



Attributable mortality of ventilator-associated pneumonia and prognostic of recurrences in COVID-19 patients admitted in ICU: a multicentric observational study from the OutcomeRea™ network

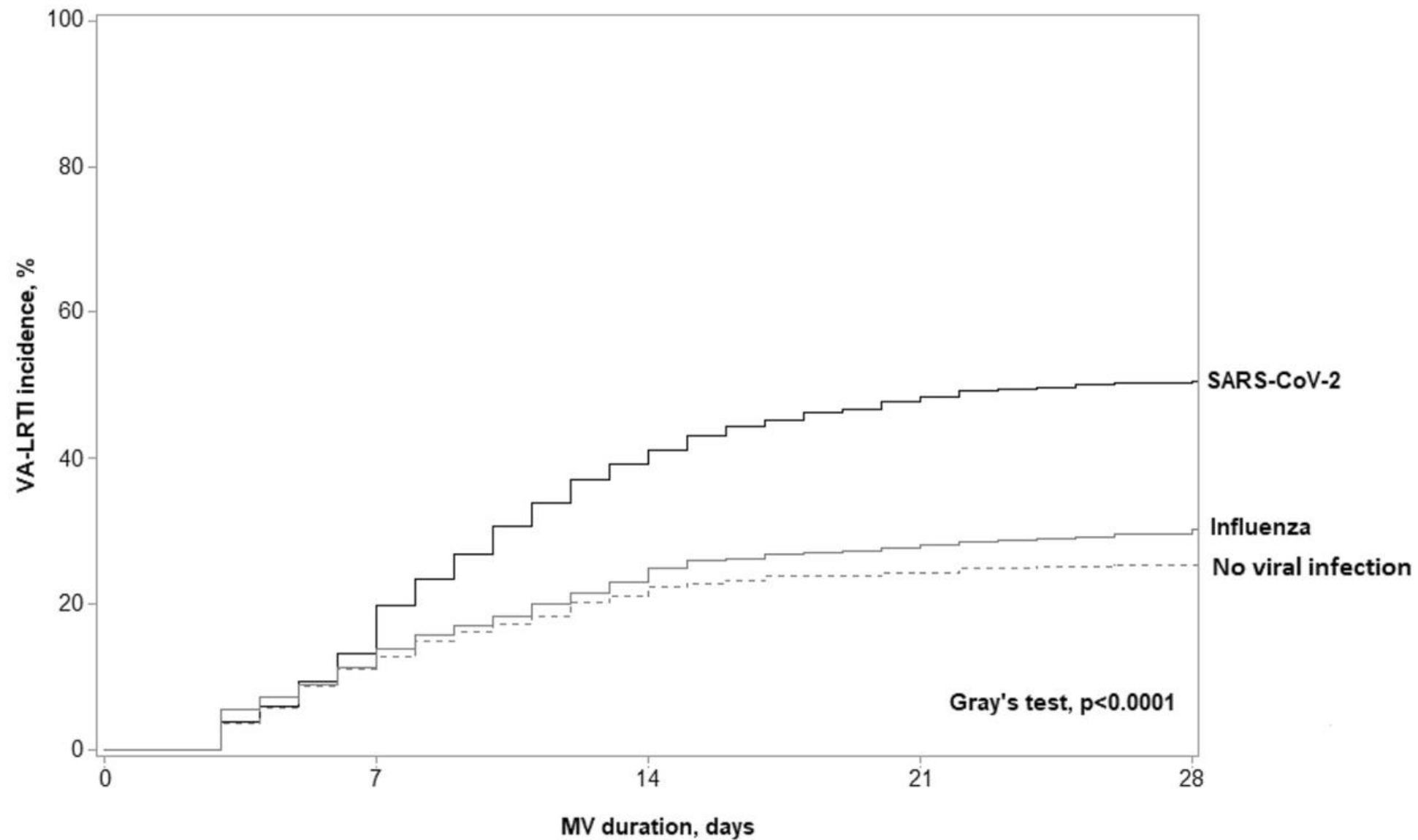
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Rationale



Rationale

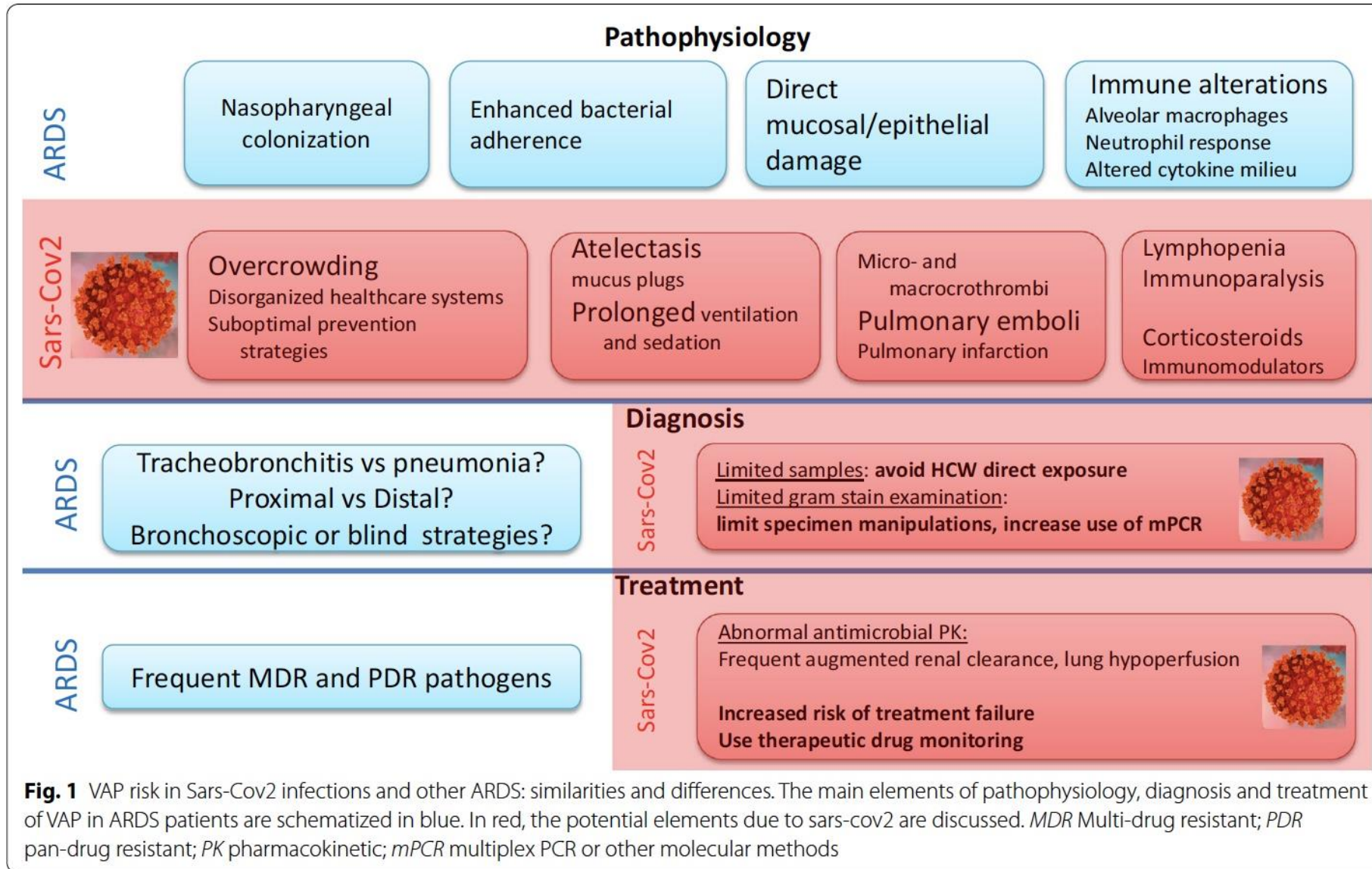
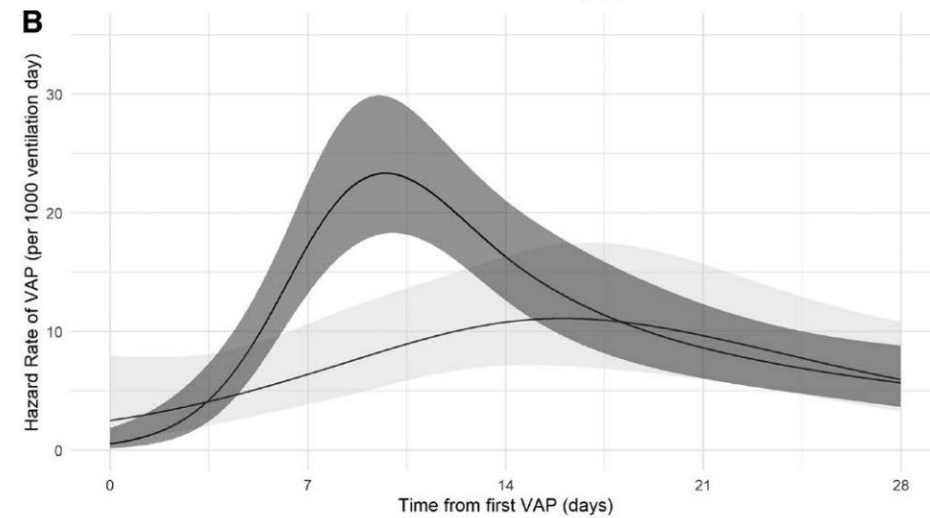
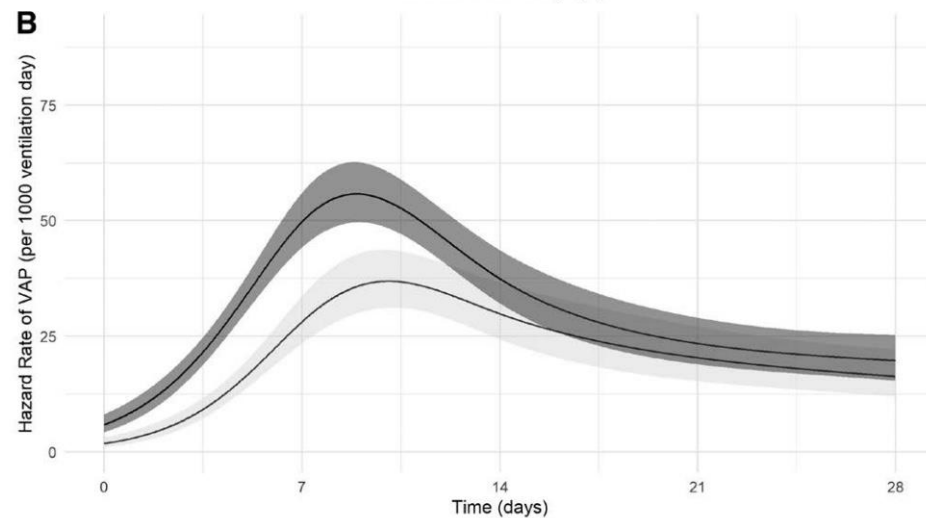
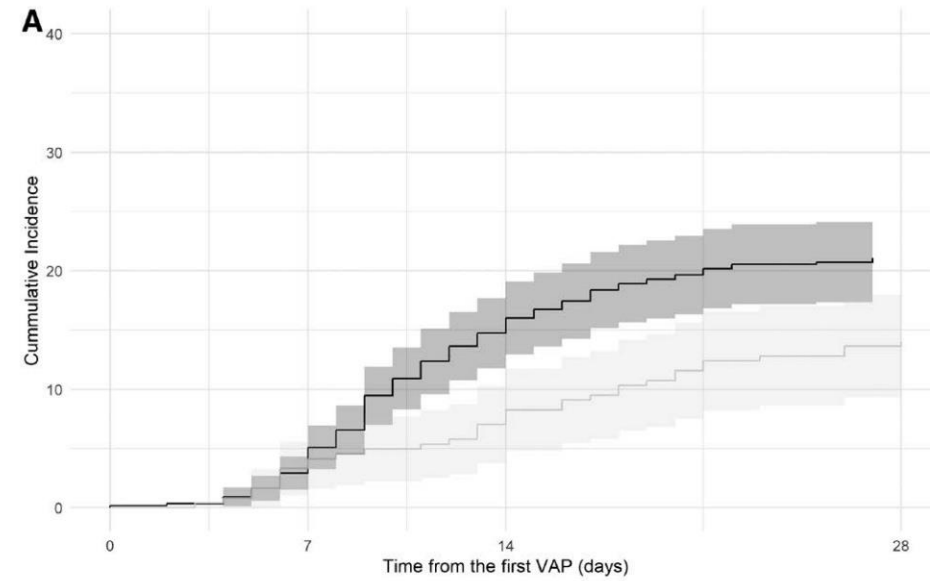
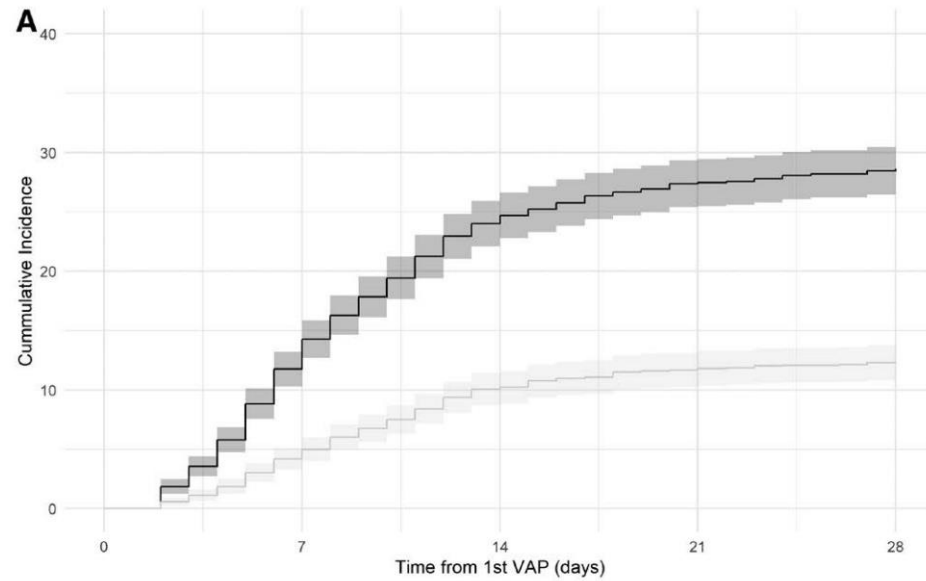


Fig. 1 VAP risk in Sars-Cov2 infections and other ARDS: similarities and differences. The main elements of pathophysiology, diagnosis and treatment of VAP in ARDS patients are schematized in blue. In red, the potential elements due to sars-cov2 are discussed. *MDR* Multi-drug resistant; *PDR* pan-drug resistant; *PK* pharmacokinetic; *mPCR* multiplex PCR or other molecular methods

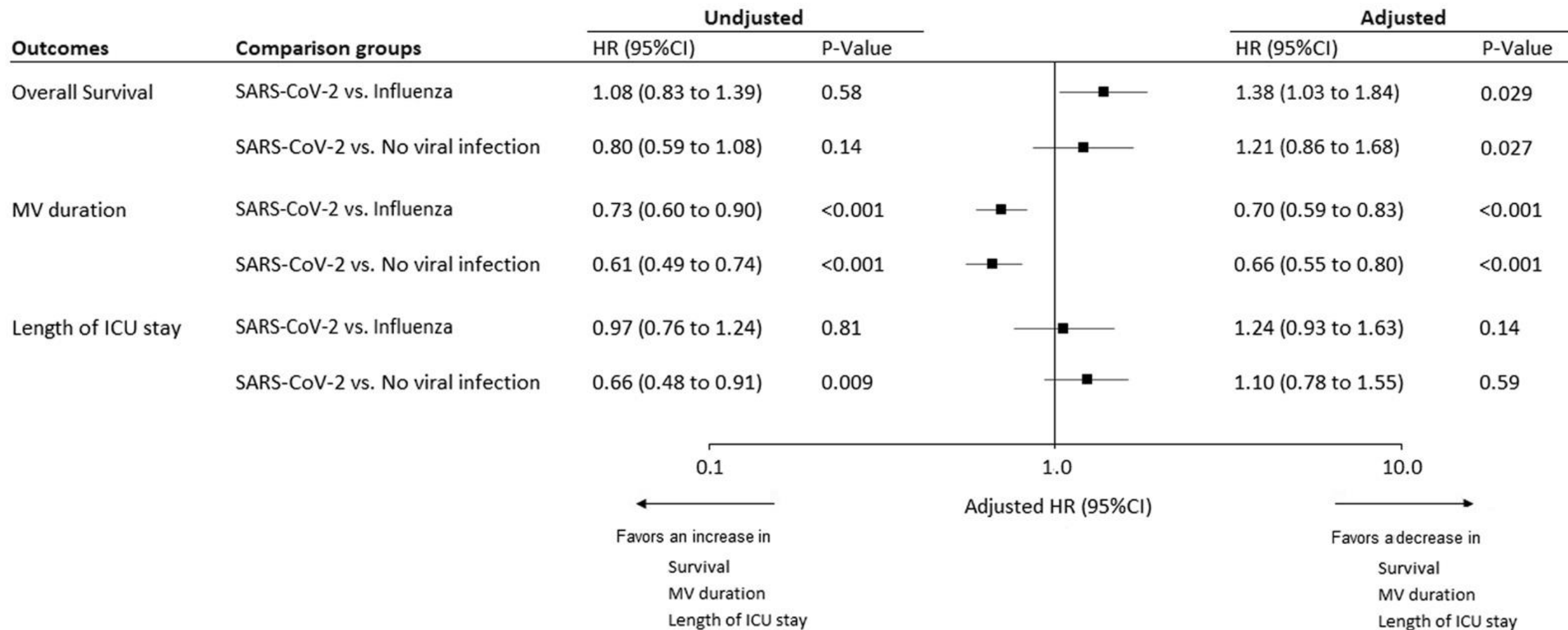
Rationale



COVID-19 non exposed COVID-19 exposed

COVID-19 non exposed COVID-19 exposed

Rationale



Rationale

Study	Sample size	VAP crude incidence (%)	VAP complications	Mortality
Rouzé et al	568	36	23% MDR	29.2%
Garcia-Vidal et al	144	25	-	9.8%
Pickens et al	179	44.4	-	19%
Gragueb-Chatti et al	151	60	37% recurrence, 66% ≥ 1 recurrence,	17% d-28, 26% d60
Luyt et al	50	86	38% polymicrobial	34%
Maes et al	81	48	-	38%
Blonz et al	188	48.9	20% multiple VAP, 3.6% empyema, 1.4% abscesses	30.4% (VAP), 29% (overall)
Razazi et al	90	64	25% recurrence (23% MDR)	40%
Llitjos et al	176	52	21% recurrence	31%
Moretti et al	39	54	-	44%
Rouyer et al	79	53	28% recurrences, 17% clinical success (d-7)	52%
Giacobbe et al	586	29	-	46%
Contou et al	73	64	73 ICU death 23% recurrence (21% MDR)	48%
Grasselli et al	774	50	-	26%
D’Humières et al	77	84.4	57.4% failure at (d-7)	51% (overall)
Beaucoté et al	161	73	14% abscess, polymicrobial	56% - 65% lung abscess

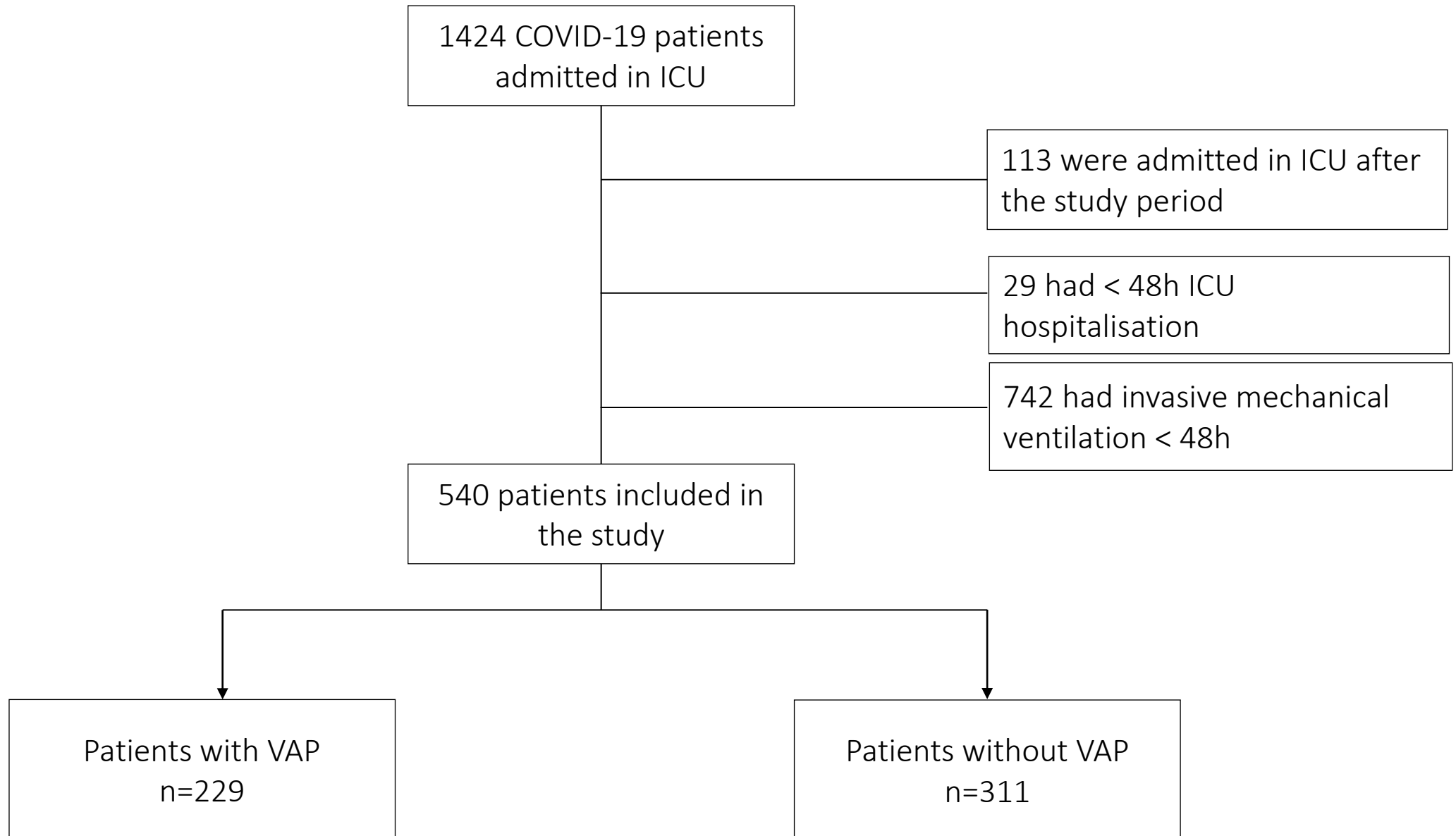
Methods

- Objectives
 - attributable day-60 mortality
 - incidence of VAP recurrence, treatment failure
- Retrospective observational multicentric design
 - data prospectively collected
 - 11 French ICU
- Inclusion criteria
 - admitted between March 2020 and June 2021
 - invasive ventilation \geq 48h

Methods

- VAP diagnosed as recommended (PTC, ETA, BAL)
 - Relapse : same pathogen
 - Superinfection : different pathogen
 - Treatment failure : Relapse, superinfection, death
- Competing outcomes
 - VAP or death
 - day-0 = day of VAP diagnostic
- Survival analysis
 - Cox's proportional hazard model, Fine and Gray's competitive risk model

Flow diagram



Population's characteristics

	All n=540	No VAP n=311	VAP n=229	p-value
Period (before May 2020)	284 (52.6)	162 (52.1)	122 (53.3)	0.79
Age	63.6 [54.6 - 71.8]	65.2 [55.8 - 72.6]	62.3 [52.5 - 71]	0.02
Gender (Male)	401 (74.2)	223 (71.7)	178 (77.7)	0.11
Body-mass index	28.8 [25.4 - 32.6]	28.4 [25 - 32.1]	29.4 [26.2 - 33.6]	< 0.01
At least one comorbidity	357 (66.2)	215 (69.1)	142 (62)	0.08
Chronic liver failure	11 (2)	7 (2.3)	4 (1.7)	0.68
Chronic cardiovascular disease	151 (28)	99 (31.8)	52 (22.7)	0.02
Chronic respiratory failure	60 (11.2)	36 (11.6)	24 (10.5)	0.69
Chronic kidney disease	48 (8.8)	33 (10.6)	15 (6.6)	0.10
Immunosuppression	58 (10.8)	44 (14.1)	14 (6.1)	<0.01
Diabetes mellitus	98 (18.2)	57 (18.3)	41 (17.9)	0.90
ICU characteristics on admission				
Time from symptoms onset (miss=54)	9 [7 - 12]	9 [6 - 12]	9 [7 - 12]	0.67
SAPS II score	38 [29 - 51]	39 [31 - 53]	38 [29 - 48]	0.09
COVID-19 specific treatments on admission				
Corticosteroids	277 (51.2)	148 (47.6)	129 (56.3)	0.04
Tocilizumab	24 (4.4)	13 (4.2)	11 (4.8)	0.72

Population's characteristics

	All n=540	No VAP n=311	VAP n=229	p-value
PEEP > 12 cmH2O	166 (30.8)	81 (26)	85 (37.1)	< 0.01
Prone position	175 (32.4)	84 (27)	91 (39.7)	< 0.01
Neuromuscular blockade	436 (80.8)	244 (78.5)	192 (83.8)	0.12
ECMO	47 (8.8)	16 (5.1)	31 (13.5)	< 0.01
Renal Replacement Therapy	56 (10.4)	35 (11.3)	21 (9.2)	0.43
Vasopressor	306 (56.6)	193 (62.1)	113 (49.3)	< 0.01
Enteral feeding	332 (61.4)	183 (58.8)	149 (65.1)	0.14
Parenteral feeding	106 (19.6)	64 (20.6)	42 (18.3)	0.52
Proto pump inhibitor	314 (58.2)	178 (57.2)	136 (59.4)	0.62
Organ supports during ICU stay				
Prone position	284 (52.6)	123 (39.5)	161 (70.3)	< 0.01
ECMO	80 (14.8)	26 (8.4)	54 (23.6)	< 0.01
Renal Replacement Therapy	178 (33)	91 (29.3)	87 (38)	0.03
Vasopressor	362 (67)	215 (69.1)	147 (64.2)	0.23

Population's characteristics

	All n=540	No VAP n=311	VAP n=229	<i>p</i> -value
Before the period at risk*				
At least one antimicrobial therapy				
Amoxicillin / Clavulanic Acid	64 (11.8)	29 (9.3)	35 (15.3)	0.03
Ureido-carboxypenicillins	91 (16.8)	42 (13.5)	49 (21.4)	0.02
3 rd -generation cephalosporin	316 (58.6)	189 (60.8)	127 (55.5)	0.22
4 th -generation cephalosporin	89 (16.4)	50 (16.1)	39 (17)	0.77
Carbapenems	40 (7.4)	28 (9)	12 (5.2)	0.10
Macrolide	193 (35.8)	111 (35.7)	82 (35.8)	0.98
Fluoroquinolone	64 (11.8)	34 (10.9)	30 (13.1)	0.44
MDR pathogens colonization	45 (8.4)	20 (6.4)	25 (10.9)	0.06
ESBL- Enterobacterales	34 (6.2)	17 (5.5)	17 (7.4)	0.35
Carbapenem-resistant Enterobacterales	7 (1.2)	1 (0.3)	6 (2.6)	0.02
MDR Pseudomonas aeruginosa	2 (0.4)	1 (0.3)	1 (0.4)	0.83
MRSA	4 (0.8)	2 (0.6)	2 (0.9)	0.76

Results – main outcomes

	All <i>n</i> =540	No VAP <i>n</i> =311	VAP <i>n</i> =229	<i>p</i> -value
Invasive mechanical ventilation duration*	13 [7 - 23.6]	9 [5 - 14]	21 [14 - 34]	< 0.01
<i>Ventilator-free days at day-60</i> *	10 [0 - 47]	29 [0 - 52]	0 [0 - 36]	< 0.01
ICU LOS*	16 [10 - 29]	13 [8 - 19]	26 [17 - 41]	< 0.01
Hospital LOS*	22 [13.6 - 40]	17 [10 - 30]	31 [19 - 50]	< 0.01
ICU death	248 (46)	138 (44.7)	110 (47.6)	0.49
Death at day-60	263 (48.8)	143 (46.3)	110 (47.6)	0.76
Number of patients still in ICU at day-60	18 (3.4)	3 (1)	15 (6.5)	< 0.01

* starting from the period at risk (≥ 48h invasive ventilation)

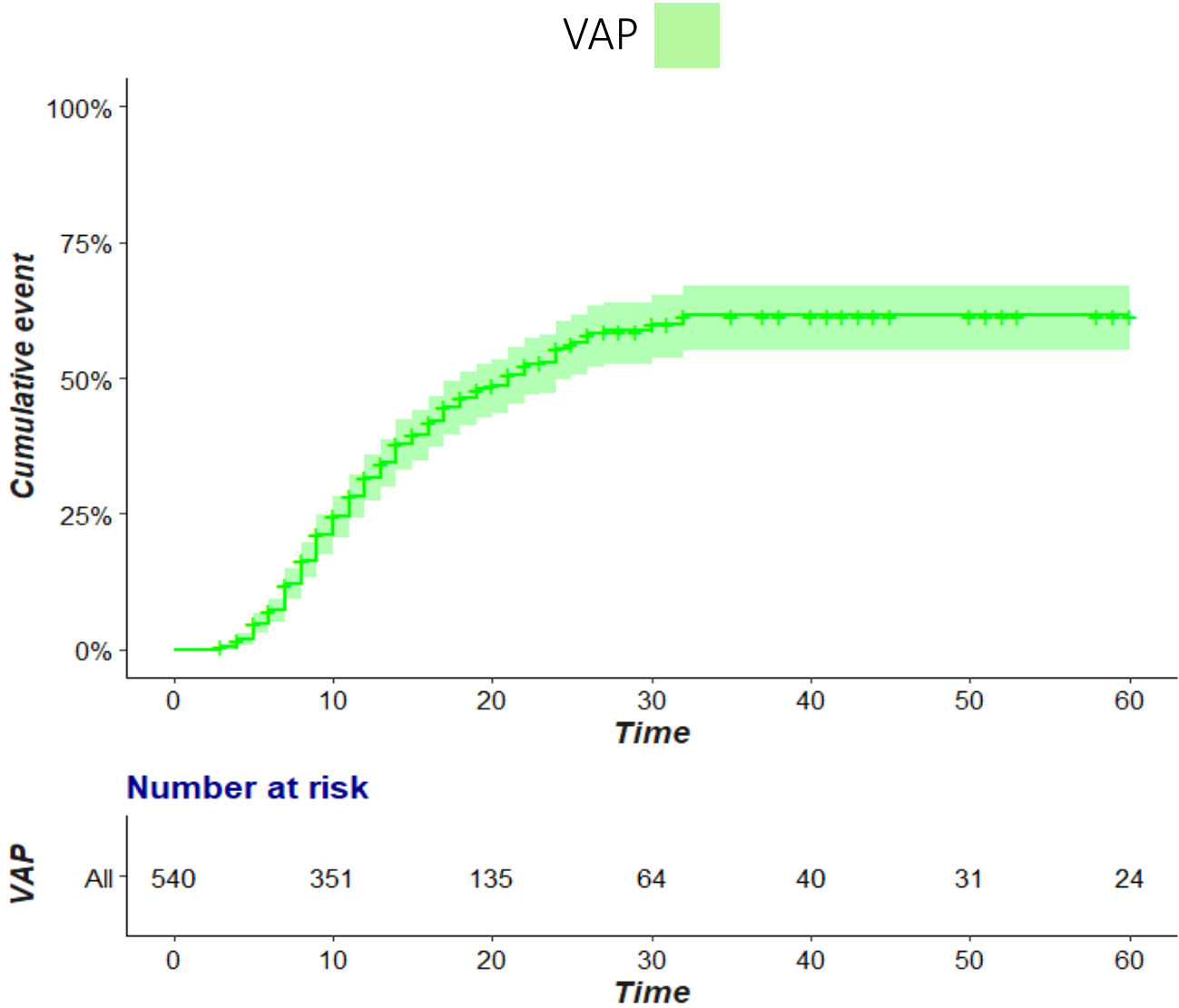
Results – main outcomes

	All <i>n</i> =540	VAP <i>n</i> =229
At least one episode of early VAP	93 (17.2)	93 (40.6)
At least one episode of late VAP	179 (33.2)	179 (78.2)
1 episode of VAP	143 (26.4)	143 (62.4)
2 episodes of VAP	53 (9.8)	53 (23.1)
≥ 3 episodes of VAP	33 (6.2)	33 (14.4)
At least one superinfection after VAP	58 (10.8)	58 (25.3)
1 superinfection	46 (8.6)	46 (20.1)
≥ 2 superinfection	12 (2.2)	11 (4.7)
At least one episode of relapse after VAP	62 (11.4)	62 (27.1)
1 relapse	39 (7.2)	39 (17)
≥ 2 relapse	23 (4.2)	22 (9.6)

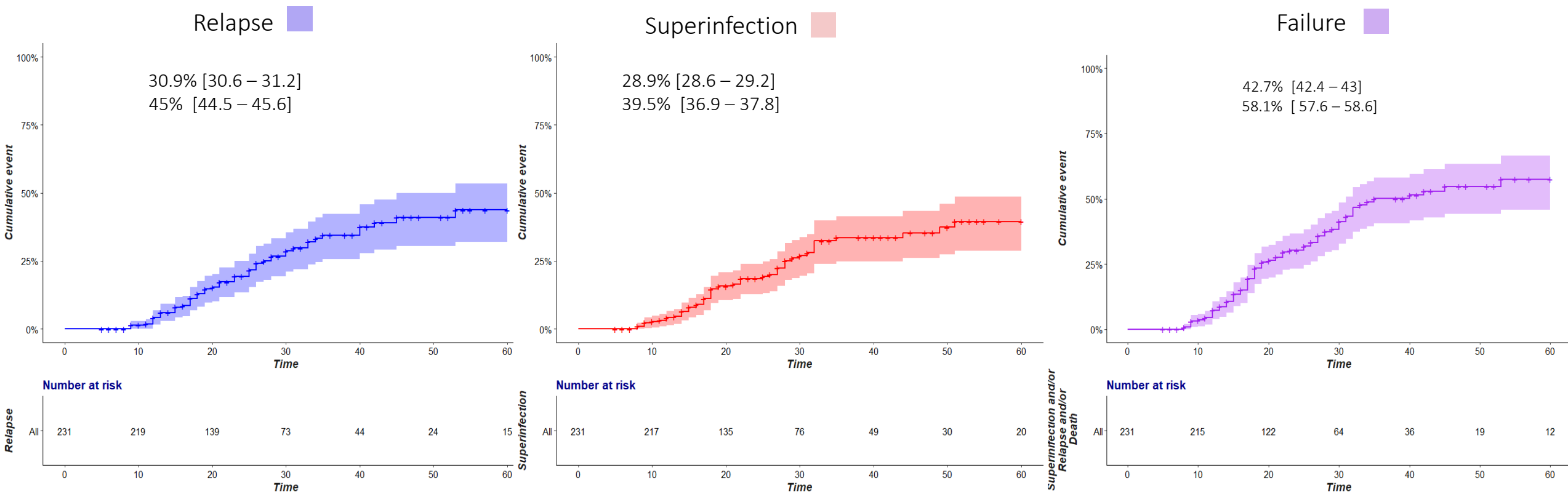
Results – incidence of VAP

VAP incidence rate
45.6 / 1000 ventilator-days

Cumulative incidence at day-30 and day-60
60% [59.8 – 60.1]
61.5% [61.3 – 61.7]



Results – incidence of recurrence



Cumulative incidence at day-30 and day-60

Results – day-60 mortality

	Hazard Ratio	HR 95% CI	<i>p</i> -value
Age			
< 50	1	-	< 0.01
50 - 60	1.54	[0.87 - 2.7]	0.14
60 - 70	2.88	[1.68 - 4.94]	< 0.01
> 70	3.69	[2.15 - 6.25]	< 0.01
Lymphocytes/Neutrophils ratio > 0.1	0.68	[0.49 - 0.94]	0.02
Parenteral feeding	1.51	[1.06 - 2.17]	0.02
Immunosuppression	1.76	[1.25 - 2.49]	< 0.01
Cardiovascular comorbidities	1.43	[1.1 - 1.87]	< 0.01
Renal replacement therapy before VAP	1.44	[0.99 - 2.10]	0.06
VAP	1.36	[1.03 - 1.8]	0.03

Results – day-60 mortality

		Hazard Ratio	HR IC 95%	<i>p</i> -value
Model 1	VAP	1.36	[1.03 - 1.8]	0.03
Model 2	Early VAP	1.04	[0.77 - 1.43]	0.78
	Late VAP	1.56	[1.14 - 2.13]	< 0.01
Model 3	Superinfection	1.04	[0.57 - 1.9]	0.91
Model 4	Relapse	1.12	[0.64 - 1.97]	0.70

Results – day-60 mortality (univariate analysis)

	Alive n=287	Dead n=253	<i>p</i> -value	Hazard Ratio	HR 95% CI	<i>p</i> -value
Type of VAP						
VAP	120 (41.8)	109 (43.1)	0.77	1.25	[0.94 - 1.65]	0.12
Early VAP	45 (15.7)	48 (19)	0.31	1.03	[0.74 - 1.43]	0.88
Late VAP	99 (34.5)	80 (31.6)	0.48	1.36	[0.99 - 1.85]	0.06
Superinfection	36 (12.5)	22 (8.7)	0.15	1.24	[0.73 - 2.1]	0.42
Relapse	38 (13.2)	24 (9.5)	0.17	1.20	[0.74 - 1.94]	0.45

Results – relapse and superinfection after VAP

	Hazard Ratio	HR 95% IC	p-value
Superinfection			
Period admission before May 2020	0.40	[0.22 - 0.71]	< 0.01
ECMO*	2.13	[1.13 - 4.00]	0.02
Non fermenting species **	0.37	[0.17 - 0.79]	0.01
Treatment failure			
Age > 70 y	1.91	[1.36 ; 2.68]	< 0.01
Steroids	1.54	[1.09 - 2.16]	0.01
RRT	1.43	[1.06 – 1.93]	0.02

* required at intubation

** causing the 1st VAP

Results – superinfection (univariate analysis)

	No Superinfection n=172	Superinfection n=57	Hazard Ratio	HR95% IC	p-value
Steroids	99 (57.6)	32 (56.1)	1.00	[0.6 - 1.68]	0.99
ECMO	20 (11.6)	17 (29.8)	2.30	[1.23 - 4.32]	0.01
PEEP > 12 cmH ₂ O	43 (25)	18 (31.6)	1.25	[0.7 - 2.25]	0.45
Prone position	50 (29.1)	17 (29.8)	1.00	[0.56 - 1.79]	1.00
Renal replacement therapy	38 (22.1)	11 (19.3)	0.80	[0.4 - 1.62]	0.54
Vasopressor	68 (39.5)	25 (43.9)	1.64	[0.86 - 3.15]	0.14
Enteral nutrition	133 (77.3)	45 (78.9)	0.92	[0.44 - 1.92]	0.83
Parenteral nutrition	53 (30.8)	18 (31.6)	1.39	[0.74 - 2.61]	0.31
Proto pump inhibitor	127 (73.8)	41 (71.9)	0.91	[0.49 - 1.71]	0.78
Lymphocytes/neutrophils ratio > 1	124 (72.1)	44 (77.2)	1.10	[0.57 - 2.11]	0.78
Highly susceptible germs	20 (11.6)	12 (21.1)	2.15	[1.18 - 3.93]	0.01
Staphylococcus aureus species	31 (18)	18 (31.6)	1.59	[0.91 - 2.78]	0.10
Group 1-2 enterobacterales	53 (30.8)	11 (19.3)	0.56	[0.28 - 1.12]	0.10
Group 3 enterobacterales	42 (24.4)	10 (17.5)	0.79	[0.39 - 1.58]	0.50
Non fermentant species	48 (27.9)	7 (12.3)	0.39	[0.18 - 0.84]	0.02
MDR or XDR	54 (31.4)	7 (12.3)	0.36	[0.16 - 0.8]	0.01
Bi antimicrobial therapy	73 (42.4)	15 (26.3)	0.51	[0.28 - 0.92]	0.03
Broad spectrum antimicrobial therapy	110 (64)	28 (49.1)	0.59	[0.35 - 1]	0.05
Adequation	81 (47.1)	29 (50.9)	1.21	[0.72 - 2.04]	0.47

Results – relapse (univariate analysis)

	No Relapse n=168	Relapse n=61	Hazard Ratio	HR 95% IC	p-value
Steroids	94 (56)	37 (60.7)	1.19	[0.72 - 1.99]	0.49
ECMO	19 (11.3)	18 (29.5)	1.69	[0.98 - 2.9]	0.06
PEEP > 12 cmH ₂ O	44 (26.2)	17 (27.9)	0.99	[0.54 - 1.83]	0.99
Prone position	45 (26.8)	22 (36.1)	1.27	[0.73 - 2.21]	0.39
Renal replacement therapy	38 (22.6)	11 (18)	0.65	[0.34 - 1.26]	0.20
Vasopressor	66 (39.3)	27 (44.3)	2.00	[1.14 - 3.51]	0.02
Enteral nutrition	125 (74.4)	53 (86.9)	1.15	[0.48 - 2.76]	0.76
Parenteral nutrition	58 (34.5)	13 (21.3)	1.24	[0.58 - 2.66]	0.58
Proto pump inhibitor	121 (72)	47 (77)	1.21	[0.64 - 2.28]	0.56
Lymphocytes/neutrophils ratio > 1	122 (72.6)	46 (75.4)	1.27	[0.71 - 2.27]	0.42
Highly susceptible germs	25 (14.9)	0 (0)			
Staphylococcus aureus species	36 (21.4)	8 (13.1)	0.57	[0.28 - 1.16]	0.12
Group 1-2 enterobacteriaceae	45 (26.8)	16 (26.2)	1.02	[0.57 - 1.84]	0.94
Group 3 enterobacteriaceae	37 (22)	18 (29.5)	1.47	[0.84 - 2.56]	0.17
Non fermentant species	38 (22.6)	23 (37.7)	1.54	[0.94 - 2.53]	0.08
MDR or XDR	45 (26.8)	16 (26.2)	1.06	[0.59 - 1.92]	0.83
Bi antimicrobial therapy	64 (38.1)	24 (39.3)	1.04	[0.62 - 1.74]	0.88
Broad spectrum antimicrobial therapy	97 (57.7)	41 (67.2)	1.48	[0.87 - 2.54]	0.15
Adequation	80 (47.6)	30 (49.2)	1.13	[0.69 - 1.86]	0.62

Results – microbiological characteristics

	VAP n=383	Early VAP n=95	Late VAP n=288	p-value
Gram positive bacteria	124 (32.4)	37 (38.9)	87 (30.2)	0.11
<i>Streptococcus pneumoniae</i>	7 (1.8)	3 (3.2)	4 (1.4)	0.26
<i>Staphylococcus aureus</i>	84 (22)	25 (26.3)	59 (20.5)	0.23
<i>Haemophilus influenzae</i>	16 (4.2)	10 (10.5)	6 (2.1)	< 0.01
Enterobacterales	191 (49.8)	37 (38.9)	154 (53.5)	0.01
Group 1 or 2 enterobacterales	103 (26.8)	21 (22.1)	82 (28.5)	0.22
<i>Proteus sp</i>	15 (4)	0 (0)	15 (5.2)	0.02
<i>Escherichia coli</i>	49 (12.8)	8 (8.4)	41 (14.2)	0.14
<i>Klebsiella pneumoniae</i>	42 (11)	12 (12.6)	30 (10.4)	0.55
Group 3 enterobacterales	88 (23)	11 (11.6)	55 (19.1)	0.09
<i>Enterobacter sp</i>	66 (17.2)	18 (18.9)	70 (24.3)	0.28
<i>Serratia marcescens</i>	16 (4.2)	5 (5.3)	11 (3.8)	0.54
<i>Citrobacter freundii</i>	3 (0.8)	1 (1.1)	2 (0.7)	0.73
Non-fermenting GNB	133 (34.8)	28 (29.5)	105 (36.5)	0.21
<i>Pseudomonas aeruginosa</i>	95 (24.8)	18 (18.9)	77 (26.7)	0.13
<i>Stenotrophomonas maltophilia</i>	17 (4.4)	5 (5.3)	12 (4.2)	0.65
<i>Acinetobacter baumannii</i>	24 (6.2)	5 (5.3)	19 (6.6)	0.64
MDR or XDR	114 (29.8)	18 (18.9)	96 (33.3)	< 0.01
Carbapenem Resistant <i>Acinetobacter baumannii</i>	11 (2.8)	2 (2.1)	9 (3.1)	0.61
MRSA	13 (3.4)	0 (0)	13 (4.5)	0.04
Susceptible species (<i>Streptococcus sp</i> , <i>Moraxella</i> , <i>Haemophilus</i>)	34 (8.8)	14 (14.7)	20 (6.9)	0.02
More than one strain	95 (24.8)	17 (17.9)	78 (27.1)	0.07

Results – microbiological characteristics

	1 st VAP	Superinfection	p-value	1 st VAP	Relapse	p-value
	n=236	n=73		n=230	n=105	
Gram positive bacteria	81 (34.3)	24 (32.9)	0.82	78 (33.9)	31 (29.5)	0.43
<i>Streptococcus pneumoniae</i>	7 (3)	0 (0)	0.14	6 (2.6)	1 (1)	0.33
<i>Staphylococcus aureus</i>	50 (21.2)	20 (27.4)	0.27	49 (21.3)	24 (22.9)	0.75
<i>Haemophilus influenza</i>	16 (6.8)	0 (0)	0.02	16 (7)	0 (0)	< 0.01
Enterobacterales	121 (51.3)	33 (45.2)	0.37	118 (51.3)	50 (47.6)	0.53
Group 1 or 2 enterobacterales	68 (28.8)	21 (28.8)	0.99	67 (29.1)	21 (20)	0.08
<i>Proteus sp</i>	8 (3.4)	6 (8.2)	0.08	8 (3.5)	2 (1.9)	0.43
<i>Escherichia coli</i>	30 (12.7)	12 (16.4)	0.42	29 (12.6)	11 (10.5)	0.58
<i>Klebsiella pneumoniae</i>	30 (12.7)	6 (8.2)	0.30	30 (13)	9 (8.6)	0.24
Group 3 enterobacterales	38 (16.1)	10 (13.7)	0.62	36 (15.7)	25 (23.8)	0.07
<i>Enterobacter sp</i>	52 (22)	15 (20.5)	0.79	50 (21.7)	32 (30.5)	0.08
<i>Serratia marcescens</i>	11 (4.7)	4 (5.5)	0.78	11 (4.8)	4 (3.8)	0.69
<i>Citrobacter freundii</i>	1 (0.4)	0 (0)	0.58	1 (0.4)	2 (1.9)	0.19
Non-fermenting GNB	57 (24.2)	33 (45.2)	< 0.01	55 (23.9)	54 (51.4)	< 0.01
<i>Pseudomonas aeruginosa</i>	42 (17.8)	25 (34.2)	< 0.01	41 (17.8)	37 (35.2)	< 0.01
<i>Stenotrophomonas maltophilia</i>	9 (3.8)	1 (1.4)	0.30	9 (3.9)	7 (6.7)	0.27
<i>Acinetobacter baumannii</i>	6 (2.5)	11 (15.1)	< 0.01	5 (2.2)	12 (11.4)	< 0.01
MDR or XDR	64 (27.1)	23 (31.5)	0.47	62 (27)	38 (36.2)	0.09
Resistant <i>Pseudomonas aeruginosa</i>	12 (5.1)	8 (11)	0.07	12 (5.2)	21 (20)	< 0.01
Carbapenem Resistant <i>Acinetobacter baumannii</i>	2 (0.8)	7 (9.6)	< 0.01	2 (0.9)	4 (3.8)	0.06
MRSA	5 (2.1)	7 (9.6)	< 0.01	5 (2.2)	7 (6.7)	0.04
More than one strain	45 (19.1)	31 (42.5)	< 0.01	43 (18.7)	35 (33.3)	< 0.01

Discussion

- No difference between VAP and non-VAP patients
 - d-60 mortality
 - ICU mortality
- Higher incidence of VAP recurrence and treatment failure !!!
- Attributable d-60 mortality increased by 36%
 - prolongation in length of stay and MV duration
 - impact of “late-onset” VAP
- Impact of initial broad-spectrum antibiotics

Discussion

- Limits
 - “center-effect” ?
 - misestimated incidence due to diagnostic methods, definitions ?
 - statistical models’ inherent bias
- Impact of antibiotic strategy
 - pharmacokinetic optimization
 - bi-antimicrobial antibiotic
 - duration of treatment
- Medico-economic evaluation would be necessary

MERCI DE VOTRE ATTENTION