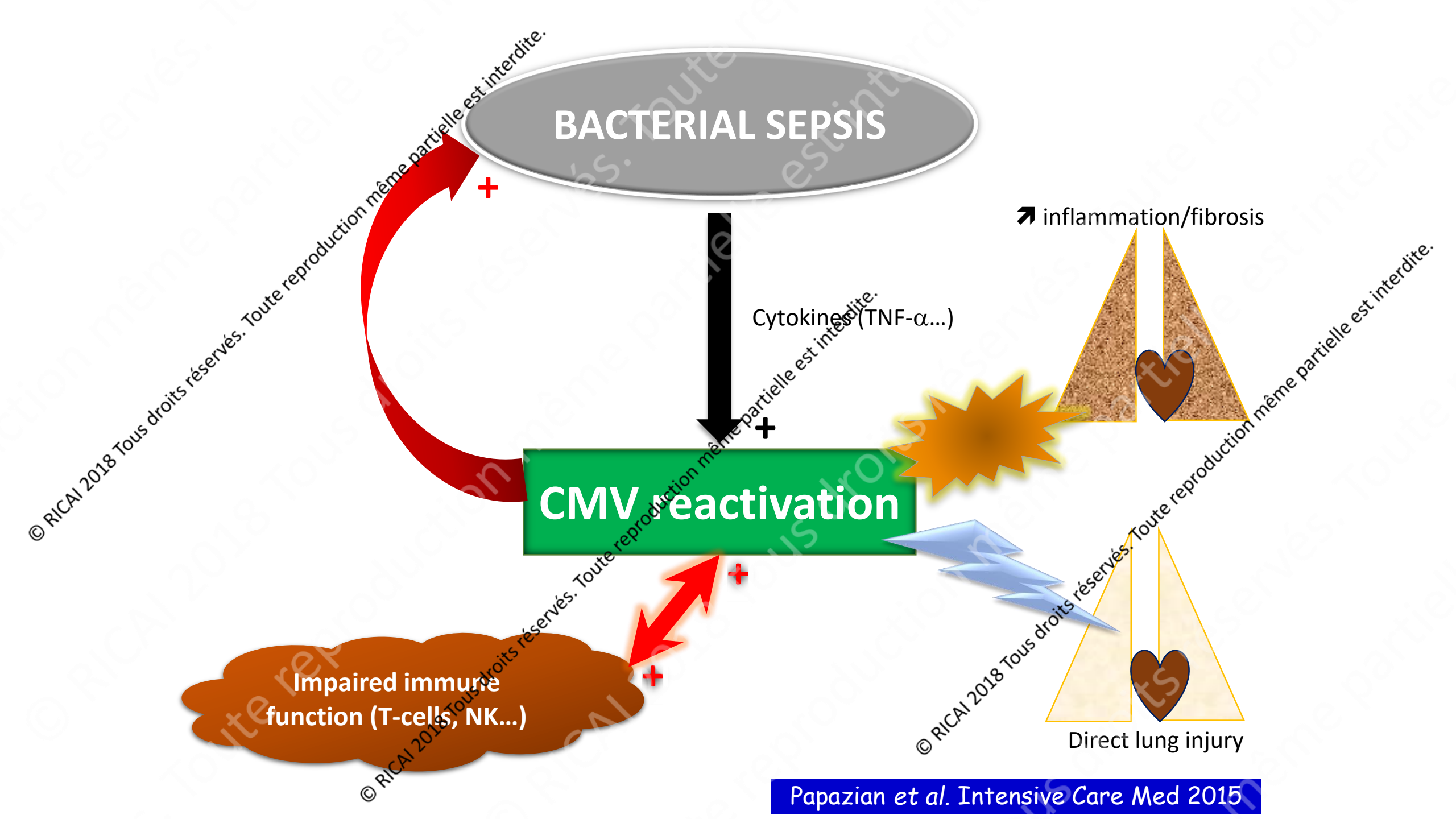


Jaber *et al.* Chest 2005

Correlation antigenemia/IL-10



Chiche *et al.* Crit Care Med 2012



When to treat?

Cytomegalovirus Control in Critical Care (CCCC)
NCT01503918

Study of Ganciclovir/Valganciclovir for Prevention of CMV Reactivation in Acute Injury of the Lung and Respiratory Failure (GRAIL)
NCT01335932

Reactivation prevention

- Single-center, open label RCT, 3-armed trial of 2 anti-CMV prophylaxis treatments and standard care for patients
  - CMV IgG + and invasive MV
- Valganciclovir hydrochloride : 450mg x 1/d by the enteral route or 2.5mg/kg Ganciclovir
- Valacyclovir hydrochloride : 2g 4 x 4/d by the enteral route or Aciclovir 10 mg/kg x 3/d
- Duration : > 14 d for 28 d max

Cowley *et al.* JAMA Intern Med 2017

Outcome	Control (n = 44)	Valacyclovir (n = 34)	Valganciclovir (n = 46)
Secondary Clinical Measures			
Organ failure-free days (SOFA score <2), median (IQR) [range]	3.5 (0-18) [0-31]	1.5 (0-13) [0-24]	2.0 (0-11) [0-36]
Moderate organ failure-free days (SOFA score <5), median (IQR) [range]	18.0 (2-24) [0-41]	11.0 (0-22) [0-28]	16.5 (4-21) [0-44]
Discharged from ICU by 3 mo, No. (%)[a]	36 (81.8)	21 (61.8)	34 (73.9)
Discharged from hospital by 3 mo, No. (%)[a]	30 (68.2)	17 (50.0)	28 (60.9)
ICU duration of stay, median (IQR), d	11.5 (7-16)	12.0 (7-31)	16.0 (11-27)
SAEs forms returned, No.	7	12	18
Patients reporting SAEs, No. (%)	7 (15.9)	10 (29.4)	16 (34.8)
Mortality at 28 d, No. (%)	7 (15.9)	14 (41.2)	10 (21.7)
Mortality in the hospital, No. (%)	9 (20.5)	15 (44.1)	12 (26.1)
Safety Measures			
Requirement for G-CSF therapy, No. (%)	0	0	0
Neutropenia (<1000/μL), No. (%)	0	0	0
Platelet count (<50 × 10^3/μL), No. (%)	10 (22.7)	9 (26.5)	10 (21.7)
Platelet transfusions, No.	44	32	42
Median (IQR)	0 (0-0)	0 (0-0.5)	0.2 (0-1)
Renal insufficiency, No. (%)			
CrCl <60 mL/min	23 (52.3)	22 (64.7)	24 (52.2)
CrCl <30 mL/min or required dialysis	19 (43.2)	16 (47.1)	18 (39.1)

GRAIL study

- Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung = phase 2 clinical trial
  - To assess safety and feasibility
  - To explore potential clinical end points for future definitive phase 3 trials
  - Main outcome = Interleukin 6 (IL-6)
- Nonimmunocompromised CMV IgG–seropositive adults with respiratory failure and severe sepsis/trauma receiving invasive MV

Limaye *et al.* JAMA 2017

	Intention-to-Treat Group (n = 156)			
	Placebo Group (n = 72)	Ganciclovir Group (n = 84)	Absolute Difference (95% CI)	*P* Value
Primary Outcome at Day 14				
Difference in plasma IL-6 level, mean, $\log_{10}$ units	−0.79 (−2.14 to 0.56)	−0.79 (2.06 to 0.48)	0 (−0.3 to 0.2)	>.99
Secondary Outcomes at Day 28				
Cumulative incidence of any plasma CMV reactivation, No. (%)	28 (39)	10 (12)	−27 (−40 to −14)	<.001
Mechanical ventilation duration, median (IQR), d[a]	6 (3 to 12)	5 (3 to 9)	−1 (−3 to −1)[b]	.16
Ventilator-free duration, median (IQR), d[a]	20 (8 to 24)	23 (16 to 25)	3 (0 to 6)	.05
ICU length of stay, median (IQR), d[a]	8 (5 to 15)	8 (4 to 14)	0 (−4 to 2)	.76
Hospital length of stay, median (IQR), d[a]	13 (8 to 23)	14 (8 to 22)	1 (−1 to 1)	.92
Secondary bacteremia or fungemia, No. (%)	11 (15)	13 (15)	0 (−10 to 10)	.97
Mortality, No. (%)	11 (15)	10 (12)	−3 (−14 to 7)	.54
Composite end point of mortality and >7 d of mechanical ventilation or >50% increase in IL-6 level, No. (%)	49 (68)	42 (50)	−18 (−33 to −3)	.02

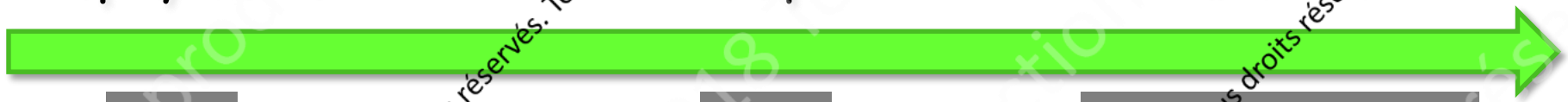
Limaye *et al.* JAMA 2017

When to treat?

Cytomegalovirus Control in Critical Care (CCCC)
NCT01503918

Study of Ganciclovir/Valganciclovir for Prevention of CMV Reactivation in Acute Injury of the Lung and Respiratory Failure (GRAIL)
NCT01335932

Preemptive Treatment for Herpesviridae (PTH)
NCT02152358



IgG

PCR

+ clinical signs

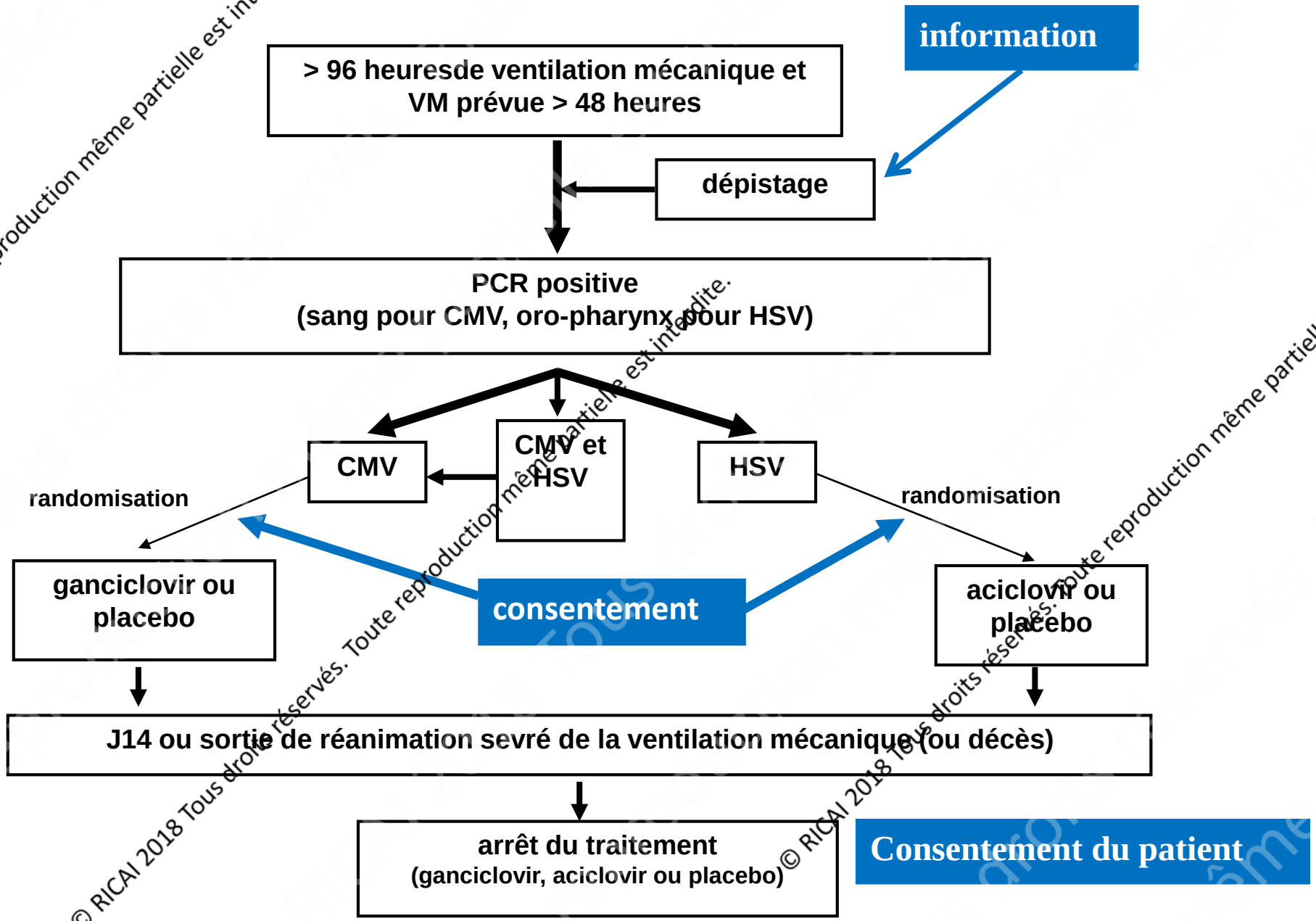
Objectif principal

- Augmentation de 8 jours du **nombre de jours où les patients sont vivants et sevrés de la ventilation** mécanique à J60 (VFD J60) après l'inclusion par :
  - un traitement de 14 j de ganciclovir devant la positivité d'une PCR sanguine à CMV
  - par un traitement de 14 j d'aciclovir devant la positivité d'une PCR oro-pharyngée à HSV

Objectifs secondaires

- Mortalité à J60 – réanimation - hôpital
- Durée de ventilation mécanique invasive - Durée d'hospitalisation
- Incidence des infections actives à CMV - Taux de réactivations
- Incidence des bronchopneumonies herpétiques
- Défaillances d'organes (définies par le score SOFA)
- Incidence infections bactériennes (pneumonies acquises sous ventilation mécanique-bactériémies)
- Incidence du SDRA - choc septique
- Négativation de la PCR CMV/HSV
- Tolérance des traitements étudiés

Design



Nombre de patients à inclure

- Nombre de patients à inclure pour augmenter de 8 jours le nombre de jours vivant et sevré de la VM dans les 60 jours suivant l'inclusion
  - Sous-étude HSV: 120 aciclovir / 120 placebo
  - Sous-étude CMV: 120 ganciclovir / 120 placebo

Résultats

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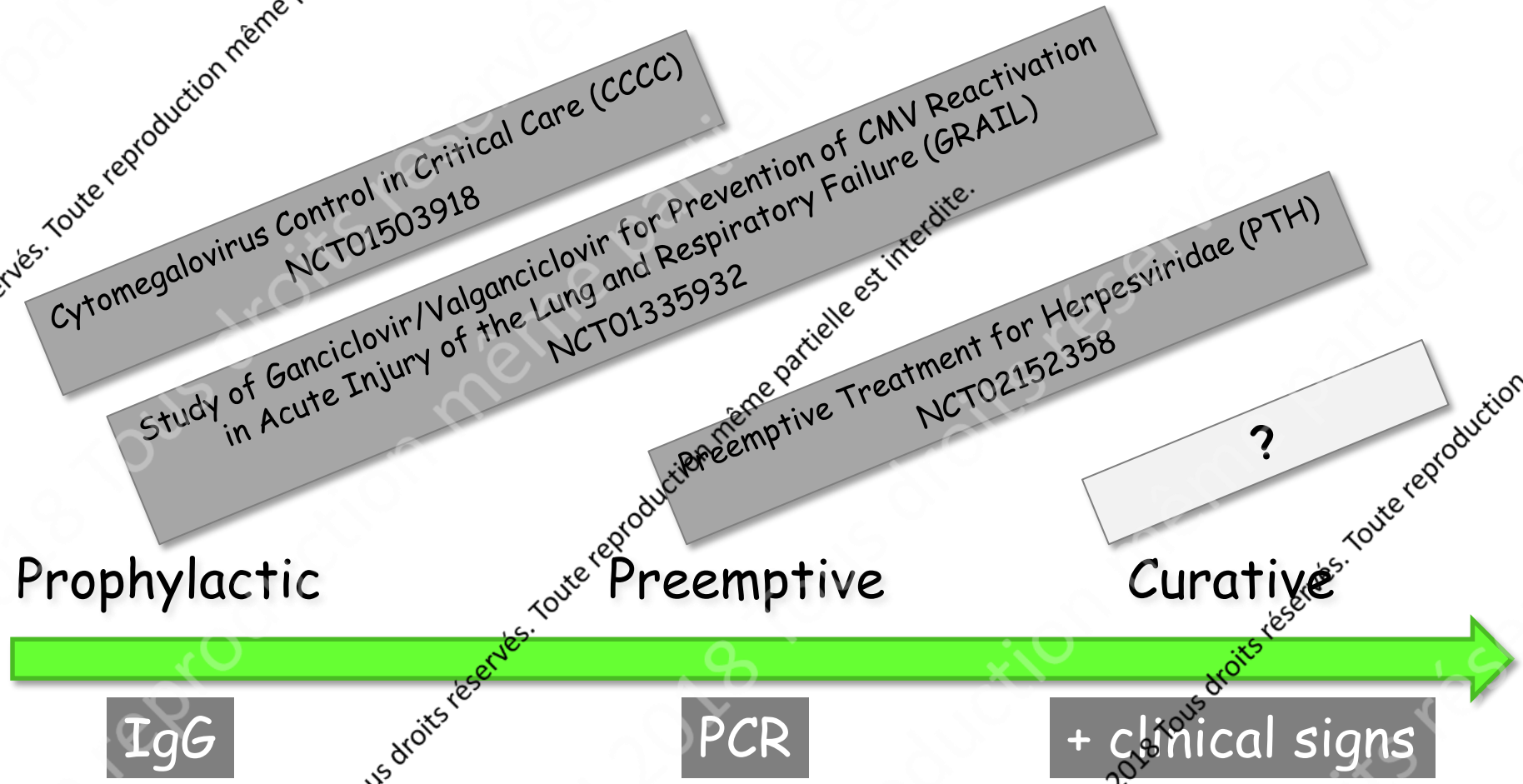
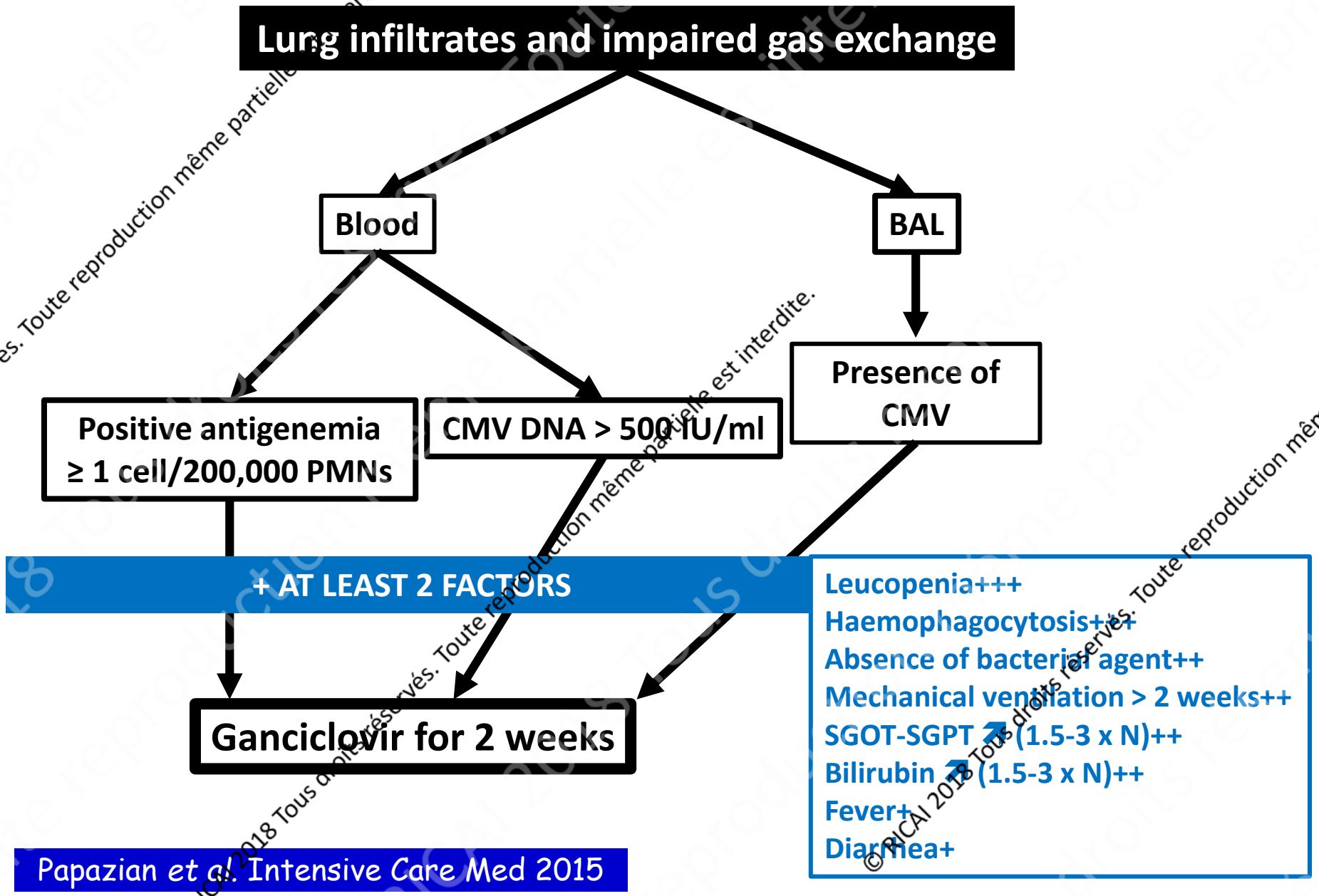
When to treat?





Papazian *et al.* Intensive Care Med 2015

Conclusions

- Reactivation is frequent
- Pathogenicity?
  - Direct and/or indirect?
- Treatment when clinical signs
- Need for interventional trials
- Risk/benefit balance
- Other new (or old) viruses