Des pneumonies communautaires sévères à Staphylococcus aureus

F. Vandenesch, MD, PhD

Centre
International
de Recherche
en Infectiologie

Disclosure

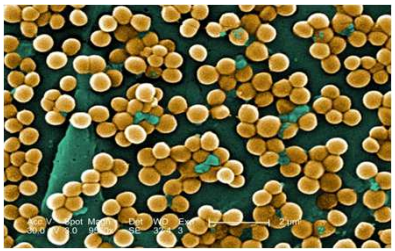
Research Grants, consulting:

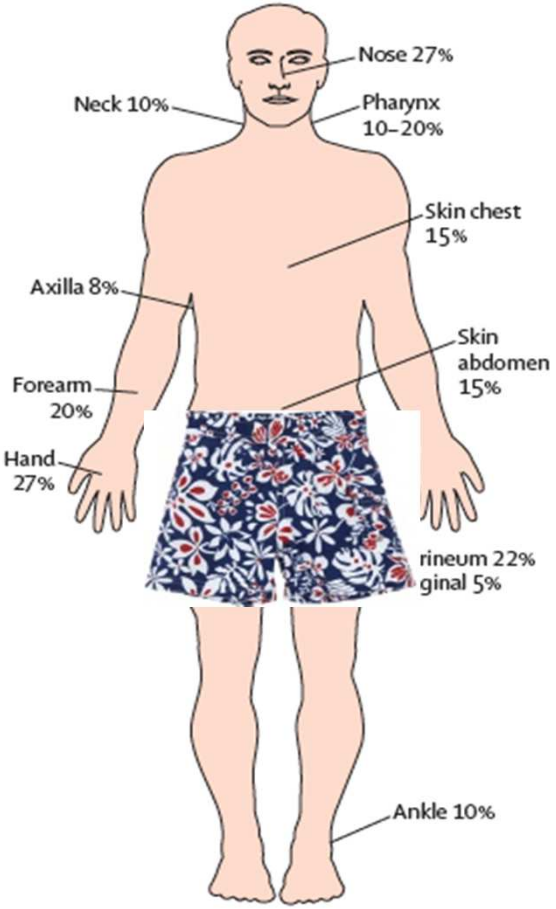
Astra Zeneca, Novartis, bioMérieux,

Sanofi-Pasteur, IRT Bioaster

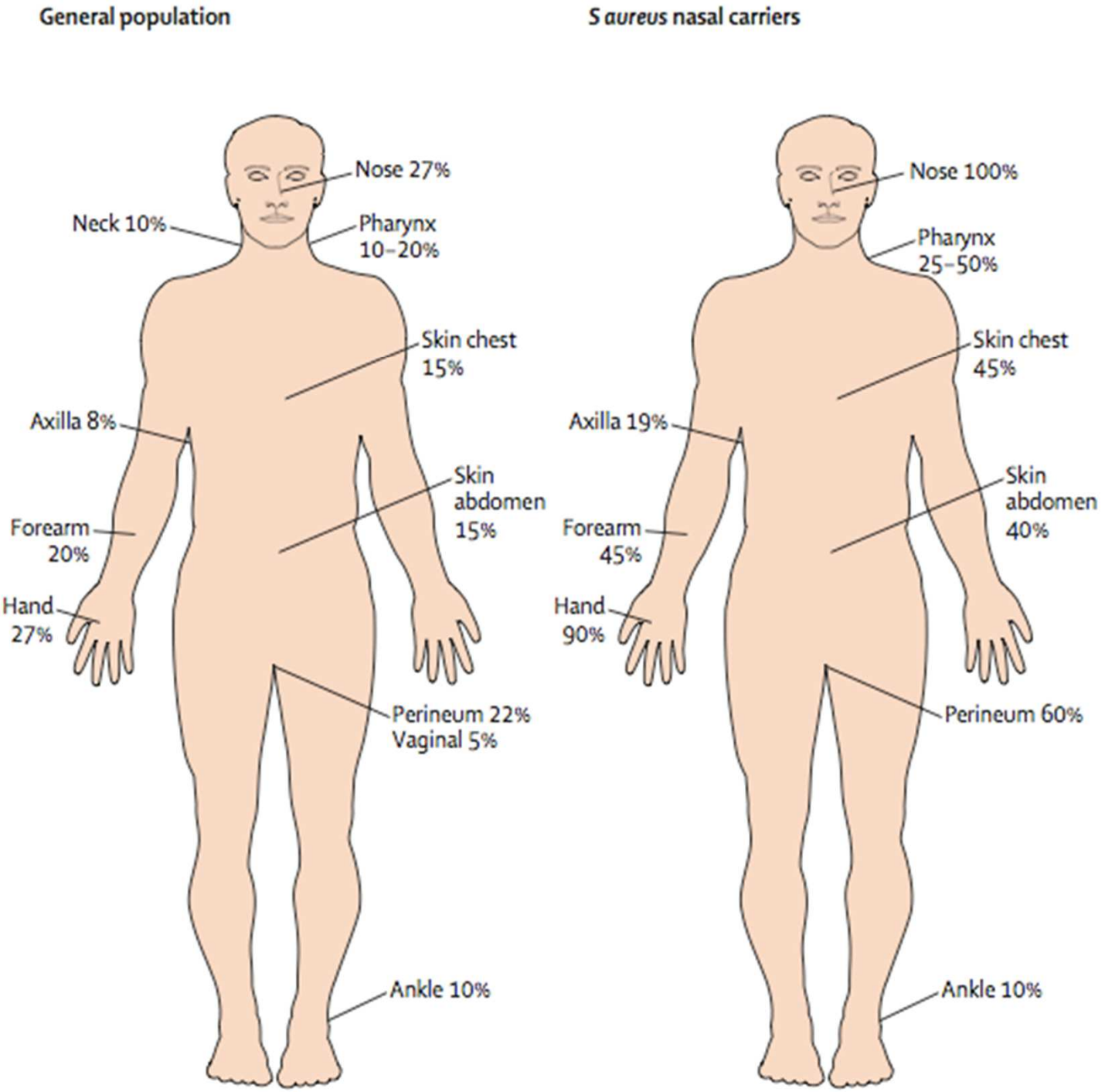
Staphylococcus aureus, from commensalism to pathogenicity

- Gram-positive bacteria
- Commensal: 30 % of carriers





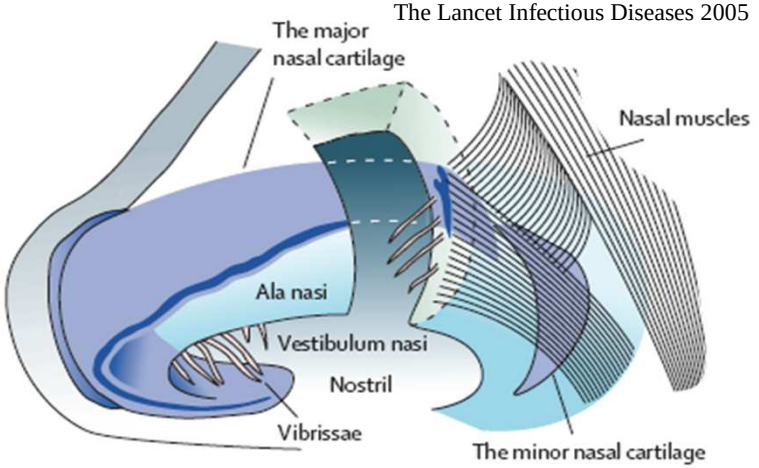
Lancet Infect Dis2005;5:751-62



Lancet Infect Dis2005;5:751-62

nasal carriage of *S. aureus* and the development of staphylococcal infection are linked

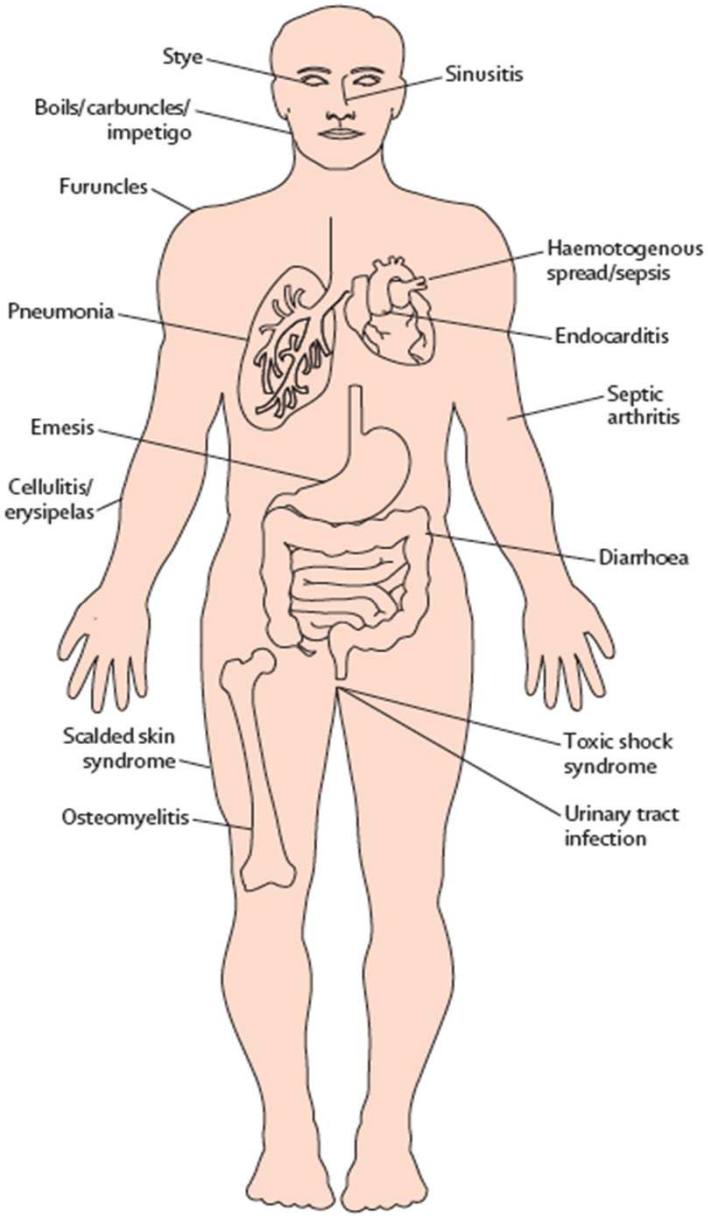
Heiman F. L Wertheim et al.
The Lancet Infectious Diseases 2005



- rates of infection are higher in carriers than in non-carriers
- individuals are usually infected with their own carriage isolate
- temporary eradication of carriage following the use of topical mupirocin has been shown to reduce nosocomial infection

Staphylococcus aureus, from commensalism to pathogenicity

- Gram-positive bacteria
- Commensal: 30 % of carriers
- Responsible for a large number of diseases
  - Suppurative infections



Staphylococcus aureus, from commensalism to pathogenicity

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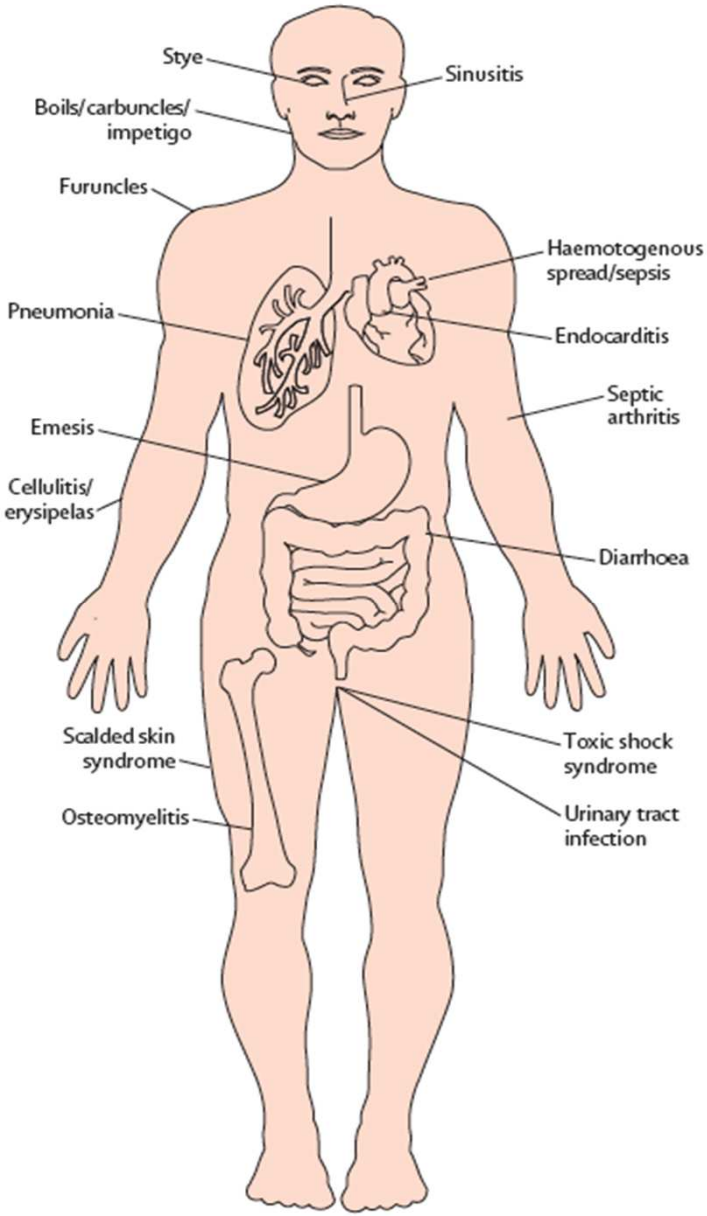

Staphylococcus aureus, from commensalism to pathogenicity

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- Commensal: 30 % of carriers
- Responsible for a large number of diseases
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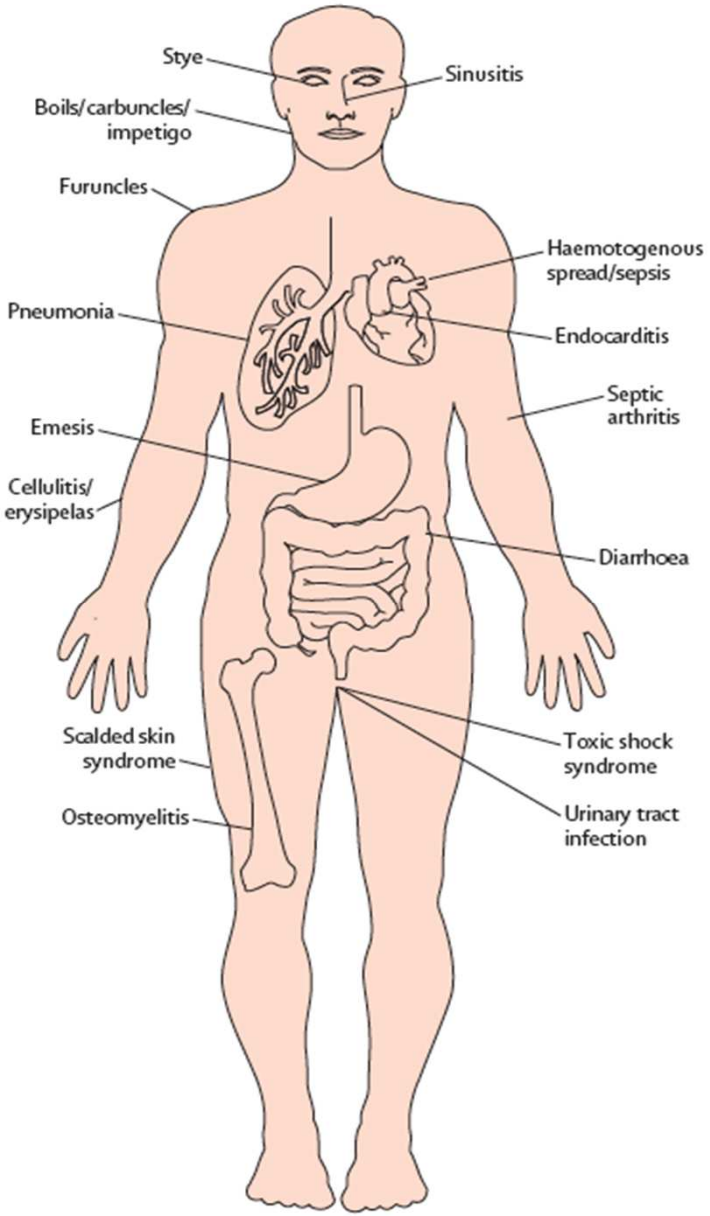
  - Toxemia : toxic shock syndrome, staphylococcal scarlet fever = SAGs



Staphylococcus aureus, from commensalism to pathogenicity

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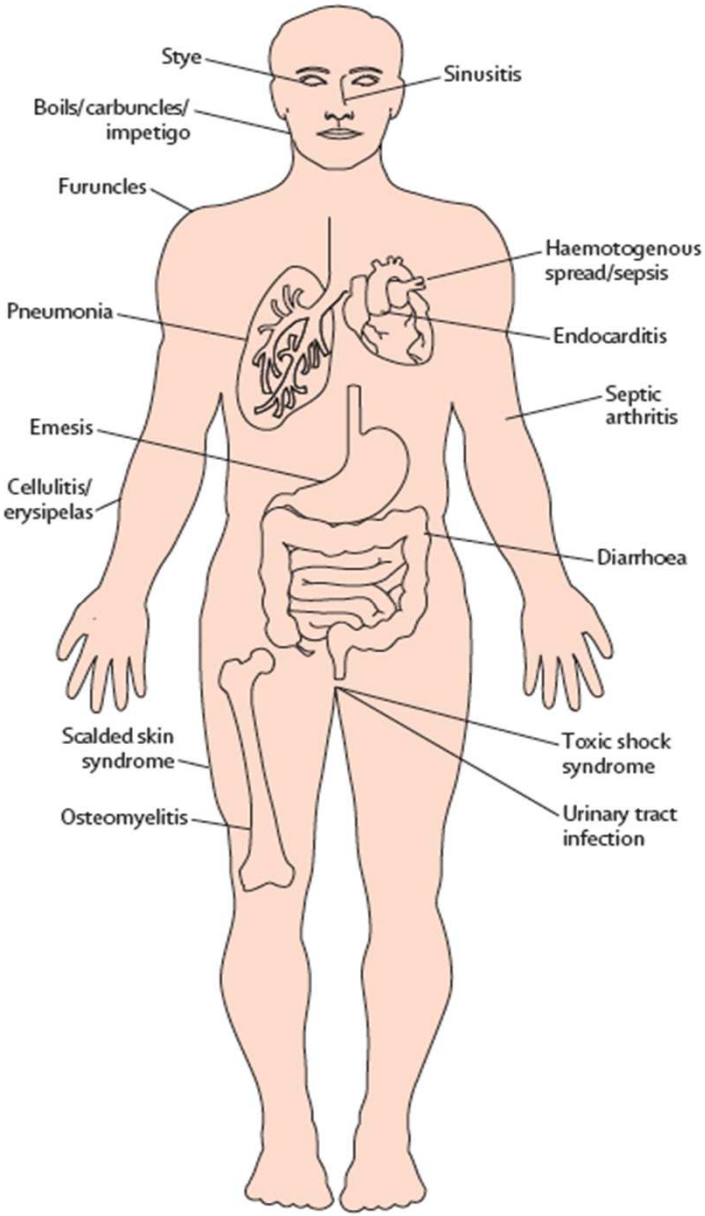
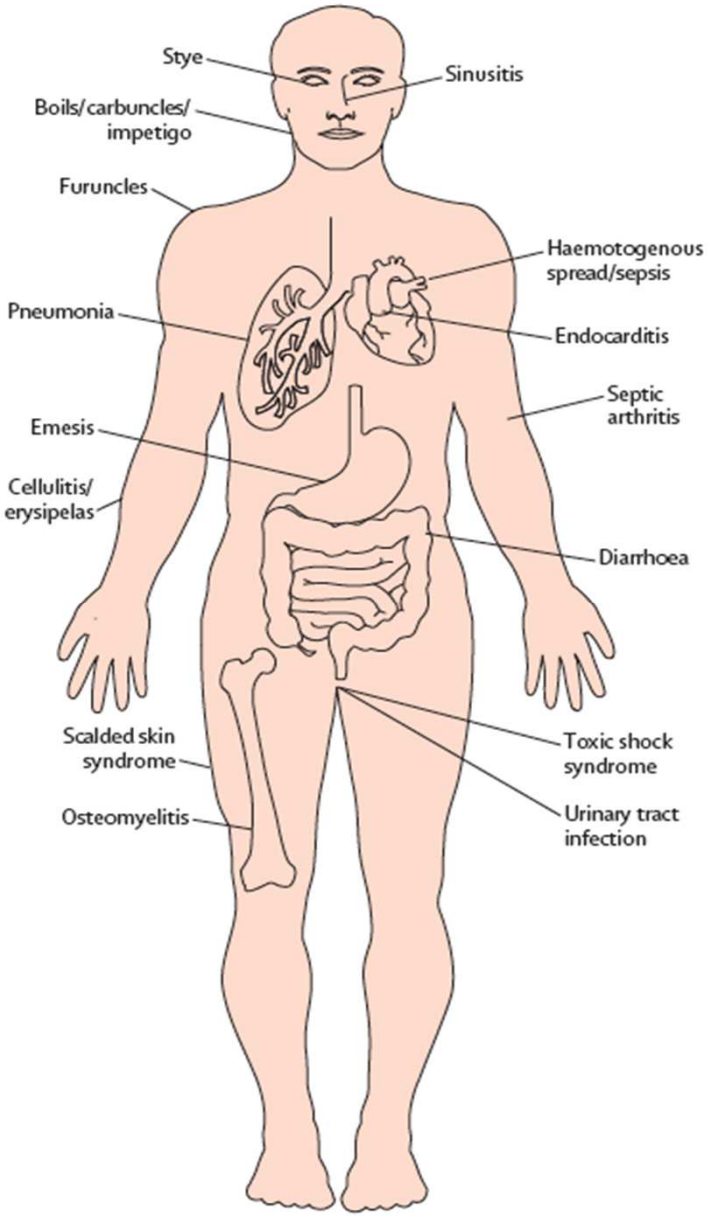
- Commensal: 30 % of carriers
- Responsible for a large number of diseases
  - Suppurative infections
  - Toxemia : bullous impetigo and SSS = exfoliative toxins



Staphylococcus aureus, from commensalism to pathogenicity

- Gram-positive bacteria
- Commensal: 30 % of carriers
- Responsible for a large number of diseases
  - Suppurative infections
  - Toxemia
  - Food poisoning : TIAC
- Community & Hospital acquired



The burden of *S. aureus* infections

- Frequency
  - 25 to 40% of community-acquired infections
  - 25% of nosocomial infection
- The burden for nosocomial infections
  - Inpatients with *S.aureus* infection:
    - 3 times the length of hospital stay (14.3 vs 4.5 days; P<.001),
    - 3 times the total charges (48,824 US dollars vs 14,141 US dollars; P<.001),
    - 5 times the risk of in-hospital death (11.2% vs 2.3%; P<.001) than inpatients without this infection

Arch Intern Med 2005;165(15):1756-61

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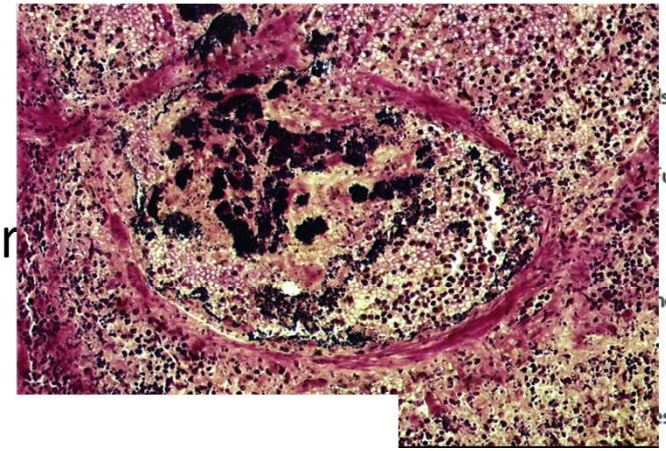

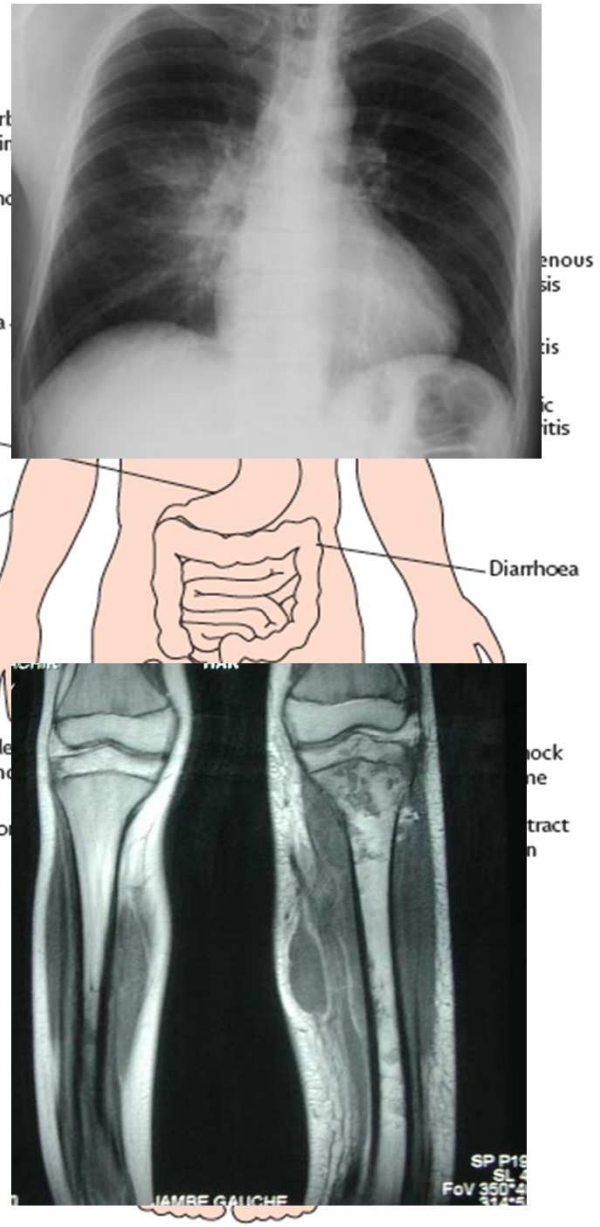

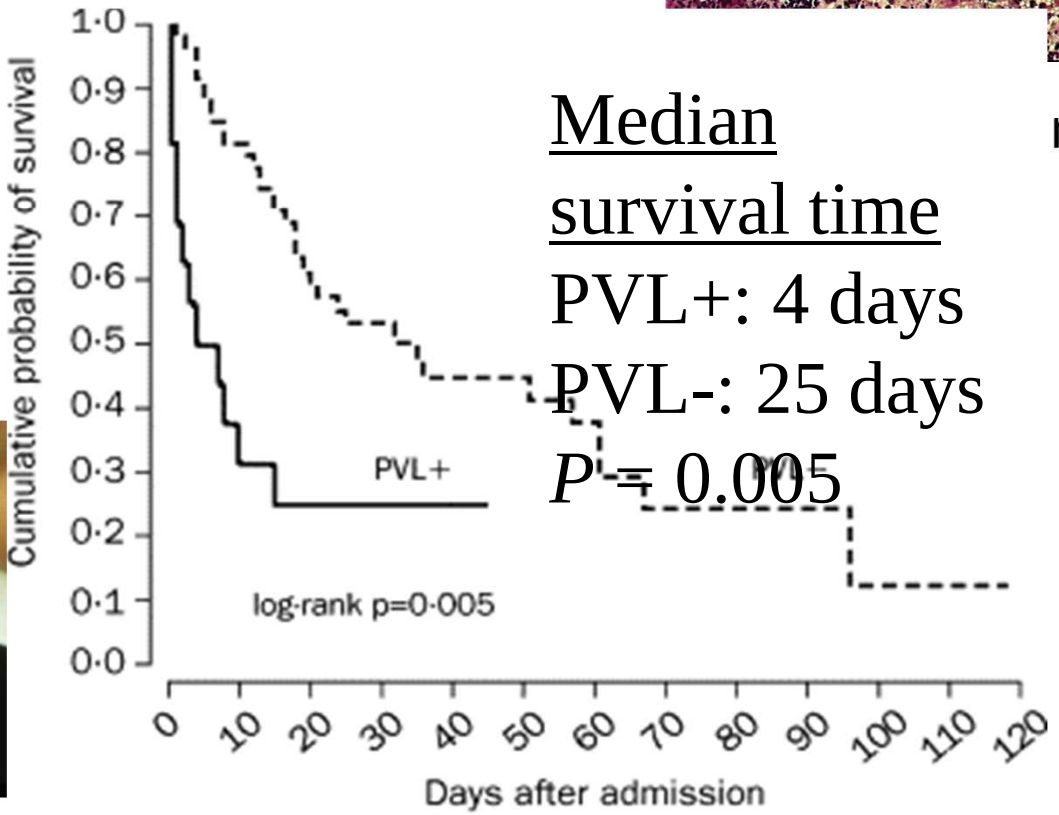

Median survival time

PVL+: 4 days

PVL-: 25 days

P = 0.005

S.aureus, a diversity of secreted and cell-wall associated virulence factors

- **Adhesion** : >20 adhesins including MSCRAMs: Microbial Surface components Recognizing Adhesive matrix molecules

- **Acquisition of nutrients:** e.g. hemolysins & siderophores

- **Immune escape and subversion:**
  - Opsonisation inhibition: e.g. Prot A
  - chemotaxis inhibition: e.g. CHIPS
  - Non-specific immune activation: superantigens
  - hemolysins, pore-forming toxins and membrane-damaging peptides

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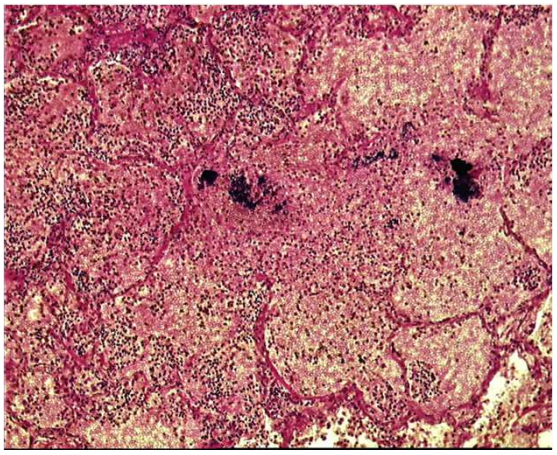
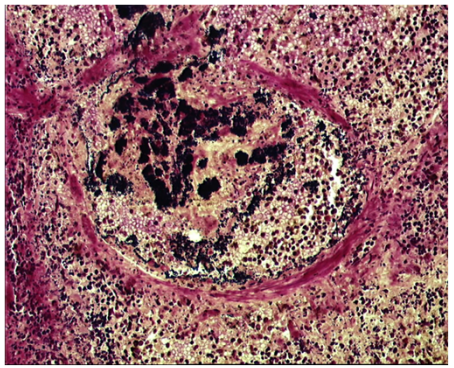
Starting point : case report

- Yves Piémont, Strasbourg, 1998
- Jeune fille 14 ans sans ATCD
- J1: consultation état pseudo grippal
- J2: admission en réanimation SDRA, leucopénie, hémophtysie
- J3: décès.
  - *S.aureus*
  - Autospsie : nécrose extensive
  - Microbio: *S.aureus* Panton Valentine positif





CNR des staphylocoques

- Label DGS-InVS
- Expertise, surveillance, alert toward resistance or emerging staphylococcal diseases
- Ca 100 different french hospitals
- Ca 3000 strains expertised each year

STAPHYLOCOQUES

Centre National de Référence

G. Lina

- Retrospective analysis of *S.aureus* isolates from the CNR
- PCR targeting Panton Valentine leukocidin
- Results stratified according to known clinical informations

Involvement of Panton-Valentine Leukocidin–Producing *Staphylococcus aureus* in Primary Skin Infections and Pneumonia

mal de Référence de Toxémies e Médecine, Lyon; [2]Institut de Pasteur, Faculté de Médecine, Doenschberg, Mulhouse, France

Table 1. Production of Panton-Valentine leukocidin by 171 *Staphylococcus aureus* strains associated with various clinical syndromes.

Type of infection	No. of strains tested	No. (%) of PVL-positive strains	*P* value
Pneumonia			
Hospital-acquired	13	0 (0)	—[a]
Community-acquired	27	23 (85)	<.001
Skin infection			
Superficial folliculitis	10	0 (0)	—[b]
Impetigo	4	0 (0)	NS
Finger pulp (felon)	15	2 (13)	NS
Cutaneous abscess	6	3 (50)	.03
Cellulitis	9	5 (55)	.01
Furunculosis	30	28 (93)	<.001
Other infection			
Infective endocarditis	21	0 (0)	—[c]
Osteomyelitis	13	3 (23)	NS
Urinary tract infection	5	0 (0)	NS
Enterocolitis	5	0 (0)	NS
Mediastinitis	5	0 (0)	NS
Toxic-shock syndrome	9	0 (0)	NS

Lina et al. Clin Infect Dis. 1999;29:1128-32. ISI web of Science: 1111 citations

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Lina et al. Clin Infect Dis. 1999;29:1128-32.

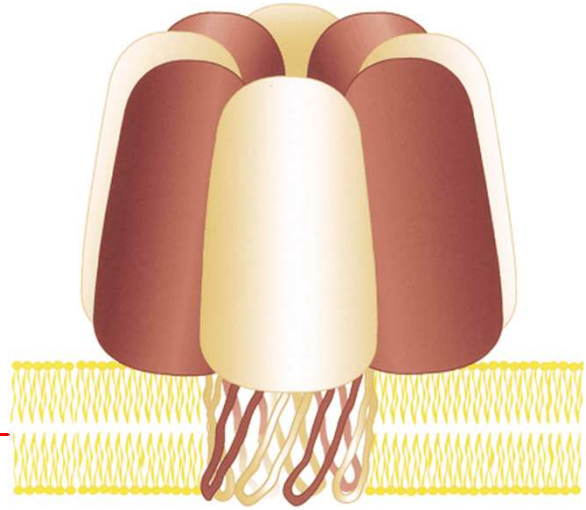
G. Lina

- Analyse rétrospective des souches de S.aureus reçues au CNR
- PCR ciblant la leucocidine de Panton Valentine
- Catégorisation / renseignement clinique connus

-> PVL significativement associé au caractère communautaire des pneumonies à *S.aureus*

Lina et al. Clin Infect Dis. 1999;29:1128-32.

Panton Valentine Leucocidine



- Phage encoded
- Two components -> hetero-octamer
- beta-barrel pore forming toxin

Denys J and Van de Velde, Cellule Fasc 1895;2:359.
Panton LA, Lancet 1932;i:56
Kaneko J et al, Biosci Biotechnol Biochem. 1997;61:1960
Miles G et al. Protein Sci. 2002 Apr;11(4):894-902

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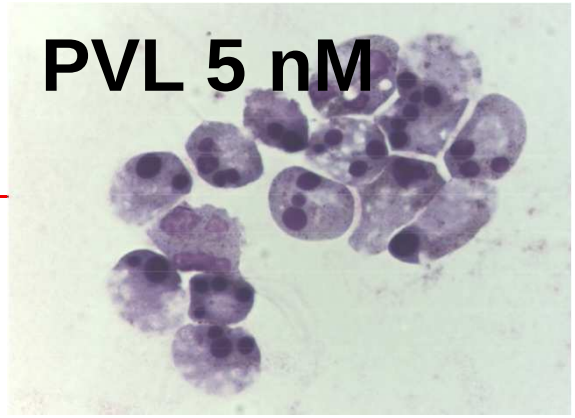
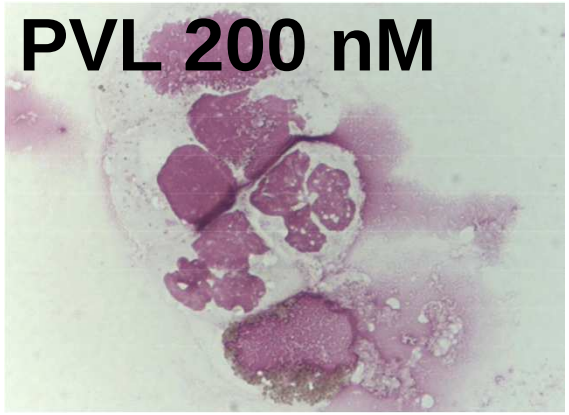
- Apoptosis and necrosis





Genestier et al, J Clin Invest 2005;115:3117

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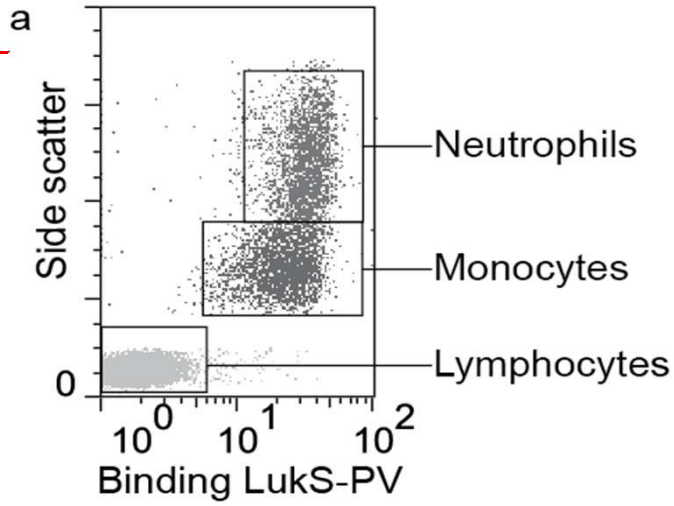
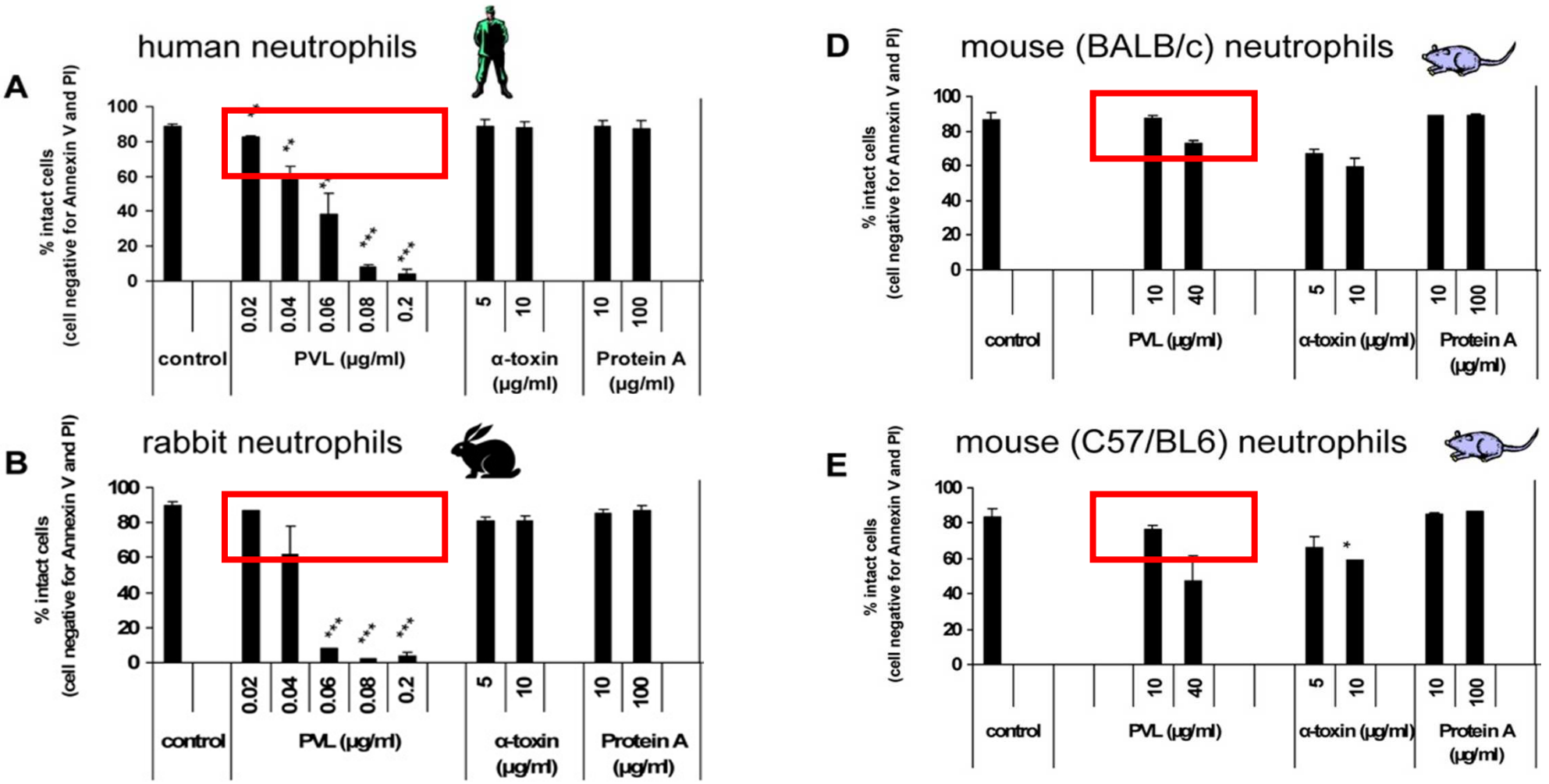


- Cell type specificity: neutrophils and macrophages
- Species specificity : human > rabbit > monkey > mice

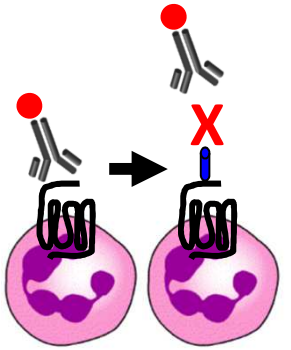
Löffler et al. PLoS Pathog 2010

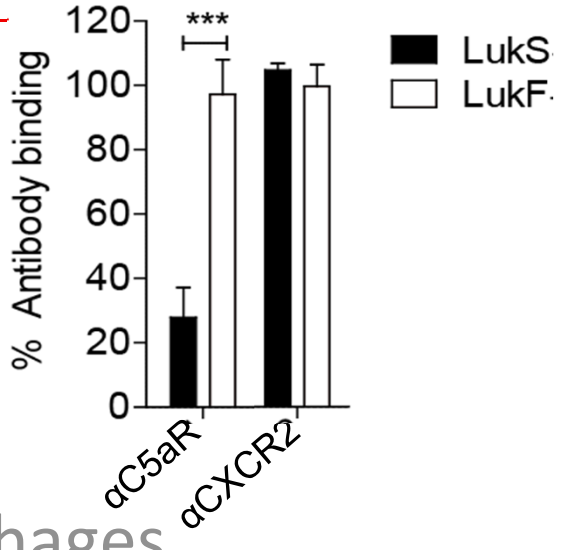
PVL induces rapid activation and cell death in human and rabbit neutrophils, but not in murine or simian cells



Löffler et al. PLoS Pathog (2010) vol. 6 (1) pp. e1000715

Panton Valentine Leucocidine





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- Receptor on myeloid cells identified: C5aR > C5L2

András Spaan et al, Cell Host Microbes, 2013

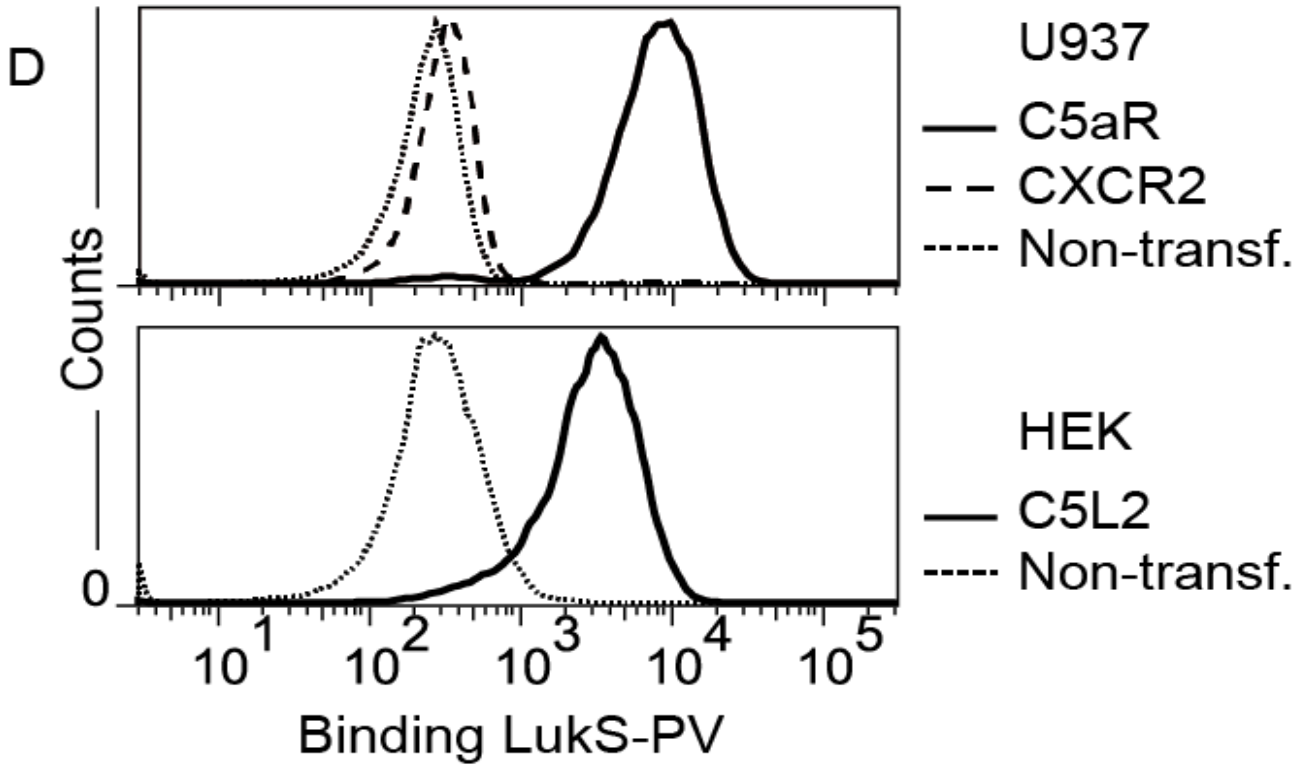
Cell PRESS

Cell Host & Microbe
Article

The Staphylococcal Toxin Panton-Valentine Leukocidin Targets Human C5a Receptors

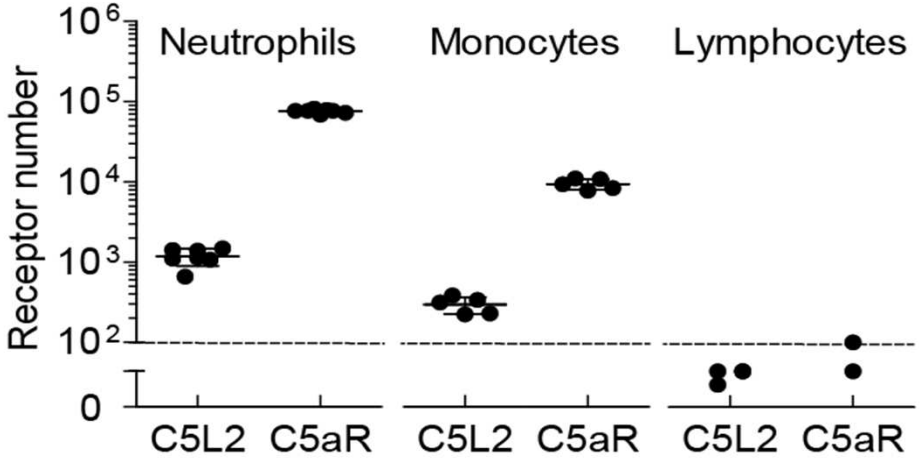
András N. Spaan,[1] Thomas Henry,[2,3,4,5] Willemien J.M. van Rooijen,[1] Magali Perret,[2,3,4,5] Cédric Badiou,[2,3,4,5] Piet C. Aerts,[1] Johan Kemmink,[6] Carla J.C. de Haas,[1] Kok P.M. van Kessel,[1] François Vandenesch,[2,3,4,5,7] Gérard Lina,[2,3,4,5,7] and Jos A.G. van Strijp[1,*]

LukS-PV binds to C5aR and C5L2 transfected cells



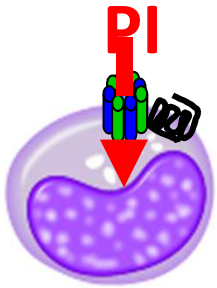
C5aRs Determine PVL Cell Specificity

C5aR is most abundantly expressed on neutrophils and monocytes but not on lymphocytes

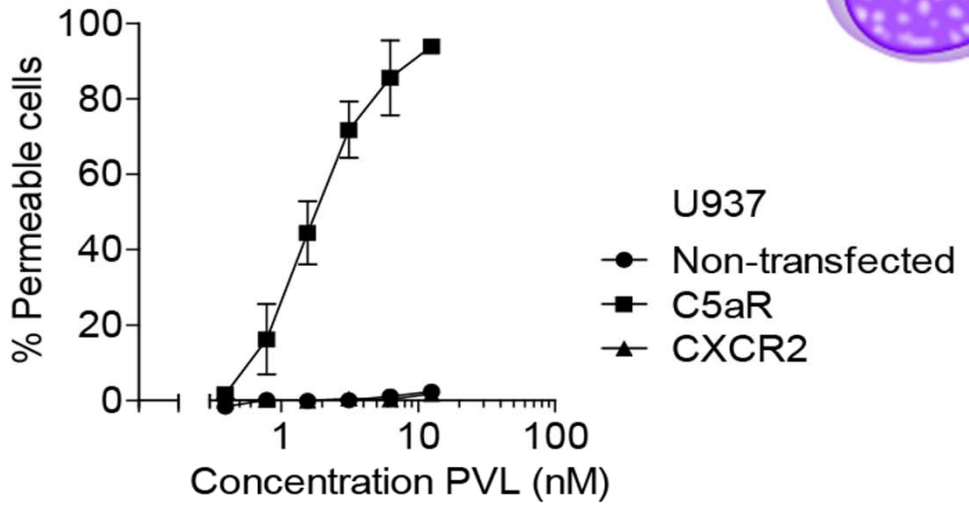


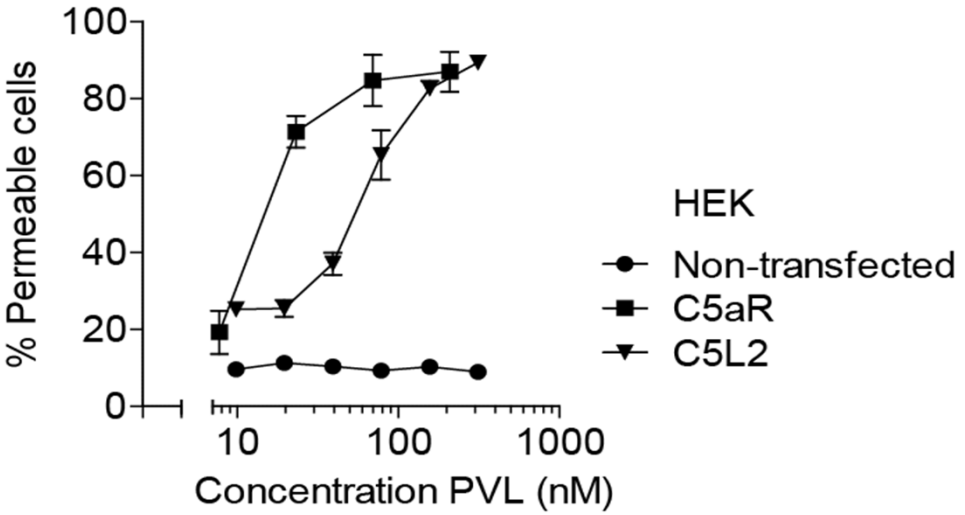
András Spaan et al, Cell Host Microbes, 2013

PVL Targets C5a Receptors



PVL induced pore formation (PI incorporation) is mediated by C5aR and C5L2

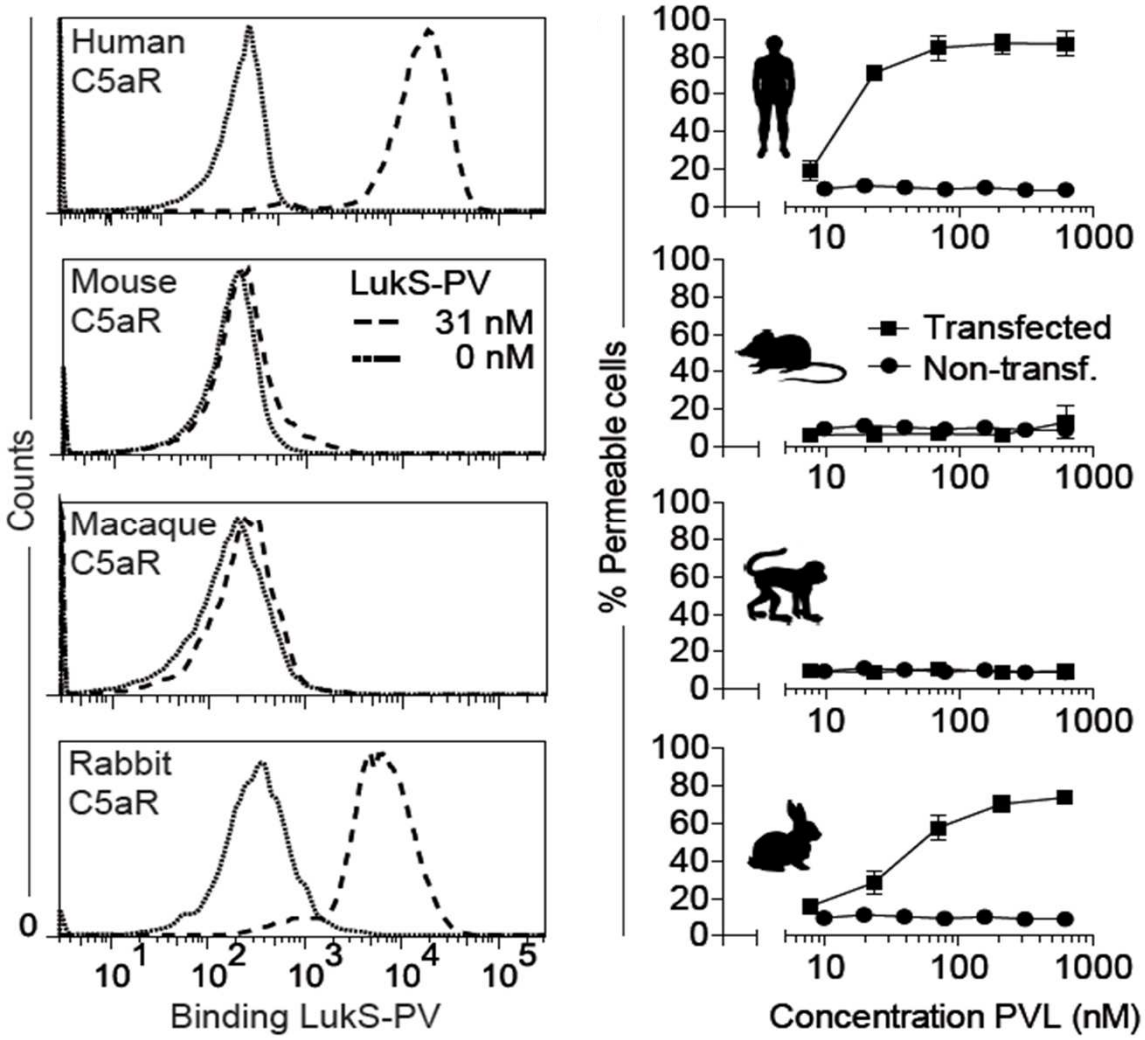




András Spaan et al, Cell Host Microbes, 2013

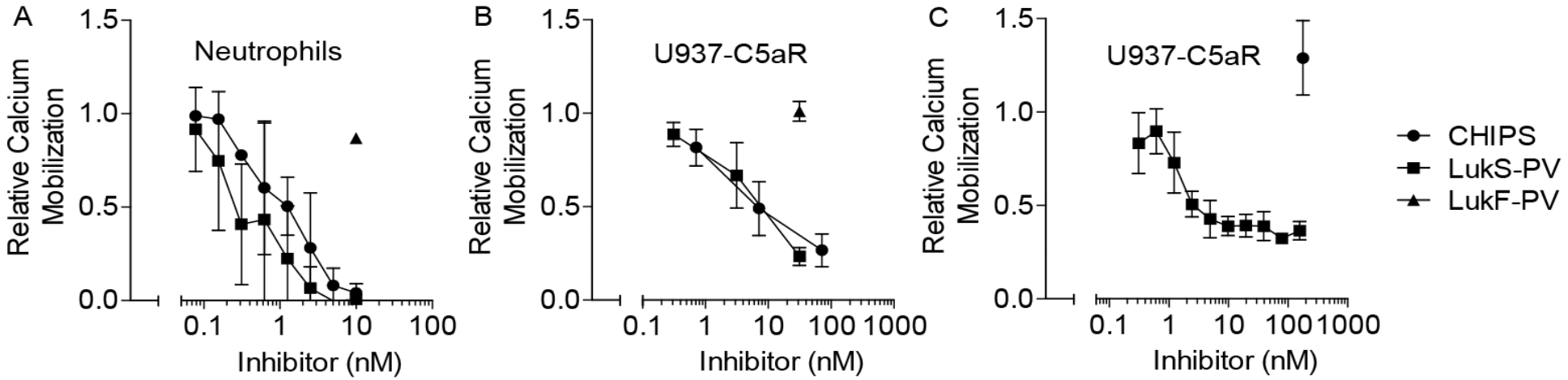
C5aR Determines PVL Species Specificity

HEK Cells transfected with C5aR from various species



András Spaan et al, Cell Host Microbes, 2O13

LukS-PV is a potent inhibitor of the human C5aR



+C5a (1 nM)

+ C5a (1 nM)

+C-terminal C5a (2.5 μM)

András Spaan et al, Cell Host Microbes, 2013

Panton Valentine Leucocidine

- Phage encoded
- Two components -> hetero-octamer
- beta-barrel pore forming toxin
- Apoptosis and necrosis
- Cell type specificity: neutrophils and macrophages
- Species specificity : human > rabbit > monkey > mice
- Receptor on myeloide cells identified: C5aR > C5L2
- -> facteur de sévérité des pneumonies communautaires ?

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- Cell type specificity: neutrophils and macrophages
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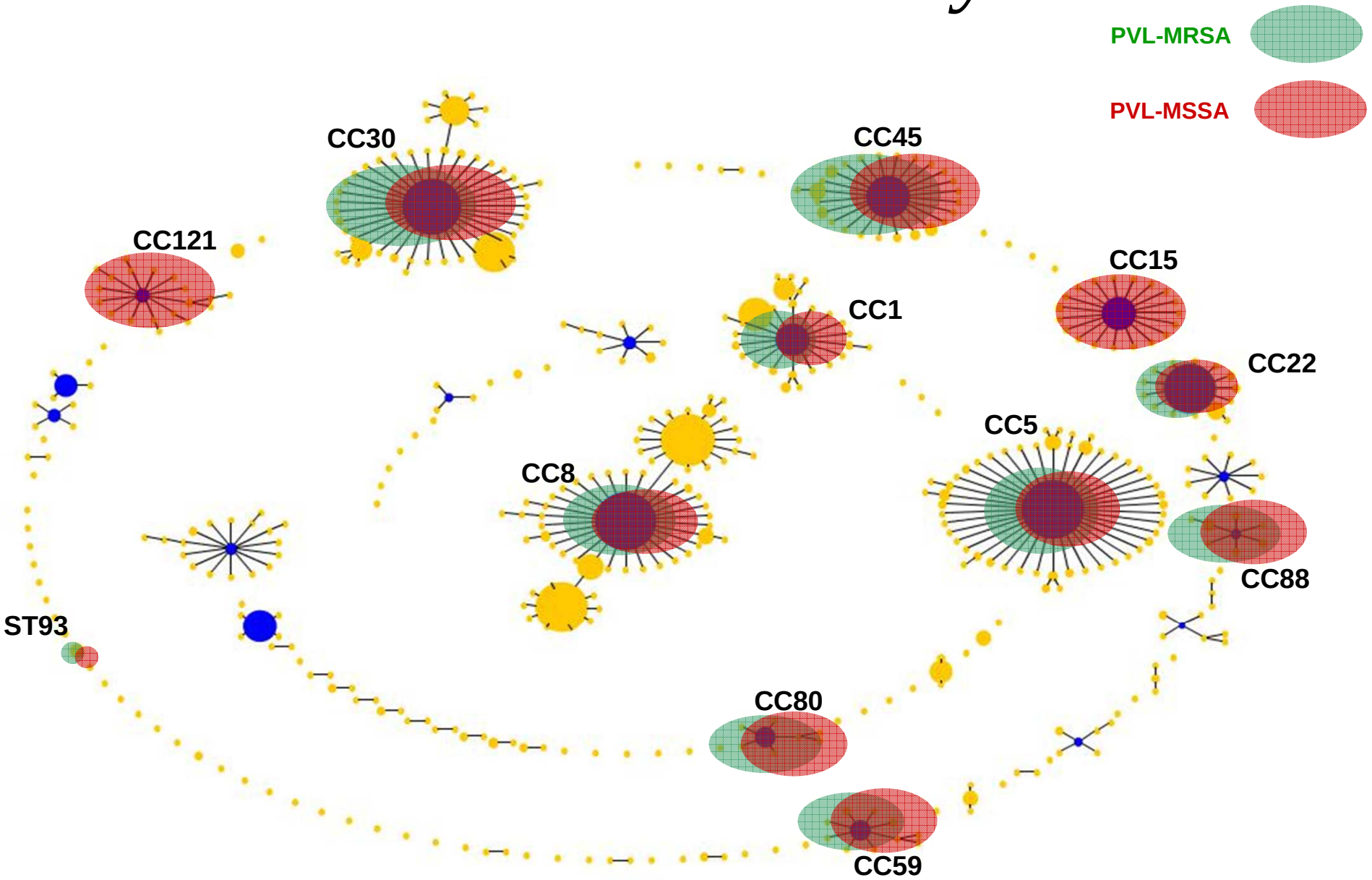
- Receptor on myeloide cells identified: C5aR > C5L2
- Prevalence: 2% of MSSA, ca 80% of CA-MRSA

PVL-SA: Genetic diversity



Courtesy Angela Kearns, Health Protection Agency, London, UK

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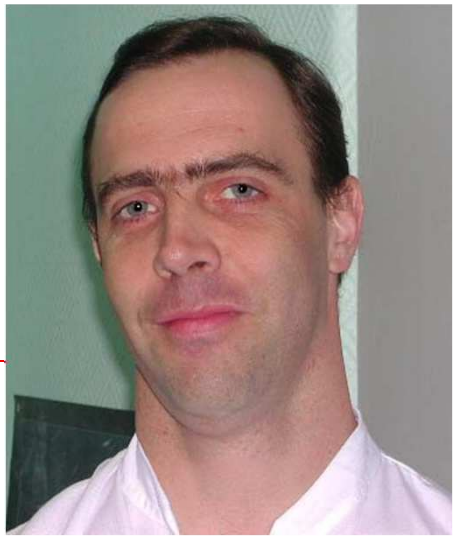
Centre National de Référence

Yves Gillet

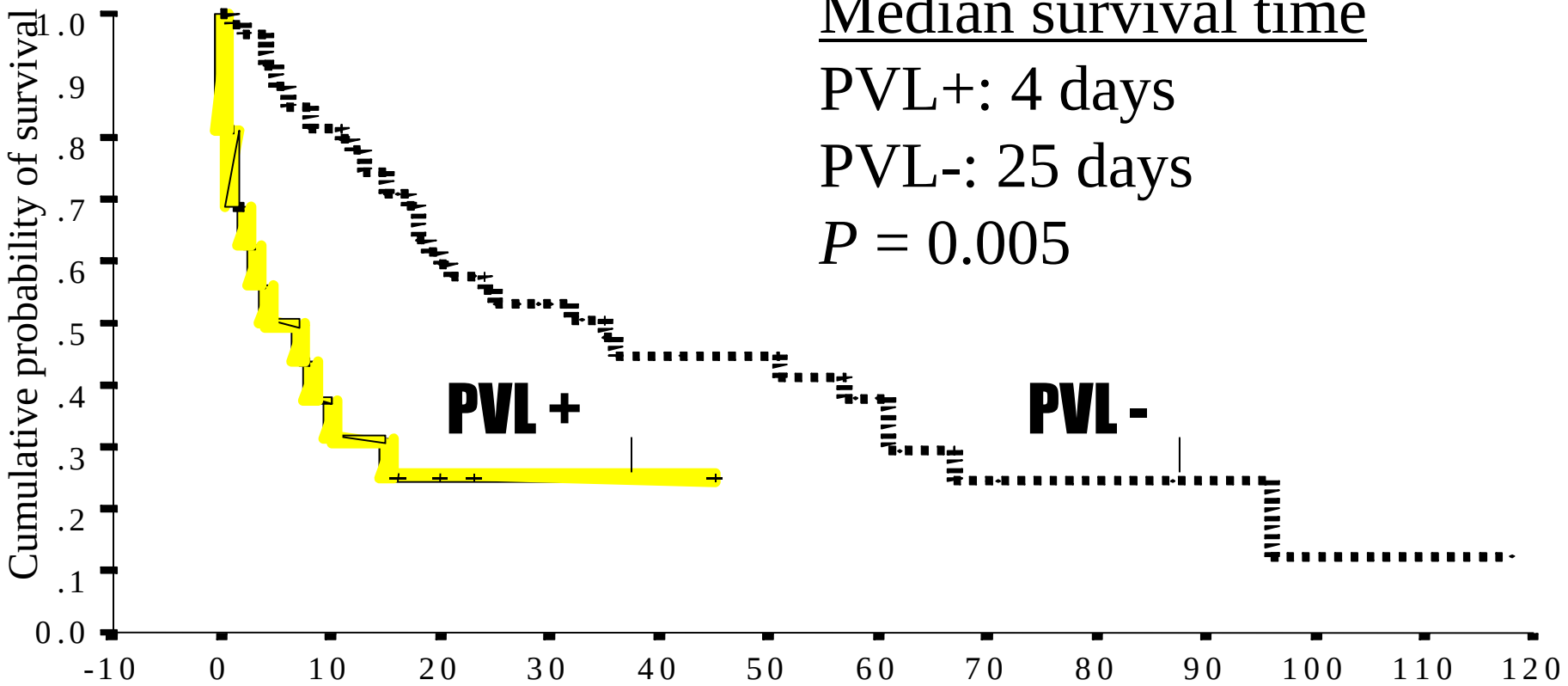


- Does PVL production correlate with community acquired pneumonia ?
- Does PVL production correlate with severity ?
- -> Prospective observational study
  - 1 year, 76 hospitals
  - 16 PVL+ cases, 36 PVL- controls

Clinical and biological features

	PVL + N = 16	PVL- N = 36	*P*
Median age	14.8 (5·4–24·0)	70.1 (59·2–81·4	0.001
Risk factor (underlying disorder)	0	20	< 0.001
Influenza-like illness (2 days before adm)	12	3	< 0.0001
Haemoptysis	6	1	0.005
Median trough leucocyte count (x109/L)	1·85 (0·6–6·4)	7·4 (4·9–9·9)	0.001

Survival of patients (16 cases, 36 controls)
Deaths : PVL+ 75%, PVL- 47%



Median survival time

PVL+: 4 days

PVL-: 25 days

P = 0.005

Mechanisms of disease

Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients

Yves Gillet, Bertrand Issartel, Philippe Vanhems, Jean-Christophe Fournet, Gerard Lina, Michèle Bes, François Vandenesch, Yves Piémont, Nicole Brousse, Daniel Floret, Jerome Etienne

necrotizing pneumonia: a new clinical entity

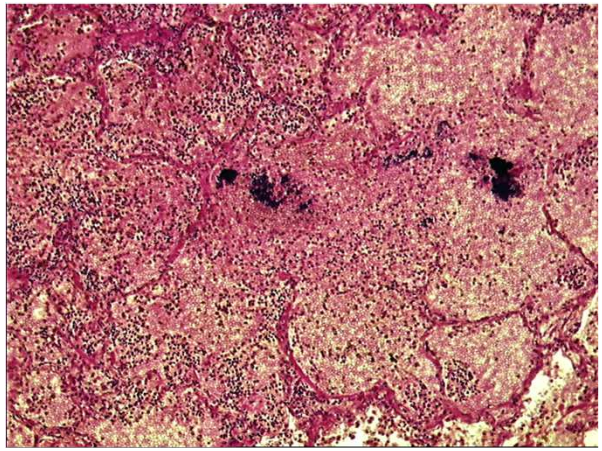
–Median age 14 year, no risk factors

–Preceded by flu-like illness

–Typical symptoms : hemoptysis, leucopenia

–Mortality 75%

–Panton Valentine leucocidin



Lancet 2002; 359 : 753-759

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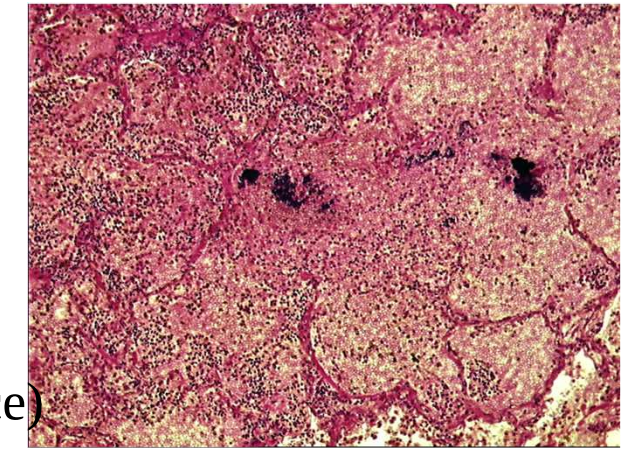


Lancet 2002; 359 : 753-759. Times Cited: 726 (from Web of Science)

Is it a new syndrome ?

Probable cases as early as 1930

/1

IV 13

PNEUMONIA IN RELATION TO AN EPIDEMIC OF "MILD" INFLUENZA, WITH THE REPORT OF THREE FULMINATING CASES APPARENTLY DUE TO STAPHYLOCOCCUS AUREUS*

BY ALEX. M. BURGESS, M.D.,† AND CHARLES F. GORMLY, M.D.†

NEJM 1930

First report CA-MRSA PVL+ infections

Four Pediatric Deaths from Community-Acquired Methicillin-Resistant *Staphylococcus aureus* — Minnesota and North Dakota, 1997–1999

Factors Predicting Mortality in Necrotizing Community-Acquired Pneumonia Caused by *Staphylococcus aureus* Containing Panton-Valentine Leukocidin

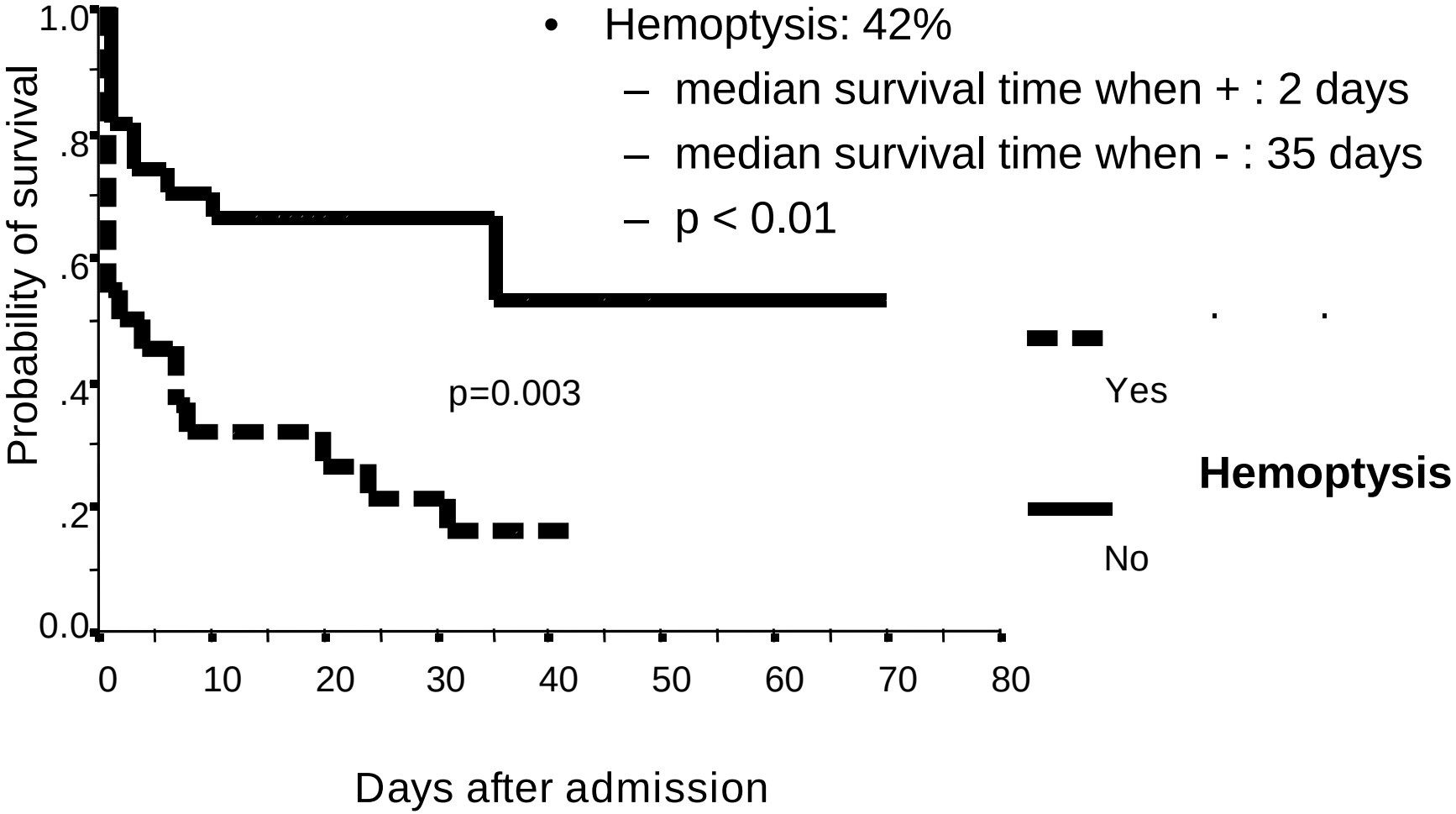
Yves Gillet,[1,2,3] Philippe Vanhems,[1,3,4] Gerard Lina,[1,2,3] Michèle Bes,[1,2,3] François Vandenesch,[1,2,3] Daniel Floret,[1,3] and Jerome Etienne[1,2,3]

- 5O PVL+ cases recruited via the NRC network
- Analysis of clinical and biological characteristics according to vital outcome

Gillet et al. Clin Infect Dis (2007), 45:315-21

Factor associated with lethality: clinical parameters

- Hemoptysis: 42%
  - median survival time when + : 2 days
  - median survival time when - : 35 days
  - p < 0.01



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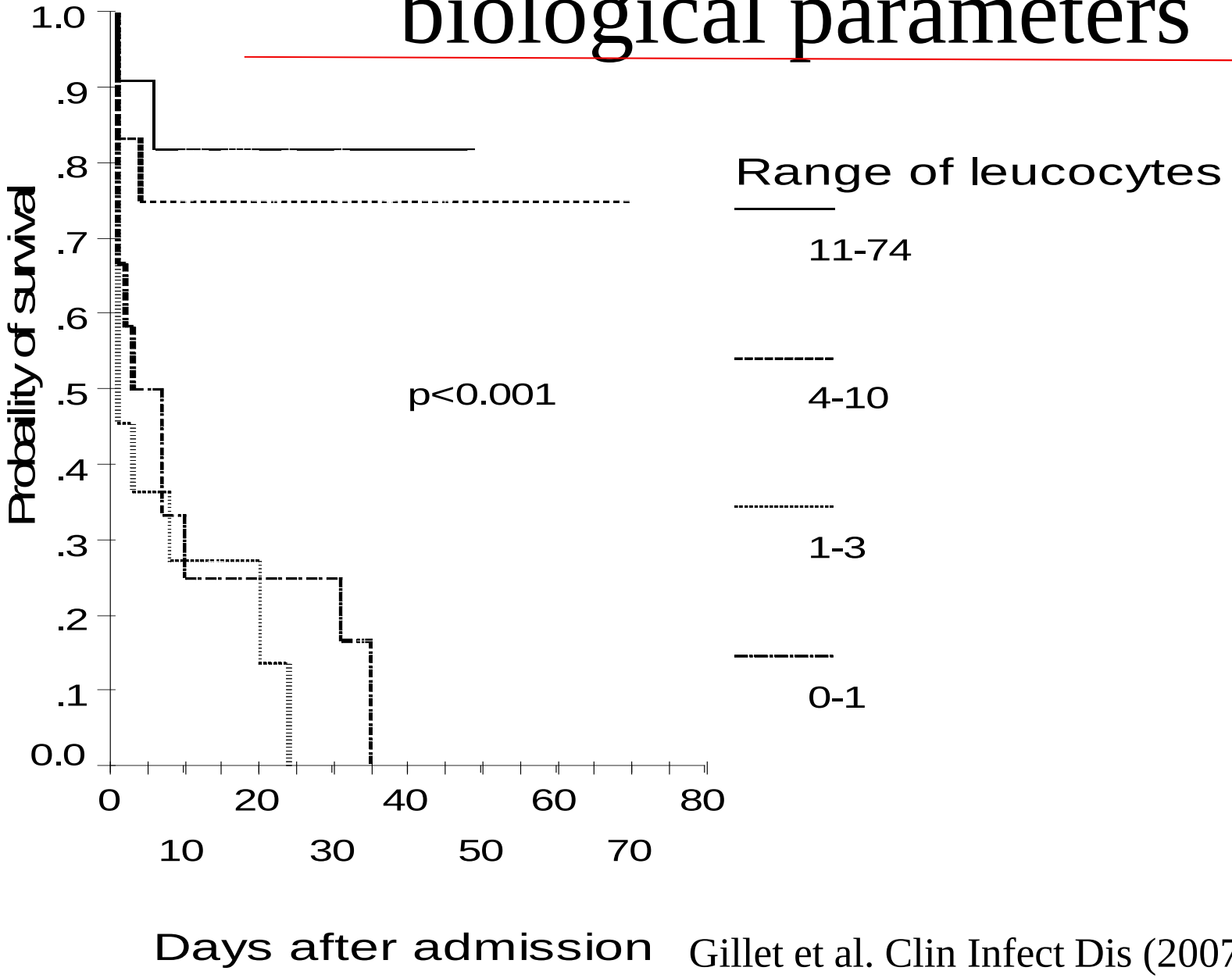
Gillet et al. Clin Infect Dis (2007), 45:315-21

Factor associated with lethality: biological parameters



Gillet et al. Clin Infect Dis (2007), 45:315-21

Factor associated with lethality: biological parameters

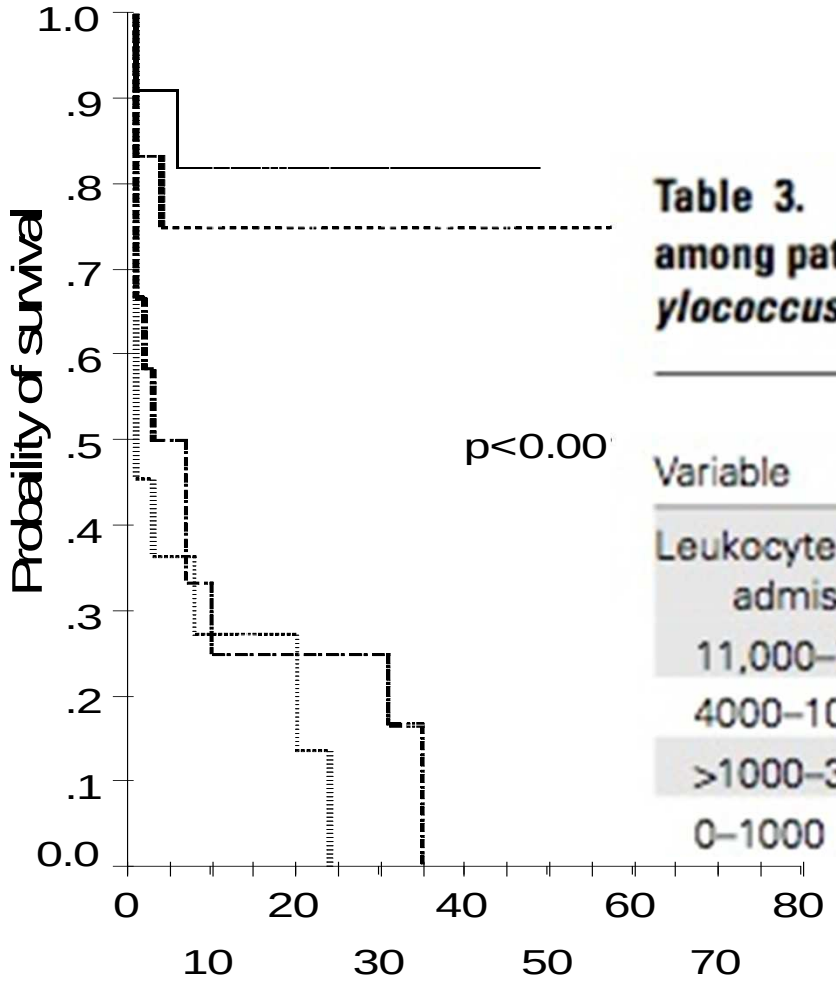


Table 3. Multivariate analysis of factors associated with death among patients with Panton-Valentine leukocidin–positive *Staphylococcus aureus* pneumonia.

Variable	Adjusted Relative Hazard (95% CI)
Leukocyte count at hospital admission, leukocytes/mL	
11,000–74,000	1.0
4000–10,000	1.29 (0.21–7.80)
>1000–3000	7.99 (1.66–38.43)
0–1000	7.38 (1.60–34.02)

Gillet et al. Clin Infect Dis (2007), 45:315-21

Khanafer *et al. BMC Infectious Diseases* 2013, **13**:359
http://www.biomedcentral.com/1471-2334/13/359

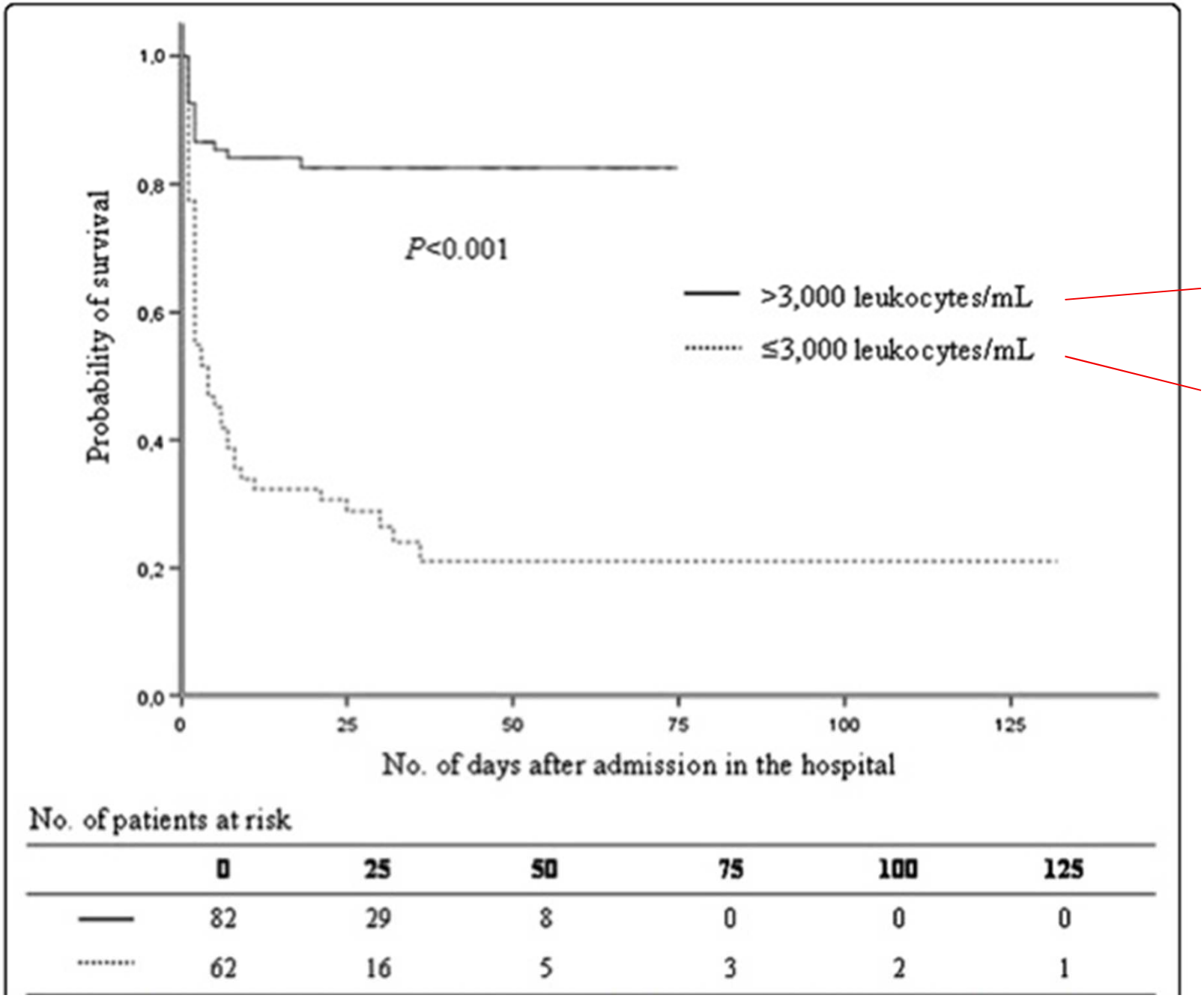
BMC
Infectious Diseases

RESEARCH ARTICLE Open Access

Severe leukopenia in *Staphylococcus aureus*-necrotizing, community-acquired pneumonia: risk factors and impact on survival

Nagham Khanafer[1,2*], Nicolas Sicot[3], Philippe Vanhems[1,2*], Oana Dumitrescu[3], Vanina Meyssonier[4], Anne Tristan[3], Michèle Bès[3], Gérard Lina[3], François Vandenesch[3,5], Yves Gillet[3,6] and Jérôme Etienne[3,5*]

- 148 cases of CA PVL+ pneumonia
- study population divided into 2 groups:
  - leukocyte count ≤3,000 leukocytes/mL, n=62
  - >3,000 leukocytes/mL, n=86



No. of patients at risk

	0	25	50	75	100	125
——	82	29	8	0	0	0
·····	62	16	5	3	2	1

75.8% death

16.3% death

Khanafer et al. BMC Infectious Diseases (2013)

Table 2 Factors associated with severe leukopenia among patients with Panton-Valentine leukocidin-positive *Staphylococcus aureus*-associated necrotizing pneumonia

Variables[a]	Adjusted odds ratios (95% CI)	*P* value
Previous influenza-like illness	4.45 (1.67-11.88)	0.003
Age >30 years	2.69 (1.08-6.68)	0.033
Airway hemorrhage	4.53 (1.85-11.13)	0.001
Personal history of furuncles	0.11 (0.01-0.96)	0.046

[a]Variables were adjusted to gender, mechanical ventilation, platelet count, pleural effusion, and time elapsed between onset of symptoms and hospitalization.

Table 3 Factors associated with death among patients with Panton-Valentine leukocidin-positive *Staphylococcus aureus* pneumonia

Variables	Adjusted hazard ratio (95% CI)	*P* value
Age (per 1-year increase)	1.02 (1.01-1.03)	0.015
Airway hemorrhage	2.05 (1.18-3.59)	0.011
Severe leukopenia (≤3,000 leukocytes/mL)	4.50 (2.38-8.51)	<0.001

Variables were adjusted to gender, mechanical ventilation, personal history of furuncles, platelet count, pleural effusion, and previous influenza-like illness.

Khanafer et al. BMC Infectious Diseases (2013)

PVL in question

Controversy: factor of severity ?

The role of the Panton-Valentine leucocidin toxin in staphylococcal disease: a systematic review and meta-analysis

Laura J Shallcross, Ellen Fragaszy, Anne M Johnson, Andrew C Hayward

Summary

www.thelancet.com/infection **Published online October 26, 2012**

- 76 studies from 31 countries.
- PVL strongly associated with SSTI, but are rare in pneumonia
- PVL-positive SSTI are more likely to be treated surgically
- Children with PVL-positive musculoskeletal disease might have increased morbidity.
- For other forms of disease [pneumonia,...] we identified no evidence that PVL affects outcome

Controversy: factor of severity ?

Correspondence

www.thelancet.com/infection Vol 13 July 2013

Panton-Valentine leucocidin and pneumonia

Laura Shallcross and colleagues[1] concluded on the basis of their meta-analyses that individuals

by which PVL induces the rapidly fatal course of haemorrhagic necrotising pneumonia. In this regard, Shallcross and colleagues' review[1] failed to identify another study[3] that elucidated mechanisms by which PVL rapidly induces severe hypoxaemia, leucopenia, lung necrosis, pulmonary

3 Diep BA, Chan L, Tattevin P, et al. Polymorphonuclear leukocytes mediate *Staphylococcus aureus* Panton-Valentine leukocidin-induced lung inflammation and injury. *Proc Natl Acad Sci USA* 2010; **107:** 5587–92.

4 Loffler B, Hussain M, Grundmeier M, et al. *Staphylococcus aureus* panton-valentine leukocidin is a very potent cytotoxic factor for human neutrophils. *PLoS Pathogens* 2010; **6:** e1000715

*Binh An Diep, Yves Gillet, Jerome Etienne, Gerard Lina, François Vandenesch
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While PVL-positive strain might have a lesser **propensity to cause** pneumonia compared with SSTI, these meta-analyses cannot be used to make any inference regarding whether or not PVL contributes to the **pathogenesis and outcomes** of pneumonia

Complexity

- Community-acquired MRSA
  - Harbor *pvl* genes
  - Can be highly epidemic (USA300)
  - Outcompete HA-MRSA in the US
- PVL and MRSA often mixed up in many articles
- Virulence and capacity to disseminate may not be linked

Methicillin resistance is not a predictor of severity in community-acquired *Staphylococcus aureus* necrotizing pneumonia—results of a prospective observational study

N. Sicot[1], N. Khanafer[2,3], V. Meyssonnier[4], O. Dumitrescu[1], A. Tristan[1], M. Bes[1], G. Lina[1], F. Vandenesch[1], P. Vanhems[2,3], J. Etienne[1] and Y. Gillet[1,5]

- 29 cases of PVL-MRSA pneumonia
- 104 cases of PVL-MSSA pneumonia

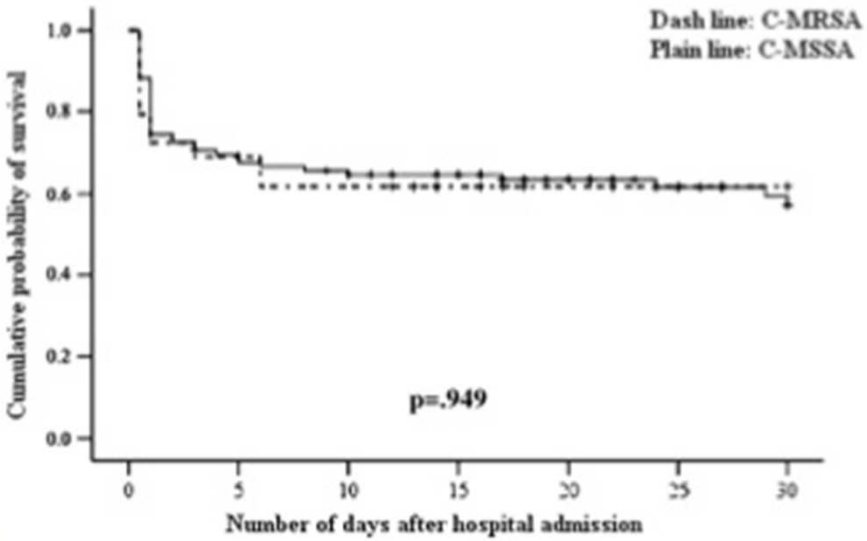


FIG. 1. Kaplan–Meier survival curves after 30 days for patients with community-acquired, Panton–Valentine-positive, *Staphylococcus aureus* necrotizing pneumonia according to methicillin susceptibility.

TABLE 2. Cox regression analysis of factors associated with 30 days mortality in community-acquired, Panton–Valentine leukocidin-positive *Staphylococcus aureus* necrotizing pneumonia[a]

Variable	p-value	Multivariate adjusted hazard ratio (95% CI)
Airway haemorrhage	0.004	2.96 (1.41–6.25)
Leucocyte count (10^9/L)[b]	0.001	0.32 (0.17–0.61)
Antitoxinic treatment	0.002	0.11 (0.03–0.49)

[a]The model was adjusted on severity and presence of the *mecA* gene.
[b]In this model, natural logarithms of leucocyte counts were used.

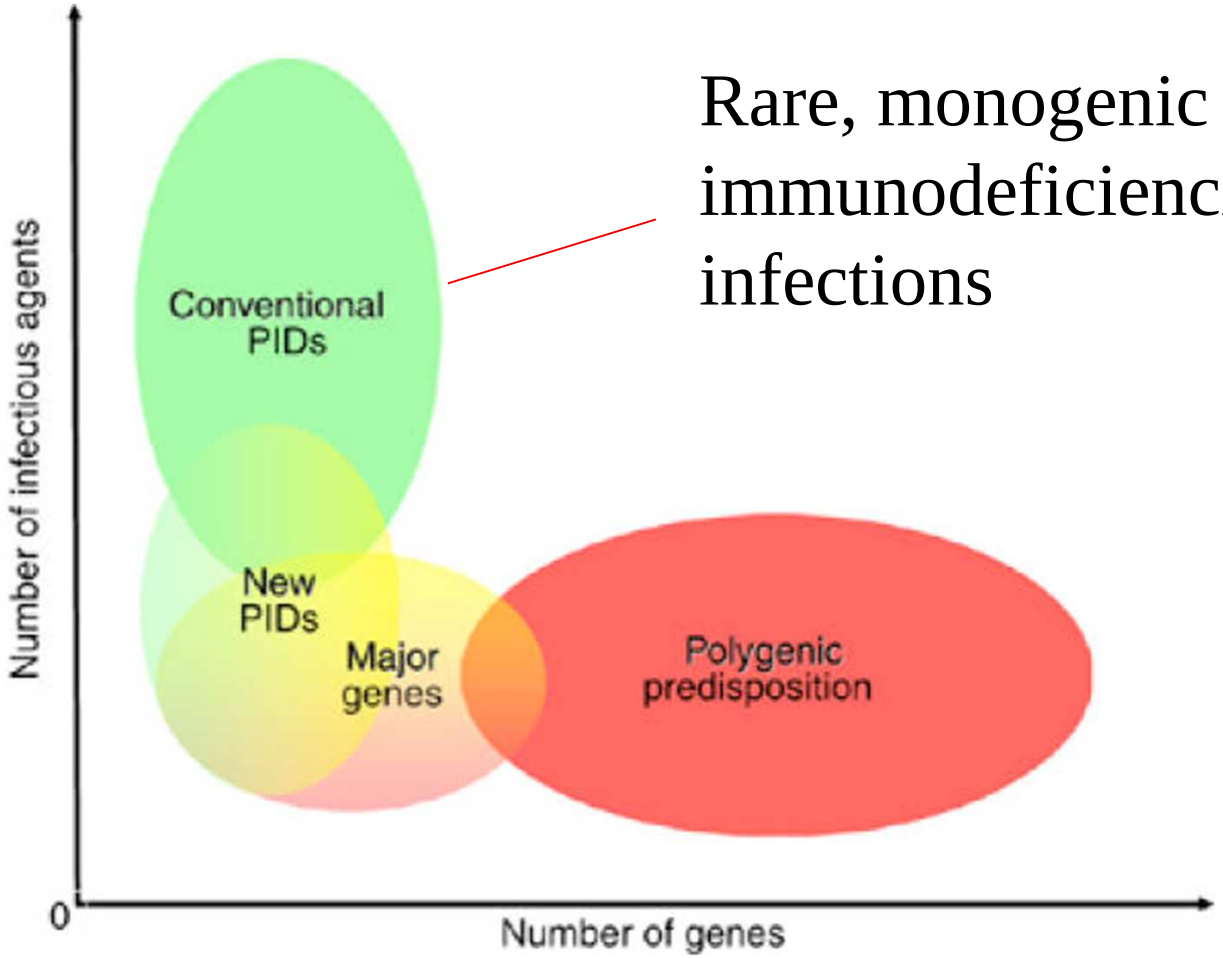
Sicot et al. CMI (2013)

Necrotizing pneumonia: pending questions

- Why so infrequent (ca. 30 cases/year in France)
  - 5% PVL among 30% S.aureus nasal carriage
- Why children and young adults ?

- -> genetic predisposition to this disease ?

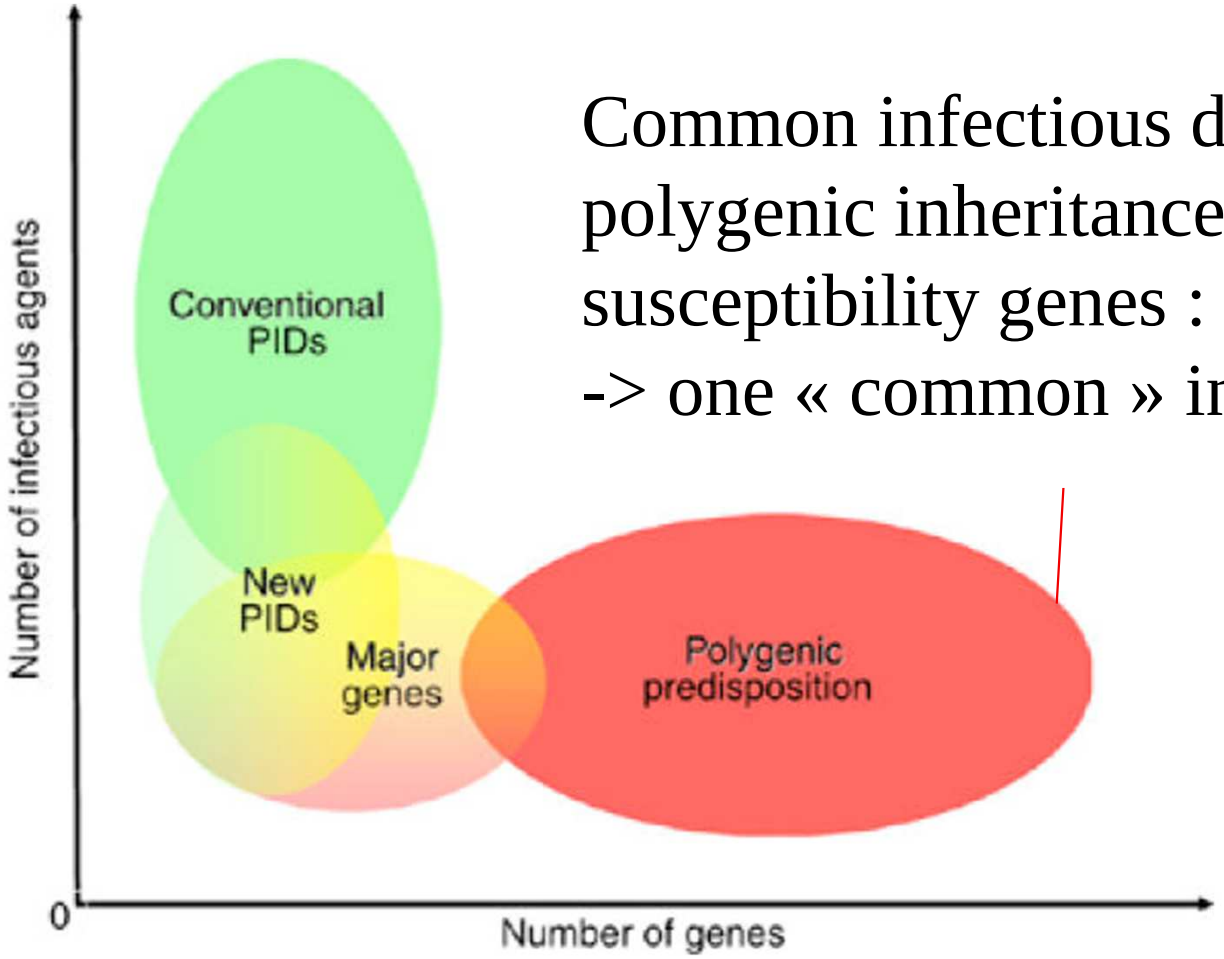
Human genetics of infectious diseases



Rare, monogenic primary immunodeficiencies: one gene, multiple infections

Jean-Laurent Casanova, et al. EMBO J. 2007

Human genetics of infectious diseases

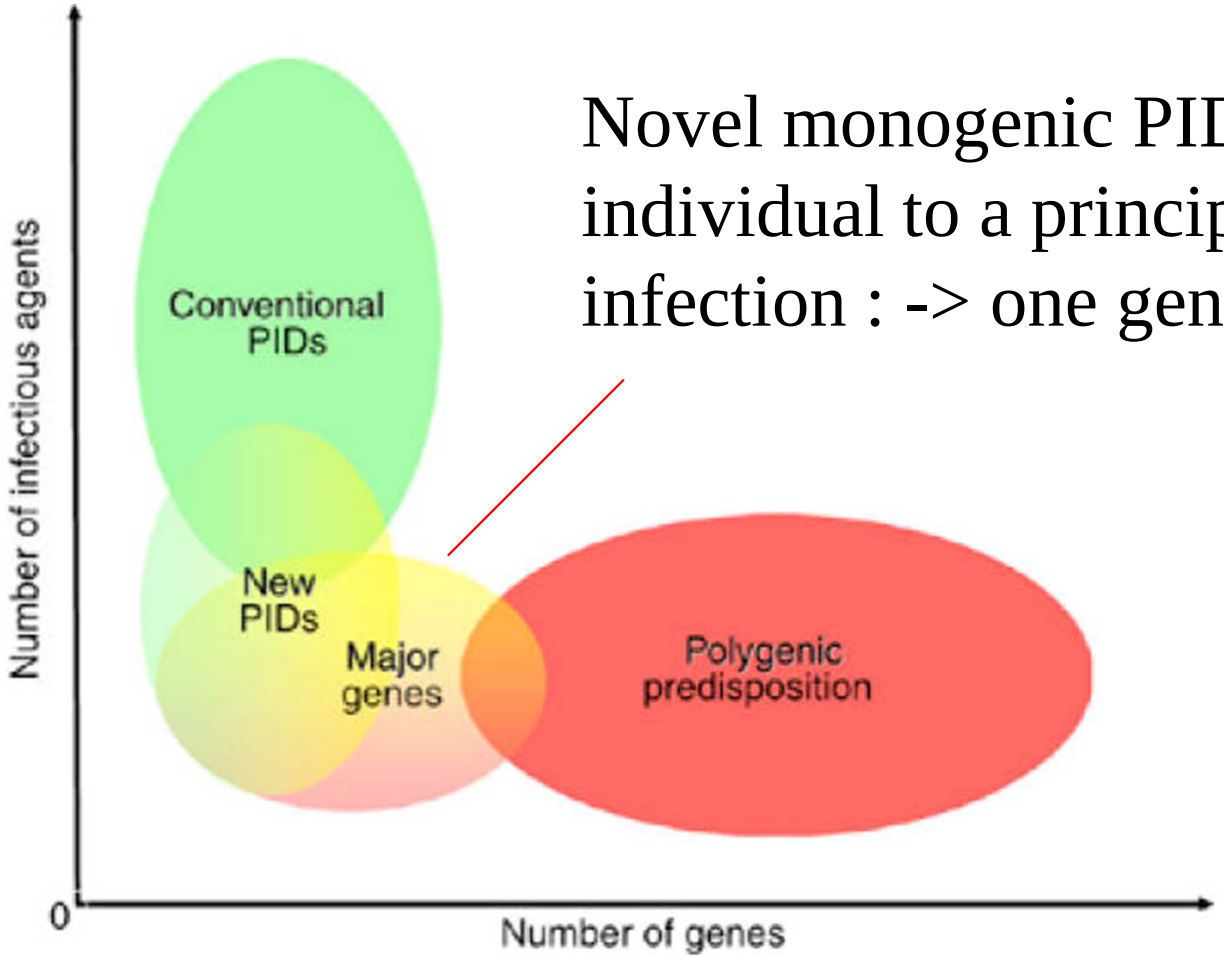


Common infectious diseases associated with polygenic inheritance of numerous susceptibility genes :

-> one « common » infection, multiple genes

Jean-Laurent Casanova, et al. EMBO J. 2007

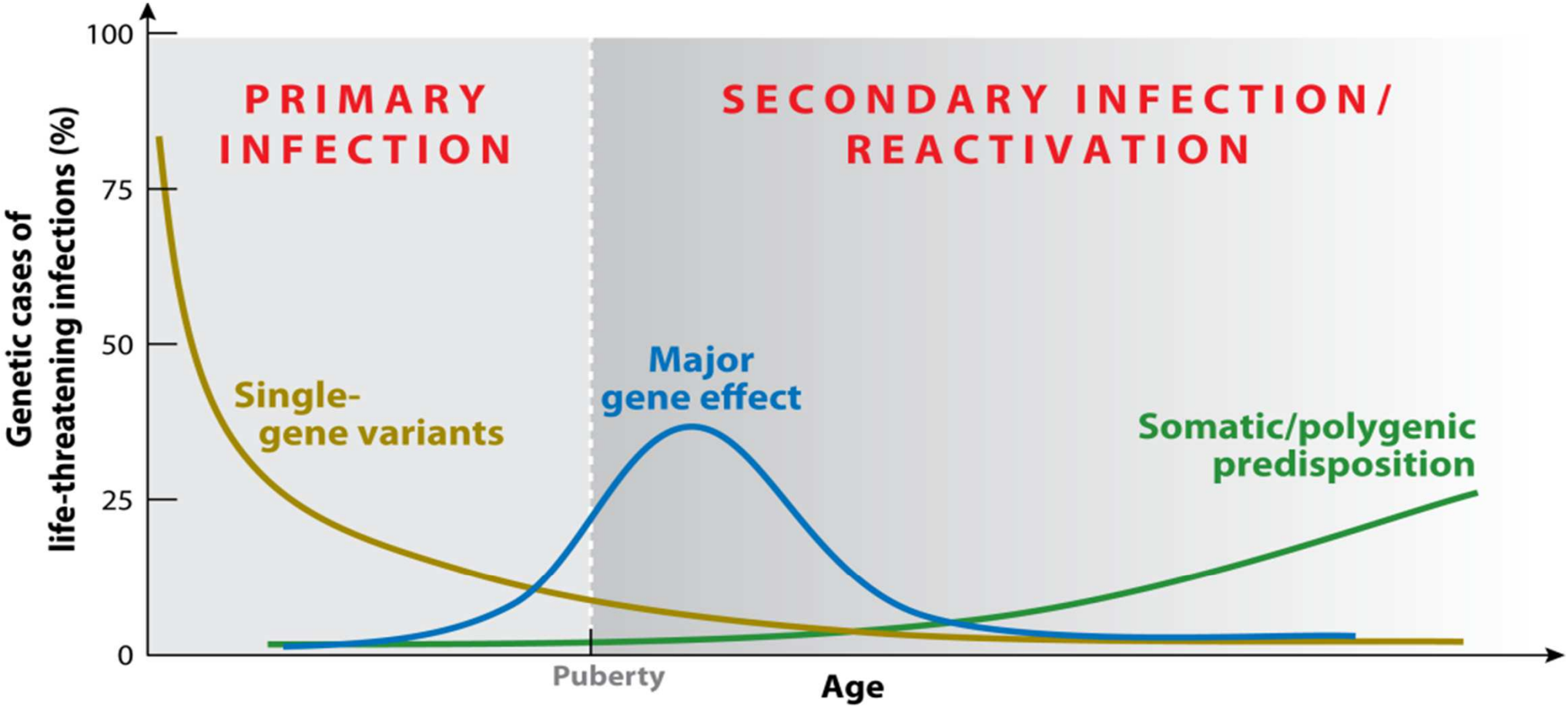
Human genetics of infectious diseases



Novel monogenic PIDs predispose the individual to a principal or single type of infection : -> one gene, one infection

Jean-Laurent Casanova, et al. EMBO J. 2007

A proposed age-dependent genetic architecture of infectious diseases



Casanova J-L, Abel L. 2013.
Annu. Rev. Genomics Hum. Genet. 14:215–43

Current study

- Prospective observationnal study
- Nationwide level
- All case of community-acquired pneumonia admitted to ICU caused by *S.aureus*
- Clinical and genetic informations collected
- Orfeome of 50 patients currently beeing analysed

Pneumonie Nécrosante : questions en suspens

- Pourquoi si rare (environ 30 cas/an en France)
- Pourquoi enfant et adulte jeune
- Comment améliorer l'évolution ?
  - Antibiotiques anti-toxiniques
  - Immunoglobulines intra-veineuses
  - Vaccin

-> PHRC recrutement National

-> ANR Blanc

PHRC 2011 -2013
(F.Vandenesch, L. Argaud, Y. Gillet)

Leucocidine de Panton Valentine :
Facteur indépendant de gravité des pneumonies à *Staphylococcus aureus*

Objectifs

- Confirmer le rôle de la PVL **comme facteur de gravité indépendant** des pneumonies à *S. aureus*
- Rechercher une **prédisposition génétique** rendant certains patients plus réactifs à l'effet de la PVL
- Impact de la prise en charge **thérapeutique** des patients sur l'évolution clinique
- Déterminer la proportion de **SARM-Co** responsables de pneumonie PVL+

Etude de cohorte

- volet observationnel adultes et enfants pneumonie communautaire grave *à S. aureus* hospitalisée en Réanimation
- volet interventionnel immunogénétique patients et famille: orfeome

Recueil

- Données cliniques
- Souche, Sérum, ADN

PHRC 2011 -2013
(F.Vandenesch, L. Argaud, Y. Gillet)

Leucocidine de Panton Valentine :
Facteur indépendant de gravité des pneumonies à
Staphylococcus aureus

Objectives

- ✓ Investigate the role of PVL as an independent factor of severity in *S. aureus* CAP
- ✓ Identify clinical/biological factors associated with the disease prognostic
- ✓ Assess the level of antibiotic sensitivity of *S. aureus* strains
- ✓ Investigate the genetic susceptibility of the host

Methodology

Inclusion criteria

- *S. aureus* CAP leading to hospitalization in ICU

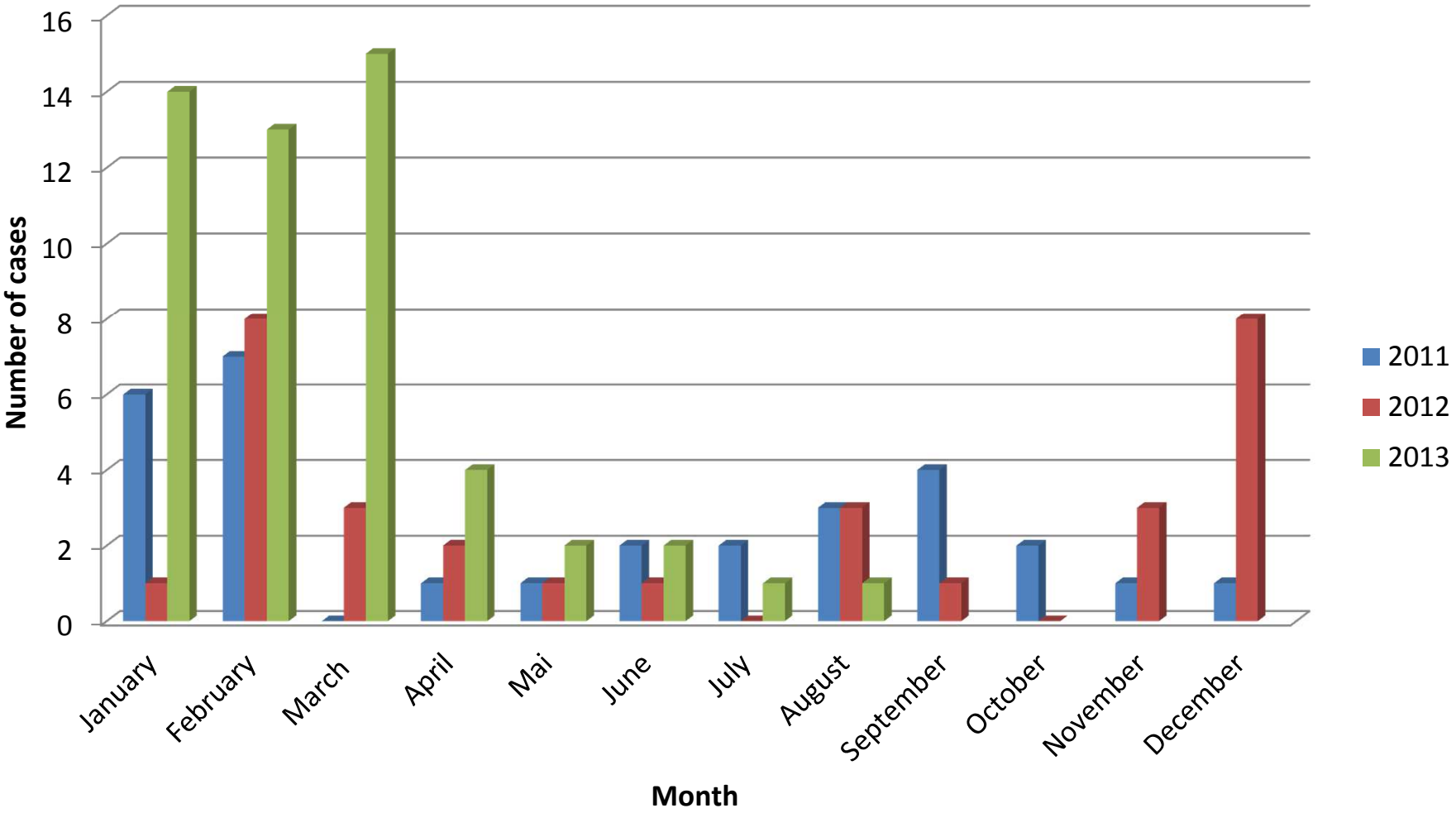
Non-inclusion criteria

- HIV-positive
- Nosocomial pneumonia
- Hospitalization during three months prior to ICU admission for pneumonia

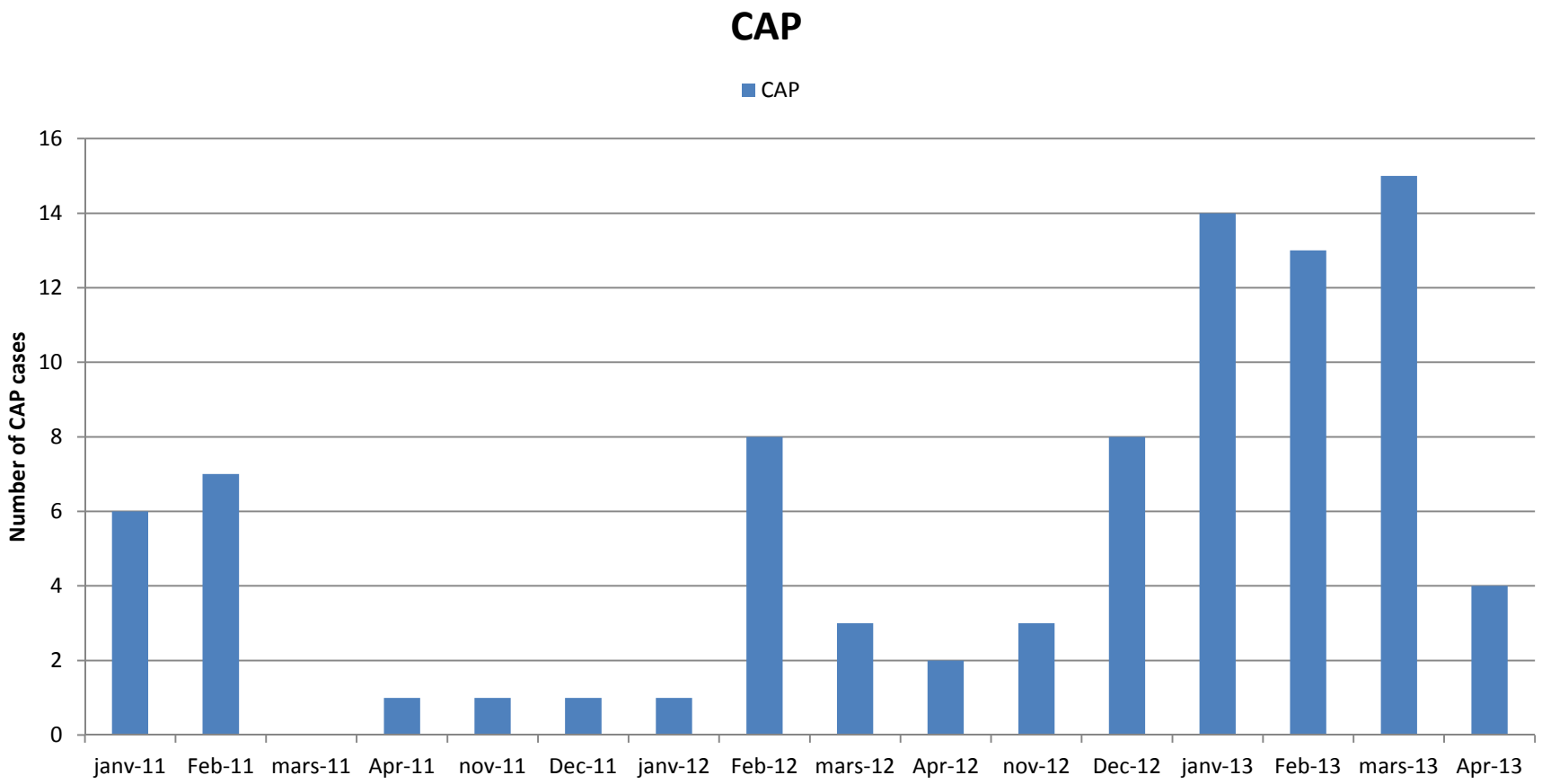
Data collection

- ✓ Demographic variables
- ✓ Medical history
- ✓ Signs and symptoms at presentation
- ✓ Radiological, laboratory and clinical findings during 7 days following hospitalization
- ✓ Biological sample: serum, total blood

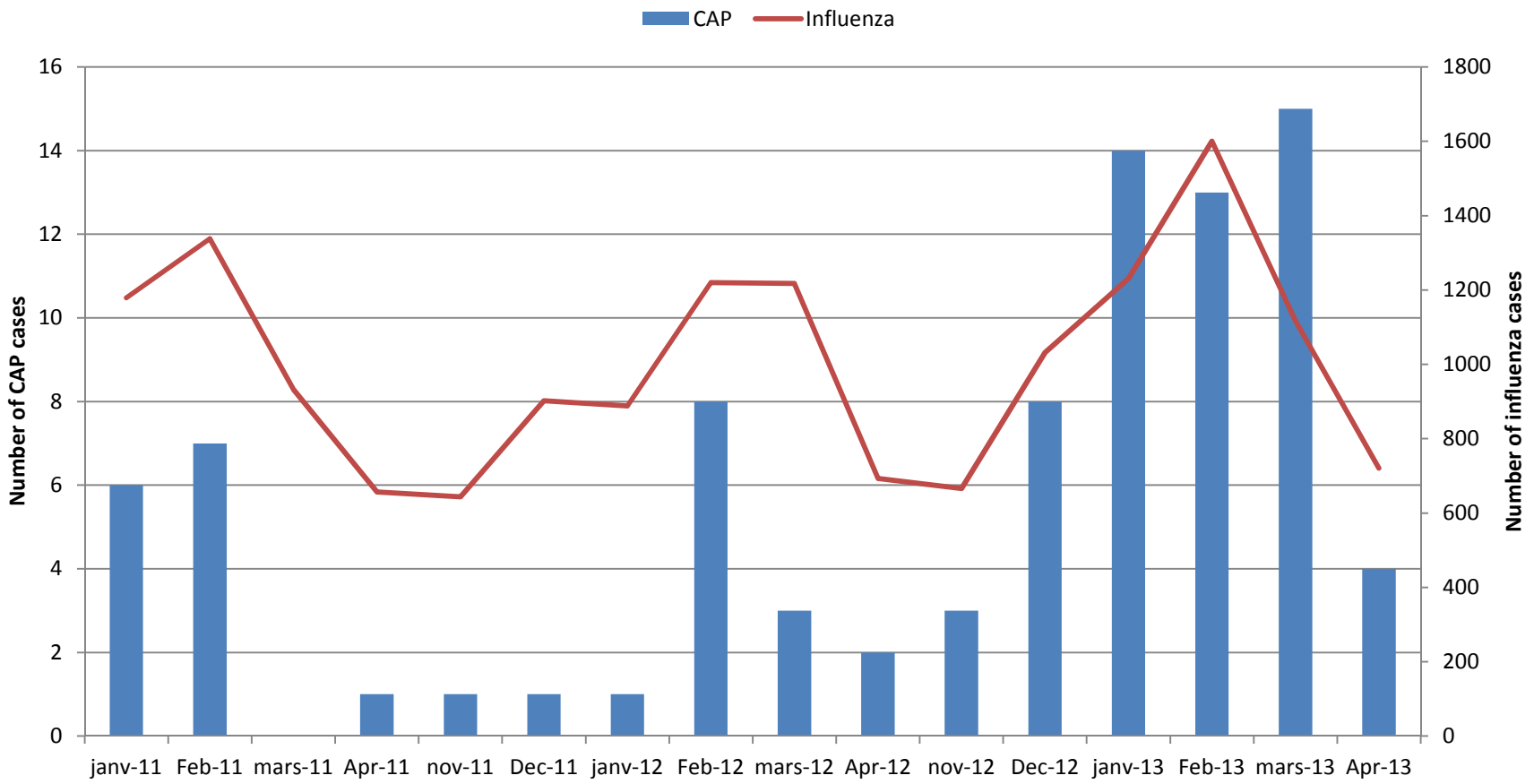
2011-2013
114 cases enrolled



2011-2013
114 cases enrolled



CAP and influenza during influenza seasons



Characteristics of enrolled patients

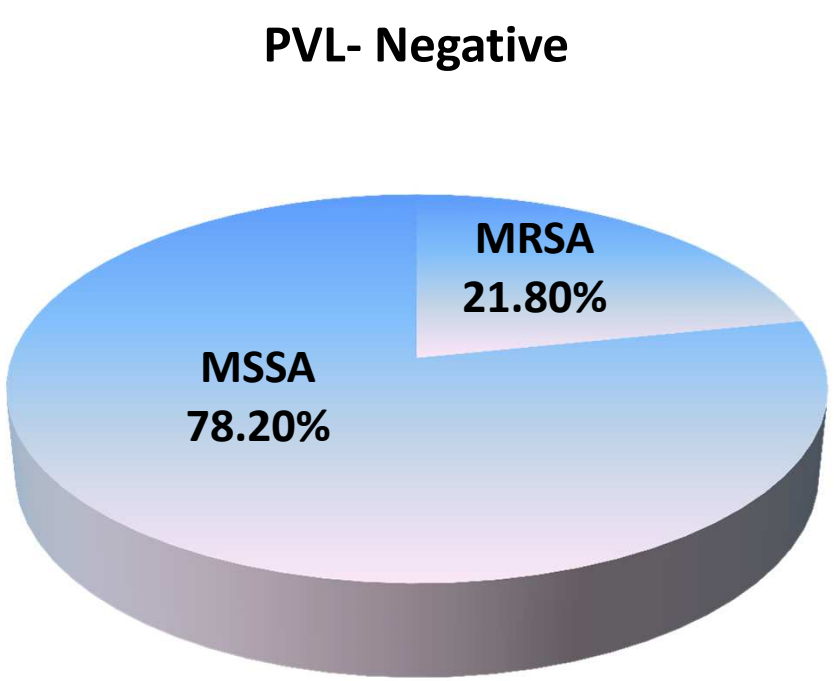
- ✓ ♂/♀: 59/55
- ✓ 61 PVL+/53 PVL-
- ✓ 92 adults and 22 children <18 years old
- ✓ Serum available for all patients
- ✓ Blood samples for genetic analyses available for 53 patients (30 PVL+) and 37 family members
- ✓ CRF available for 70 patients

Interim analysis for 70 patients with available CRF

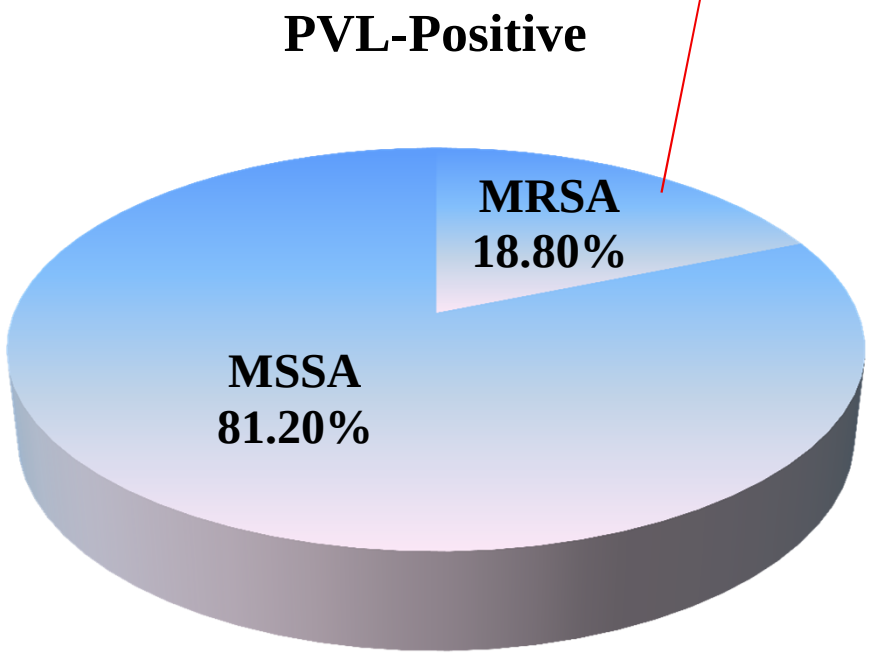
Clinical and biological features at admission

Variable	PVL-positive (n=38)	PVL-negative (n=32)	p
Male sex	16 (42.1%)	22 (68.8%)	**0.03**
Age (years), Median (min-max)	37.5 (0.2-79)	58 (16-82)	**0.001**
Purulent aspiration	15 (41.7%)	21 (65.6%)	**0.04**
Diarrhoea	6 (15.8%)	0	**0.02**
Erythrodermia	8 (21%)	0	**0.006**
Median (min-max) CRP	291 (10-504)	203(20-486)	**0.04**

Antibiotic susceptibility of isolated strains

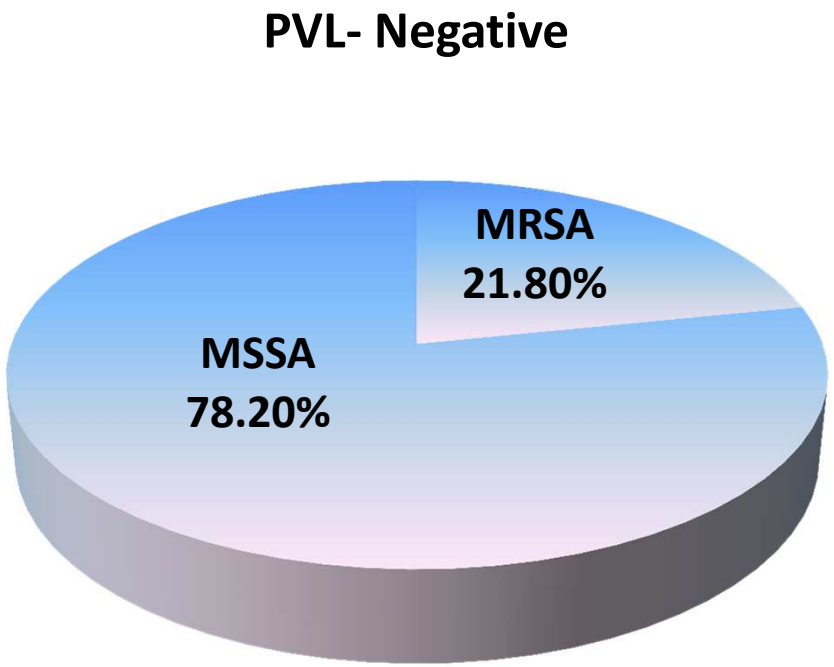


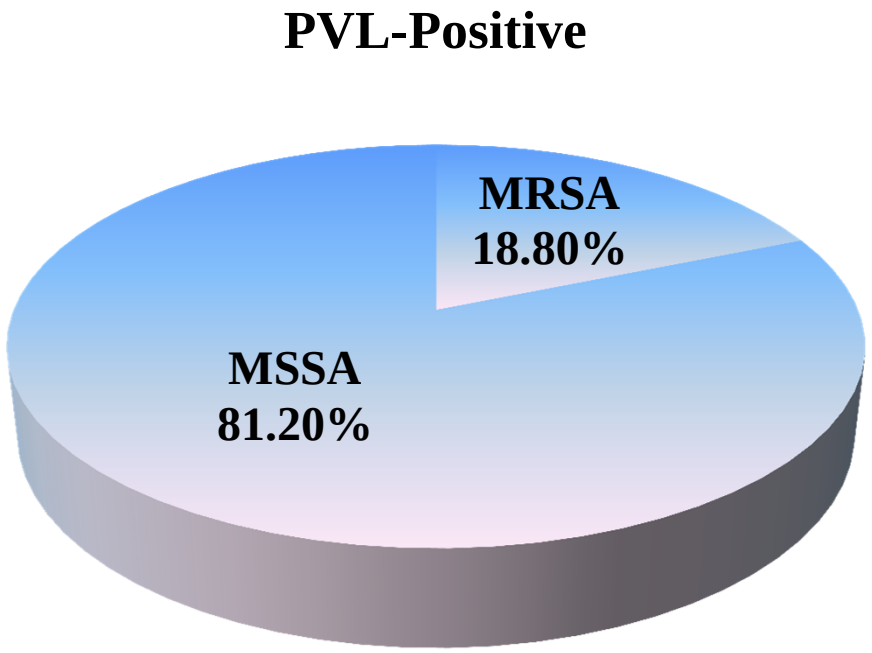
6 CC80-MRSA-IV
3 CC5-MRSA-IV
3 ST8-MRSA-IV, USA300
3 CC88-MRSA-IV



-> Severe CA pneumonia:
MRSA = ca. 20%

Antibiotic susceptibility of isolated strains





-> Severe CA pneumonia:
MRSA = ca. 20%

Clinical and biological features during hospitalization

Variable	PVL-Positive (n=38)	PVL-Negative (n=32)	p
Fever	24 (70.6%)	19 (61.3%)	0.24
Diarrhoea	9 (25.7%)	8 (25.8%)	0.61
Erythrodermia	9 (27.3%)	2 (6.3%)	**0.03**
Pulmonary abscess	12 (38.7%)	5 (16.1%)	**0.04**
Pneumothorax	6 (18.7%)	1 (3.3%)	**0.06**
Haemoptysis	18 (52.9%)	15 (48.4%)	0.45
Unilateral condensation	15 (46.9%)	6 (19.4%)	**0.02**
Bilateral condensation	23 (69.7%)	27 (84.4%)	0.13
Median (min-max) peak Leucocytes	15 (1.5-292)	13.2 (3.8-41.3)	0.65
Median (min-max) trough Leucocytes	6.5 (0.7-117)	8.6 (0.4-18.5)	0.95
Mechanical ventilation	28 (80.0%)	27 (87.1%)	0.33

Treatment during the first 24h of hospitalization

✓Appropriate empirical antibiotic therapy

PVL+:93.3%

PVL-: 84.4%

✓Antibiotic with antitoxin properties

PVL+: 30%

PVL-: 21.9%

No differences between the two groups

Mortality

Survival status known for 58 patients

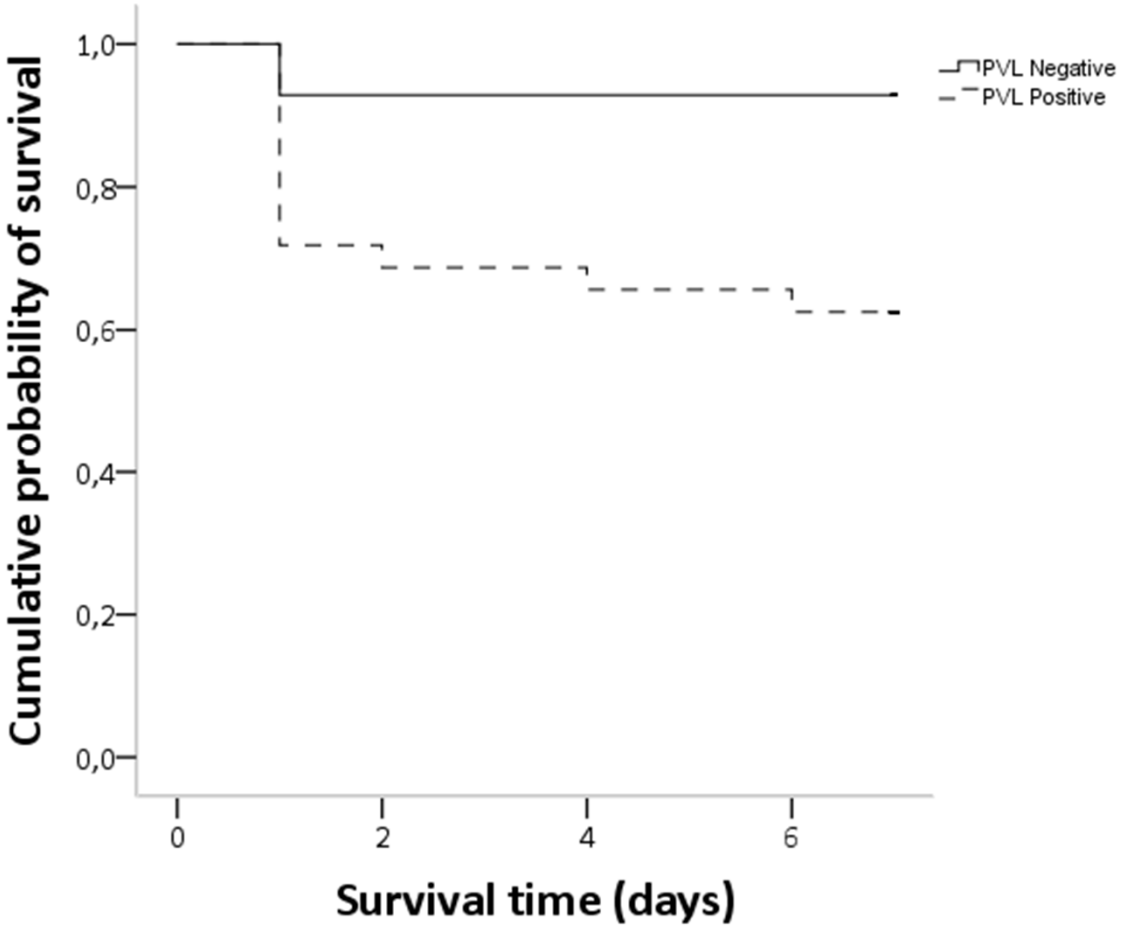
Overall mortality rate

✓No differences between PVL-positive and PVL-negative patients (40.0% *vs* 23.3%; p=0.2)

Mortality rate at Day-7

✓ Significantly higher among PVL-positive as compared to PVL-negative patients(31.6% vs 6.6%, p=0.009)

PVL affects mortality



<u>Overall mortality</u>

PVL+ 40%,

PVL- 23.3%, p=NS

<u>Day-7 mortality</u>

PVL+ 31.6%,

PVL- 6.6%, p=0.009

Factors associated with death regardless of PVL status

	Survival (n=37)	Death (n=21)	p
Non-pulmonary cancer	2 (2.2%)	5 (4.8%)	0.03
Hemoptysis during hospitalization	15 (40.5%)	13 (72.2%)	0.03
Toxin eruption during hospitalization	2 (5.7%)	5 (27.8%)	0.04
Currarisation at admission	5 (13.5%)	10 (50%)	0.001
Curratisation during hospitalization	14 (38.9%)	13 (72.2%)	0.02
Abscess at admission	9 (25%)	0	0.03
Abscess during hospitalization	15 (35.3%)	0	0.006

Finding summary

- ✓ Characteristics of PVL-associated necrotizing CAP
  - ✓ younger adults
  - ✓ Rapid death at day-7
  - ✓ Presence of Diarrhea and erythordermia at admission in 15% and 20% of these patients
  - ✓ Higher rates of pneumothorax, eryhthrodermia and unilateral condensation during hospitalization
  - ✓ High prevalence of MRSA

Finding summary

✓ Appropriate antibiotic therapy at admission in the large majority of patients

✓regardless of PVL-status

- ✓Death associated with haemoptysis and toxin eruption during hospitalization
- ✓ Survival associated with abscess at admission and during hospitalization

✓Peaks of influenza seasons overlapped with an increase in the incidence of CAP

Perspectives

- ✓ Recruitment to be completed
- ✓ Study of genetic susceptibility of the host
  - ✓ Orfeome of 50 patients curently beeing analysed
- ✓ Study of bacterial co-factors by Meta-genomic analysis

Conclusions

✓Biological evidence and animal experiments converge toward a role of PVL in pathogenesis

✓PVL remains a factor of severity in *S. aureus* CAP

✓ PVL-associated CAP: young adults and rapid death

✓Severe leukopenia and airway haemorrhage associated with death

✓ Severe CA pneumonia: MRSA = ca. 20% regardless PVL -> optimize the empirical treatment

✓Parallelism between influenza epidemics and higher incidence of CAP

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- Magalie Perret

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- Thierry Defrance

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