Virus respiratoires: de la botanique à l'impact clinique

L Kaiser

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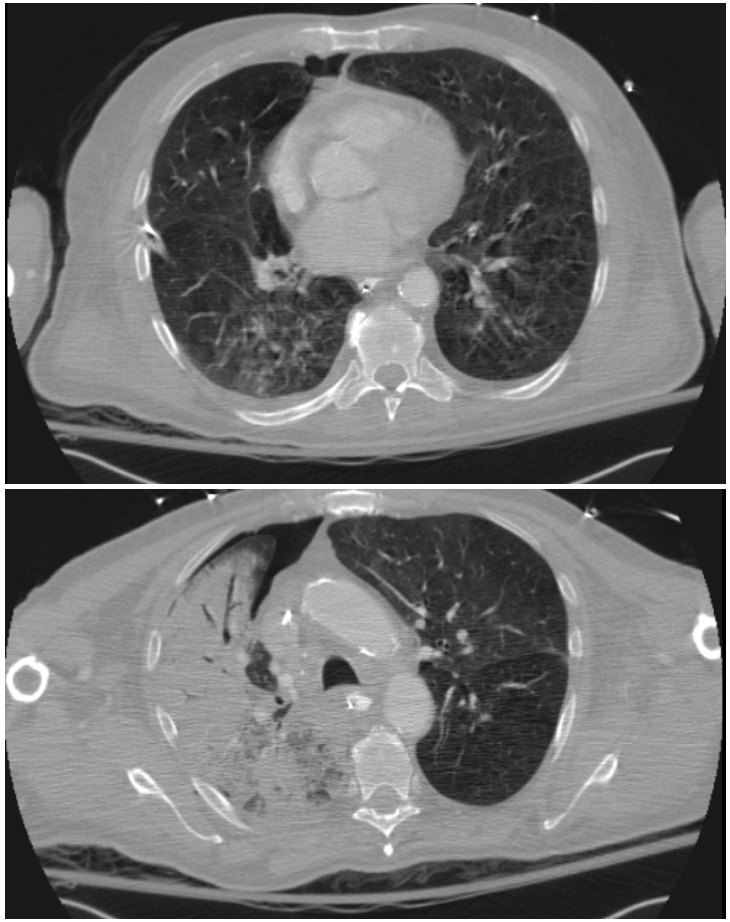
STS 553

UNIVERSITÉ DE GENÈVE

Hôpitaux Universitaires de Genève

Homme 75 ans, LLC:

- Pneumonie avec hypoxémie sévère
- Admission aux SI
- Absence de réponse à une antibiothérapie large
- LBA 185 cell. M/l, 96% macrophages
- Investigations bactériologiques négatives



PCR quantitative adénovirus :
LBA du 14.02: **3,8E9 copies / ml**
Plasma du 17.02:**1,5E9 copies / ml**
Urine du 17.02: **3,5E9 copies / ml**

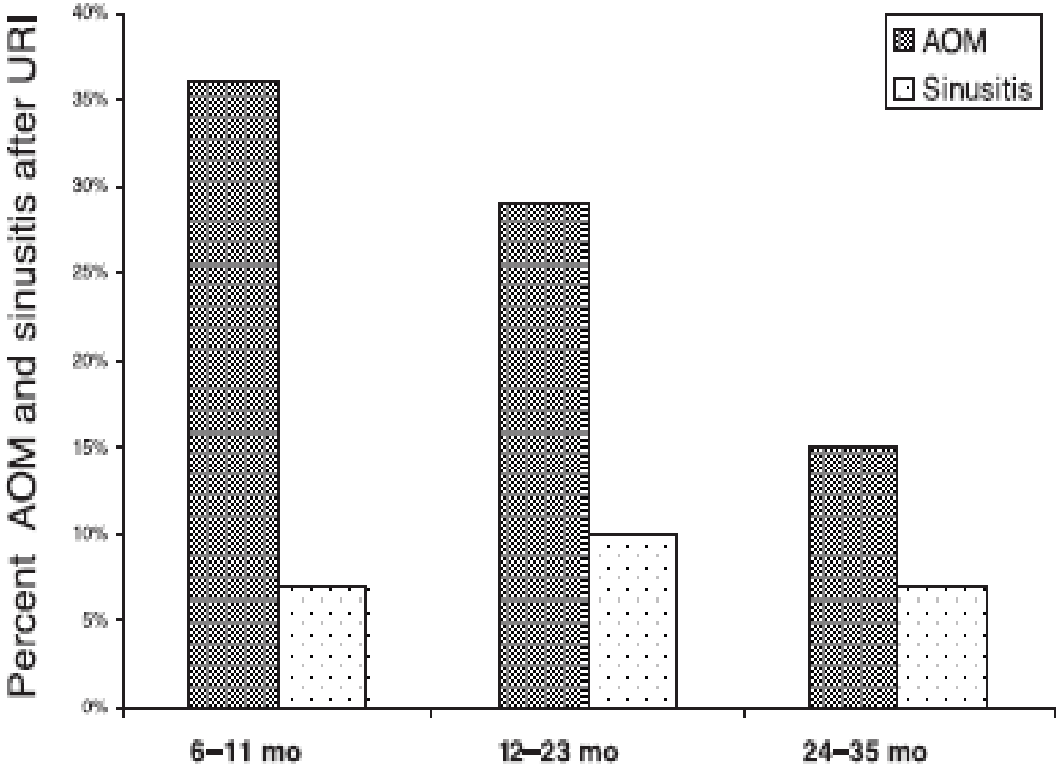
Le clinicien: extraits

- L'image radiologique exclu une pneumonie virale…
- Ce virus n'est pas la cause des symptômes
- PCR positive: c'est un contaminant, trop sensible, on en trouve partout, ce n'est pas spécifique…
- De toute façon « y a pas de traitement »
- ...

Virus respiratoires

- 1ère cause de rhinopharyngites
  - Sinusites
  - Otites
  - Prescription antibiotiques
  - Infections bactériennes secondaires

AOM or sinusitis incidence after URTI in children



Incidence of Acute Otitis Media and Sinusitis Complicating Upper Respiratory Tract Infection: The Effect of Age

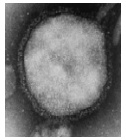
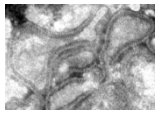
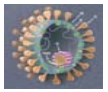
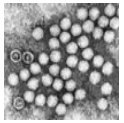
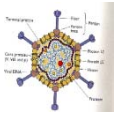
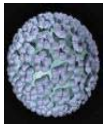
Krystal Revai, Laura A. Dobbs, Sangeeta Nair, Janak A. Patel, James J. Grady and Tasnee Chonmaitree

Pediatrics 2007;119;e1408-e1412

DOI: 10.1542/peds.2006-2881

Virus respiratoire

- 1ère cause de rhinopharyngites
  - Sinusites
  - Otites
  - Prescription antibiotiques
  - Infections bactériennes secondaires
- "1ère" cause d'exacerbations
  - Asthme
  - COPD

	Virus	Structure	Genome	Subtypes
	Rhinovirus	Capsid	+ RNA	>100
	Influenza	Env.	8 – RNA	A/B/C
	RSV	Env.	- RNA	A/B
	Parainfluenza	Env.	- RNA	4
	Hum. metapn.	Env.	+ RNA	2
	Coronavirus	Env.	- RNA	4
	Enterovirus	Capsid	+ RNA	>70
	Adenovirus	Capsid	DNA	>50
	Bocavirus	Capsid	DNA	?

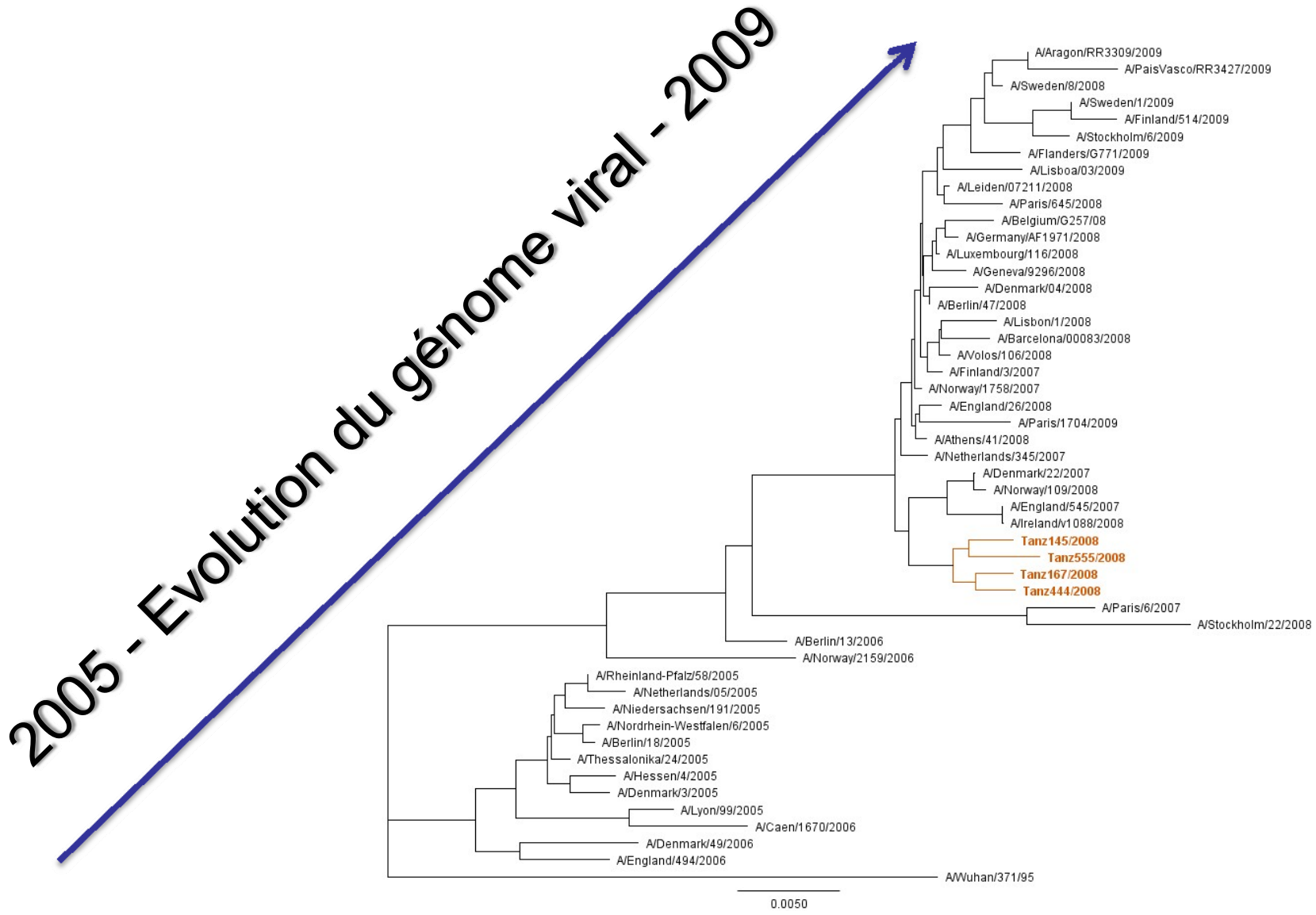
Immunité

Protection immune limitée:

- Variabilité des sérotypes
- Réponse immune non protectrice
- Réponse immune de courte durée (?)
- Evolution des antigènes viraux (influenza)
- Réponse humorale vs. Cellulaire (?)
- Absence de vaccin « universel »
  - But: immunité muqueuse
- Réinfections fréquentes

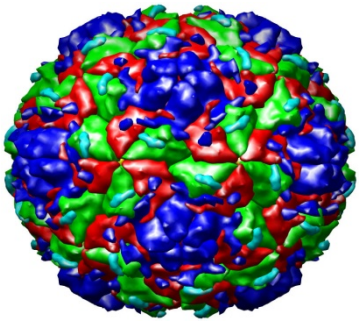
Virus respiratoires

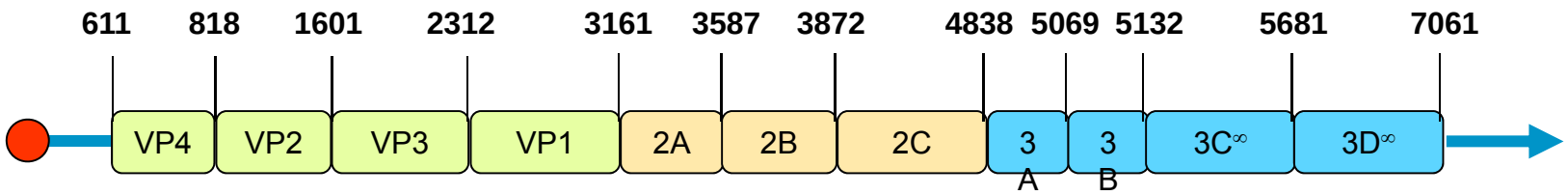
- Influenza
  - Influenza A
    - H3N2
    - H1N1
      - Saisonnier
      - Porcin
        - 2009
        - 2010
        - 2011
    - H1N2
    - H5N1
  - Influenza B
  - Influenza C
- RSV
- Parainfluenza
- Metapneumovirus
- Enterovirus
- Coronavirus
- Adenovirus
- Bocavirus

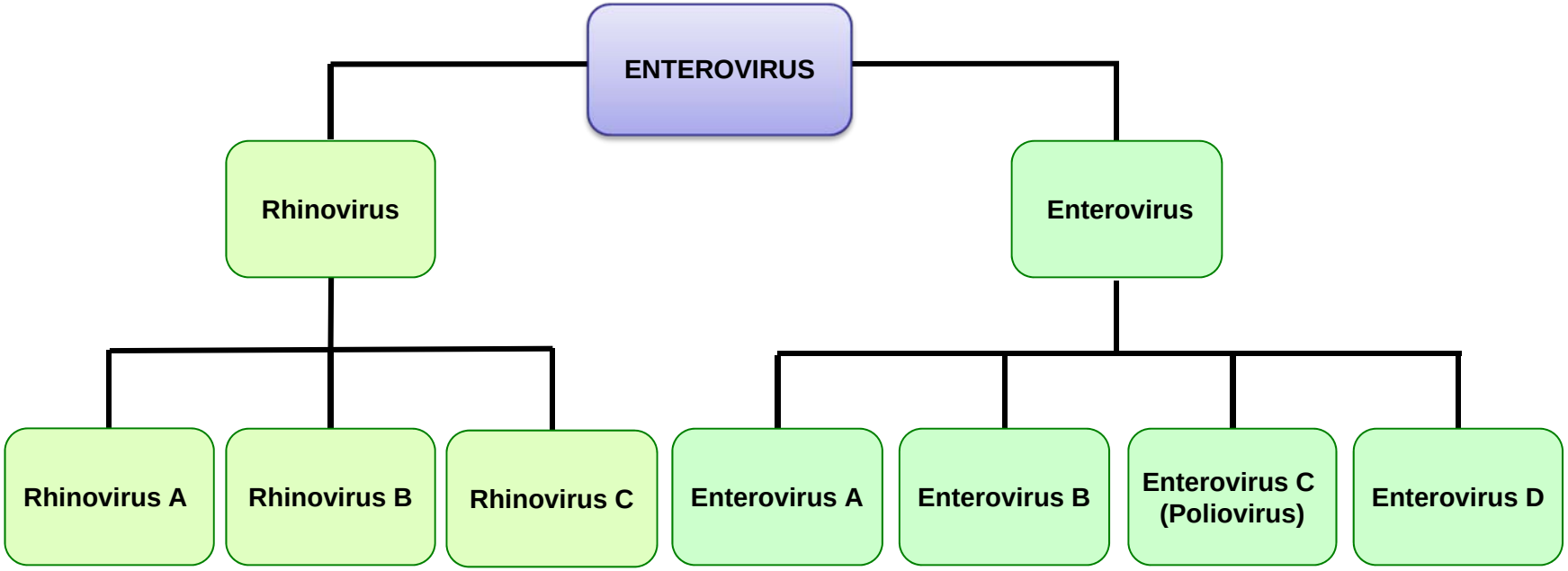

2005 - Evolution du génome viral - 2009
A/Aragon/RR3309/2009
A/PaisVasco/RR3427/2009
A/Sweden/8/2008
A/Sweden/1/2009
A/Finland/514/2009
A/Stockholm/6/2009
A/Flanders/G771/2009
A/Lisboa/03/2009
A/Leiden/07211/2008
A/Paris/645/2008
A/Belgium/G257/08
A/Germany/AF1971/2008
A/Luxembourg/116/2008
A/Geneva/9296/2008
A/Denmark/04/2008
A/Berlin/47/2008
A/Lisbon/1/2008
A/Barcelona/00083/2008
A/Volos/106/2008
A/Finland/3/2007
A/Norway/1758/2007
A/England/26/2008
A/Paris/1704/2009
A/Athens/41/2008
A/Netherlands/345/2007
A/Denmark/22/2007
A/Norway/109/2008
A/England/545/2007
A/Ireland/v1088/2008
Tanz145/2008
Tanz555/2008
Tanz167/2008
Tanz444/2008
A/Paris/6/2007
A/Stockholm/22/2008
A/Berlin/13/2006
A/Norway/2159/2006
A/Rheinland-Pfalz/58/2005
A/Netherlands/05/2005
A/Niedersachsen/191/2005
A/Nordrhein-Westfalen/6/2005
A/Berlin/18/2005
A/Thessalonika/24/2005
A/Hessen/4/2005
A/Denmark/3/2005
A/Lyon/99/2005
A/Caen/1670/2006
A/Denmark/49/2006
A/England/494/2006
A/Wuhan/371/95
0.0050

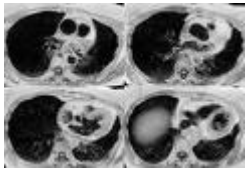
Rhinovirus

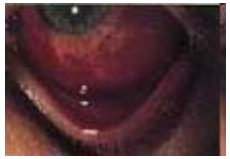
« 1ère cause d'épisodes infectieux chez l'homme? »

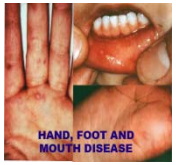


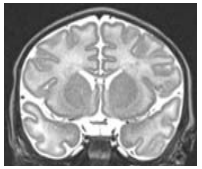

611
818
1601
2312
3161
3587
3872
4838
5069
5132
5681
7061
VP4
VP2
VP3
VP1
2A
2B
2C
3 A
3 B
3C∞
3D∞


ENTEROVIRUS
Rhinovirus
Enterovirus
Rhinovirus A
Rhinovirus B
Rhinovirus C
Enterovirus A
Enterovirus B
Enterovirus C (Poliovirus)
Enterovirus D






HAND, FOOT AND
MOUTH DISEASE



Diagnostic: bactéries vs. virus

- Bactéries:
  - Détection générique « facile »
  - « toutes » cultivables (conditions standards ou spécifiques)
  - Cible moléculaire commune (16sRNA), « PCR broad range » (sensibilité limitée)
  - Recherche d’antigènes
  - « Sérologies »

Diagnostic: bactéries vs. virus

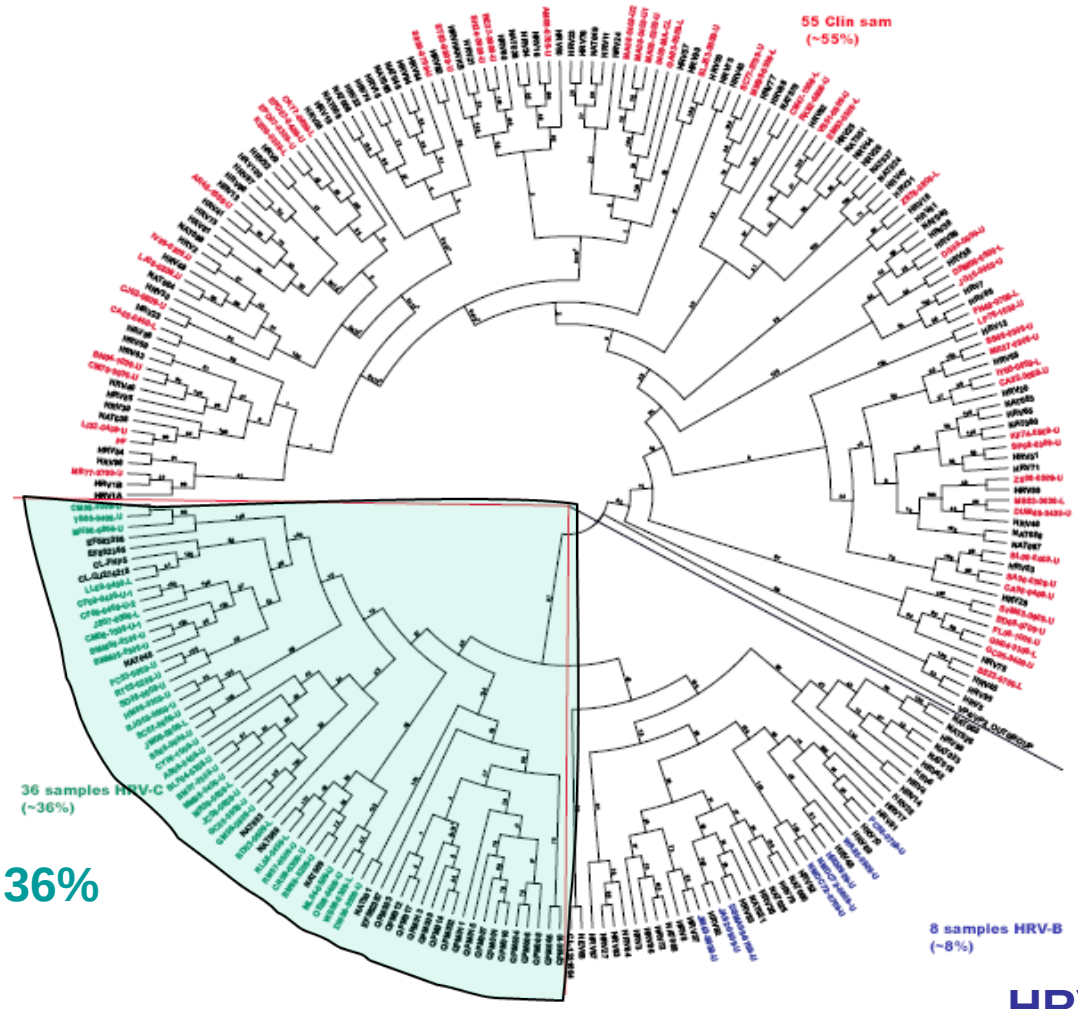
- Culture laborieuse, longue ou impossible
- Pas de cible moléculaire commune
- Virus ADN: différencier primo- vs réactivation (infection latente)
- Détection d'ARN viral:
  - en général signe une réplication active ou récente
  - « synonyme » d'infection (infection ≠ maladie)
- Epidémiologie saisonnière
- Recherche d'antigènes: RSV
- Sérologies: rarement applicables

(RT)-PCR

- Méthode de référence en virologie mais…
  - Cible spécifique prédéterminée sur la base de la connaissance des séquences disponibles
  - …« on ne trouve que ce qu'on cherche »…
  - Nouveaux virus ou variants inconnus (?)

  - Préserver à 4°C l'échantillon respiratoire (frottis nasopharyngé) dans un milieu spécifique

Genotyping of rhinovirus strains (n=99)
University Hospital of Geneva 2009

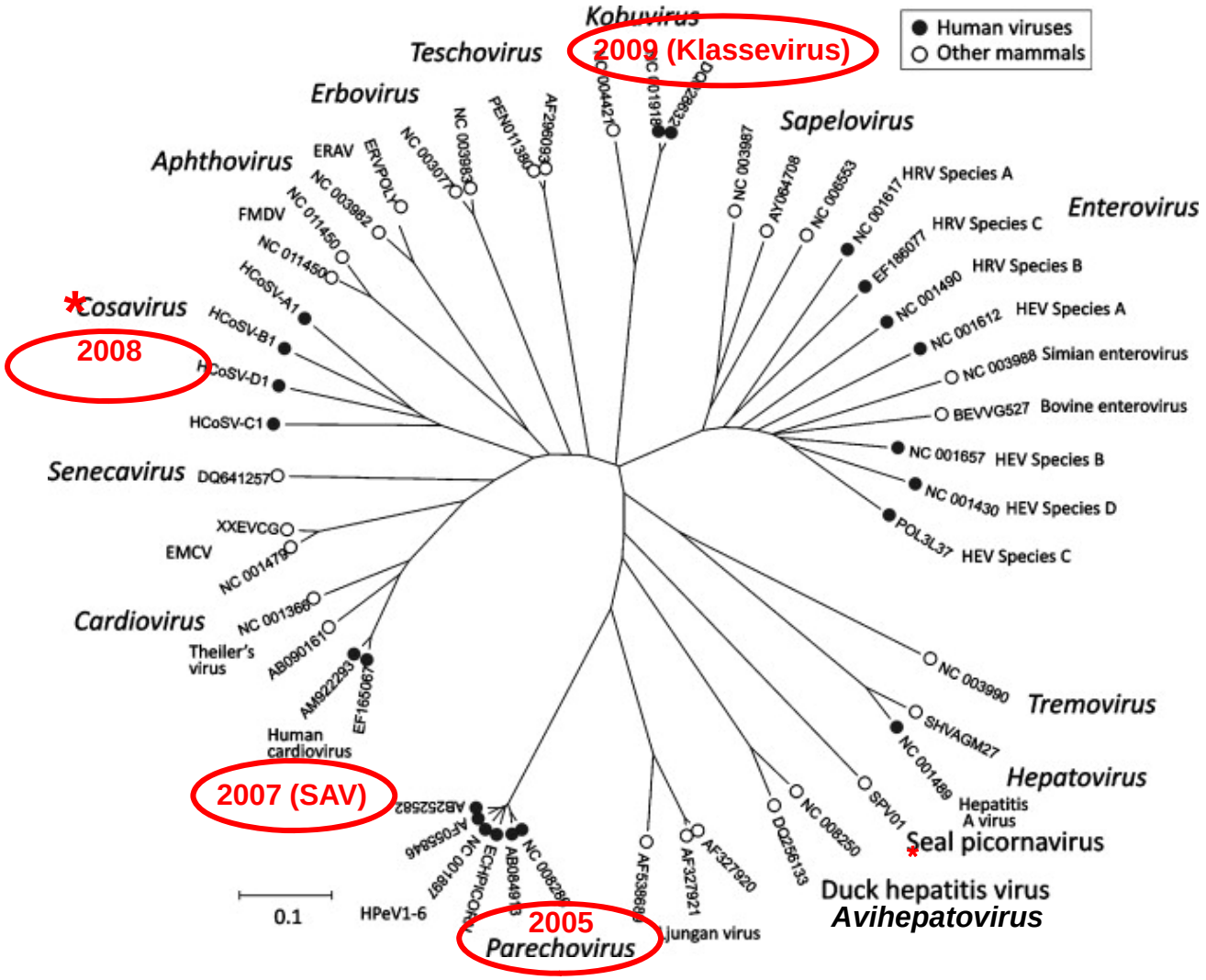


HRV-A: ~ 55%

HRV-C: ~ 36%

HRV-B: ~ 8%

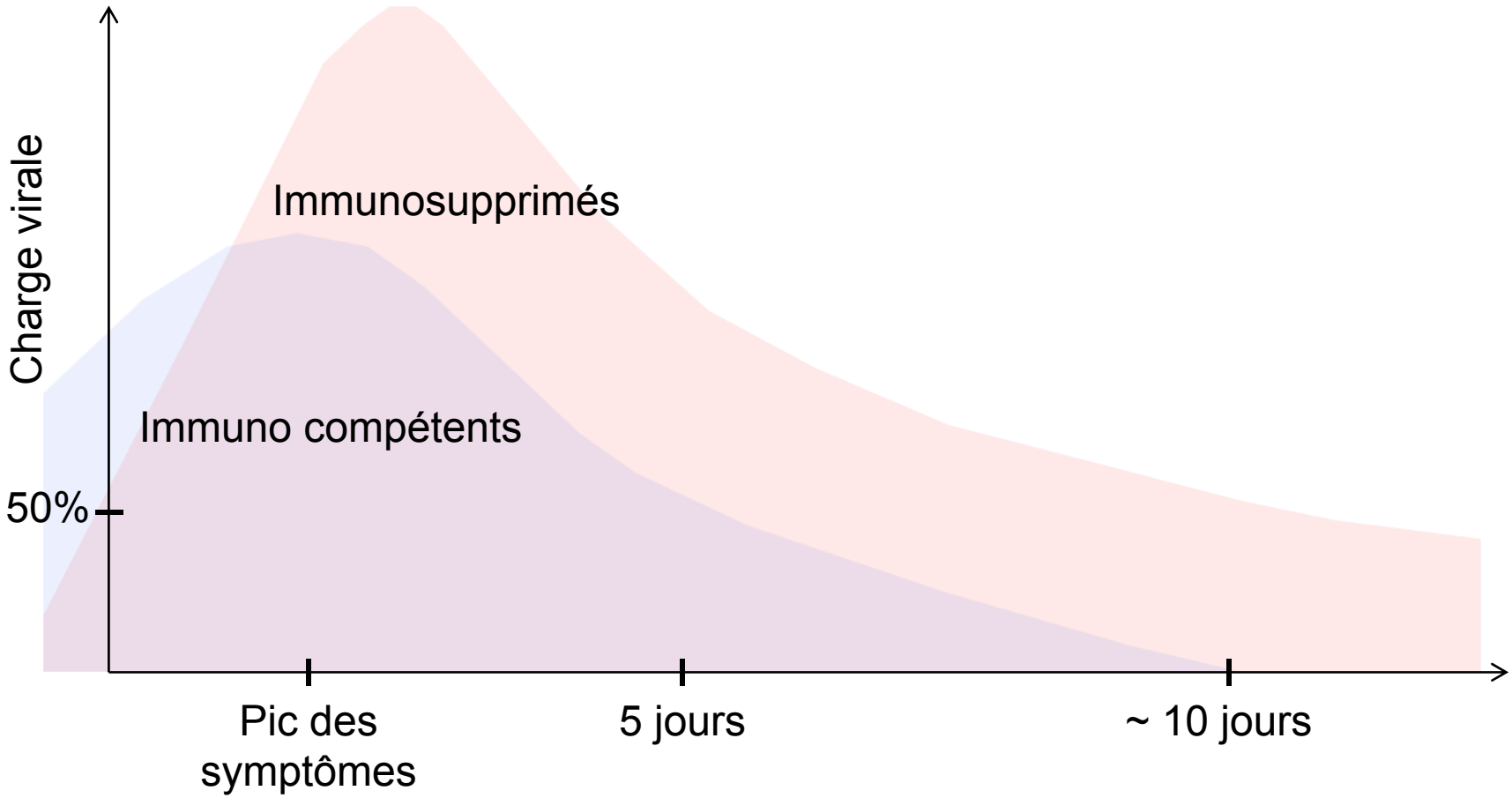
Picornaviridae: new members
New diseases?



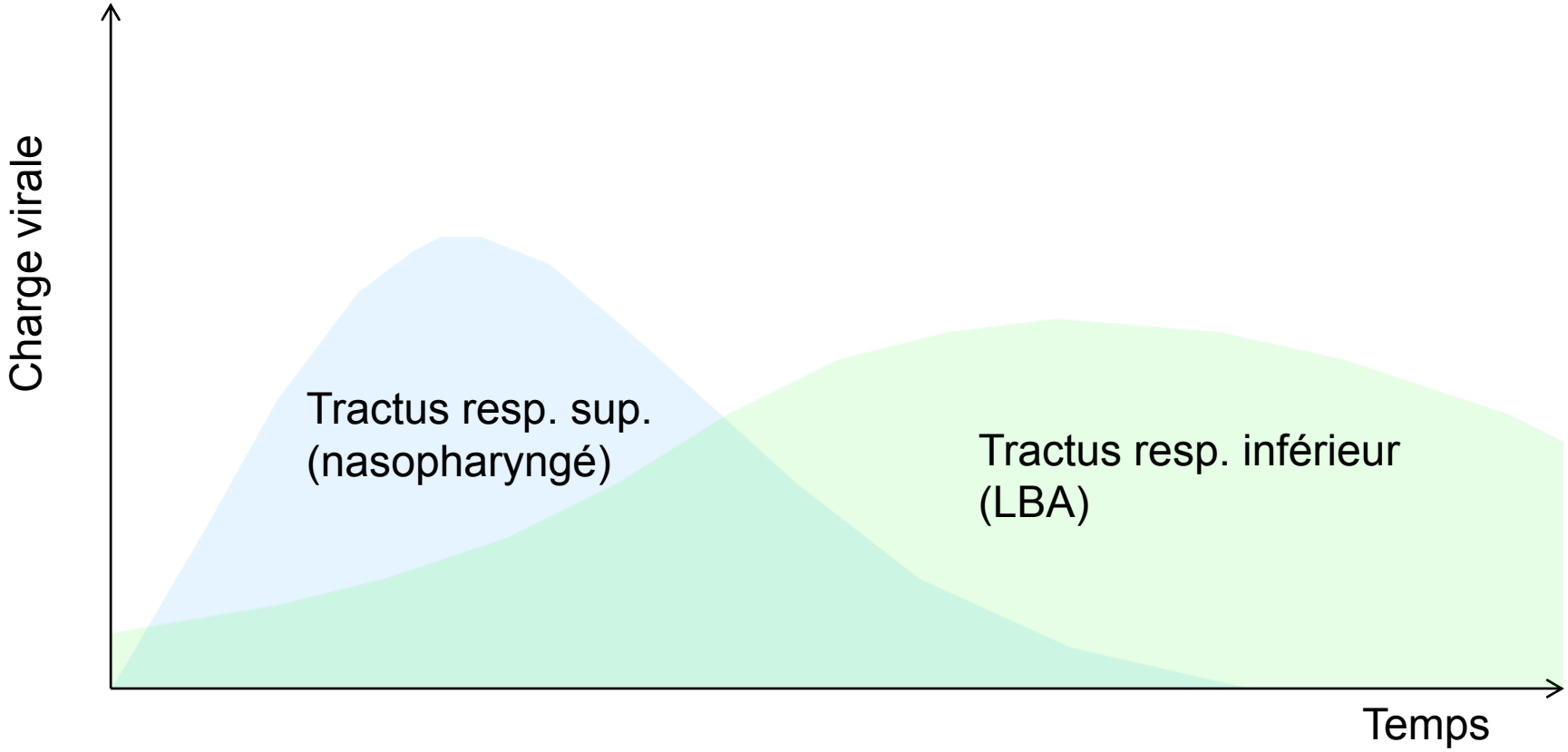
Harvala and Simmonds, J.Clin.Vir. 2009

Virus respiratoires: site et durée de l'infection

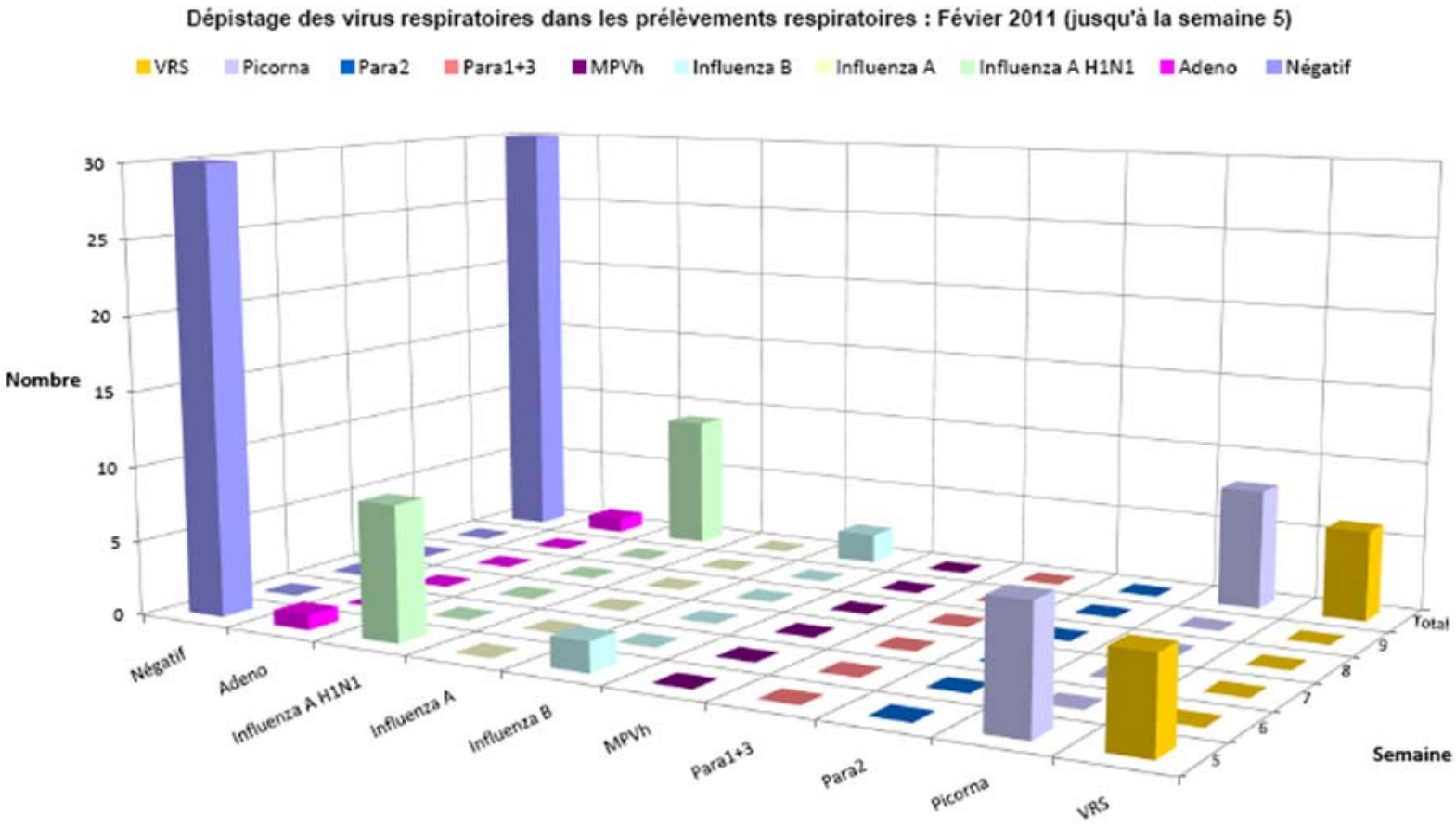
- Site primaire: nasopharynx
  - Infection du tractus respiratoire inférieur
    - RSV et nouveaux-nés: le prototype
  - Pneumonies virales rares: H1N1, RSV, PIV3
- Durée chez l'hôte immunocompétent:
  - Pic de la charge virale = pic des symptômes
  - Sans complications:
    - PCR positive < 10 jours
    - Virus cultivable et transmissible << 10 jours

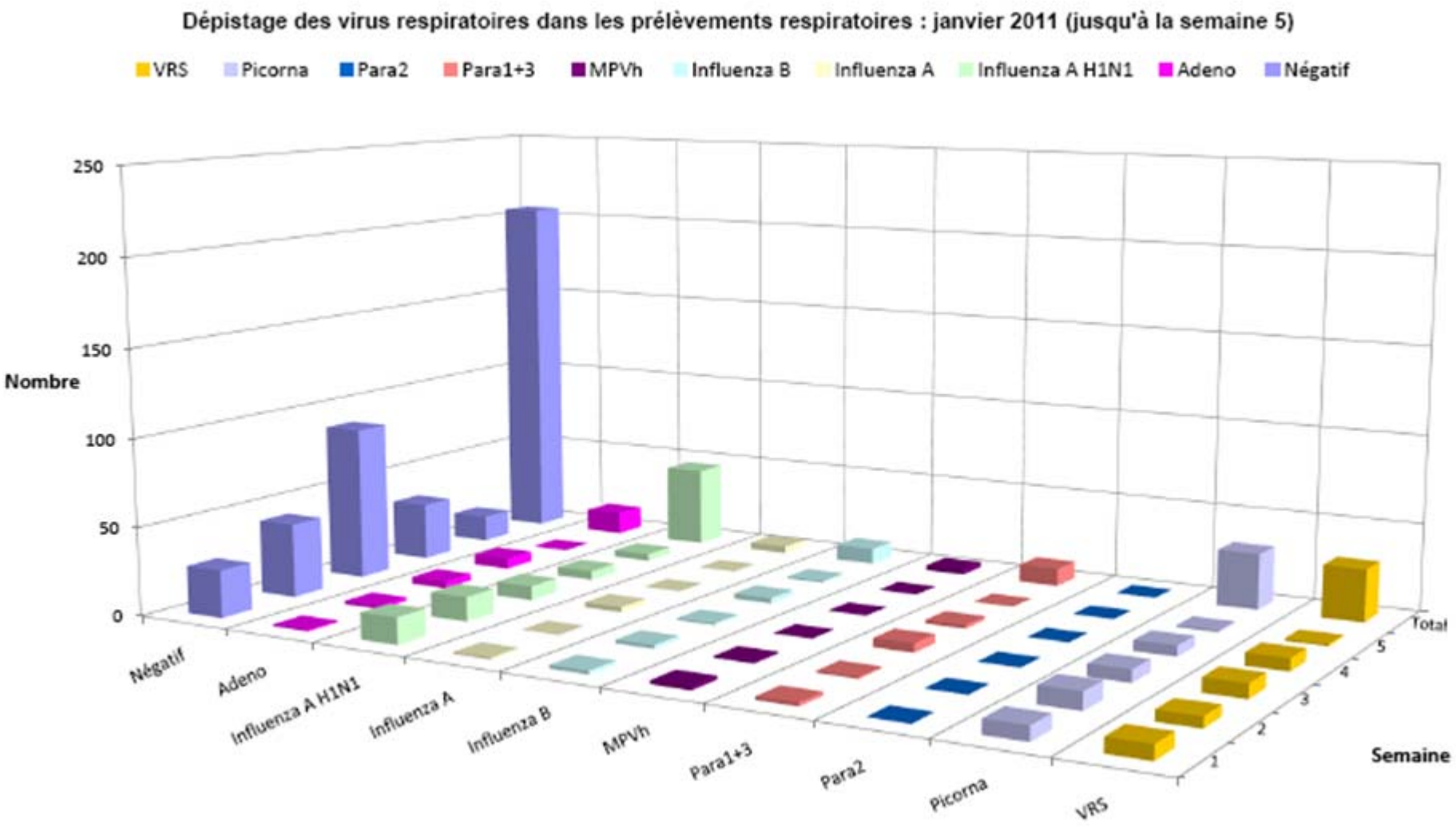

Charge virale
Immunosupprimés
Immuno compétents
50%
Pic des symptômes
5 jours
~ 10 jours

Charge virale H1N1 chez les patients avec pneumonie

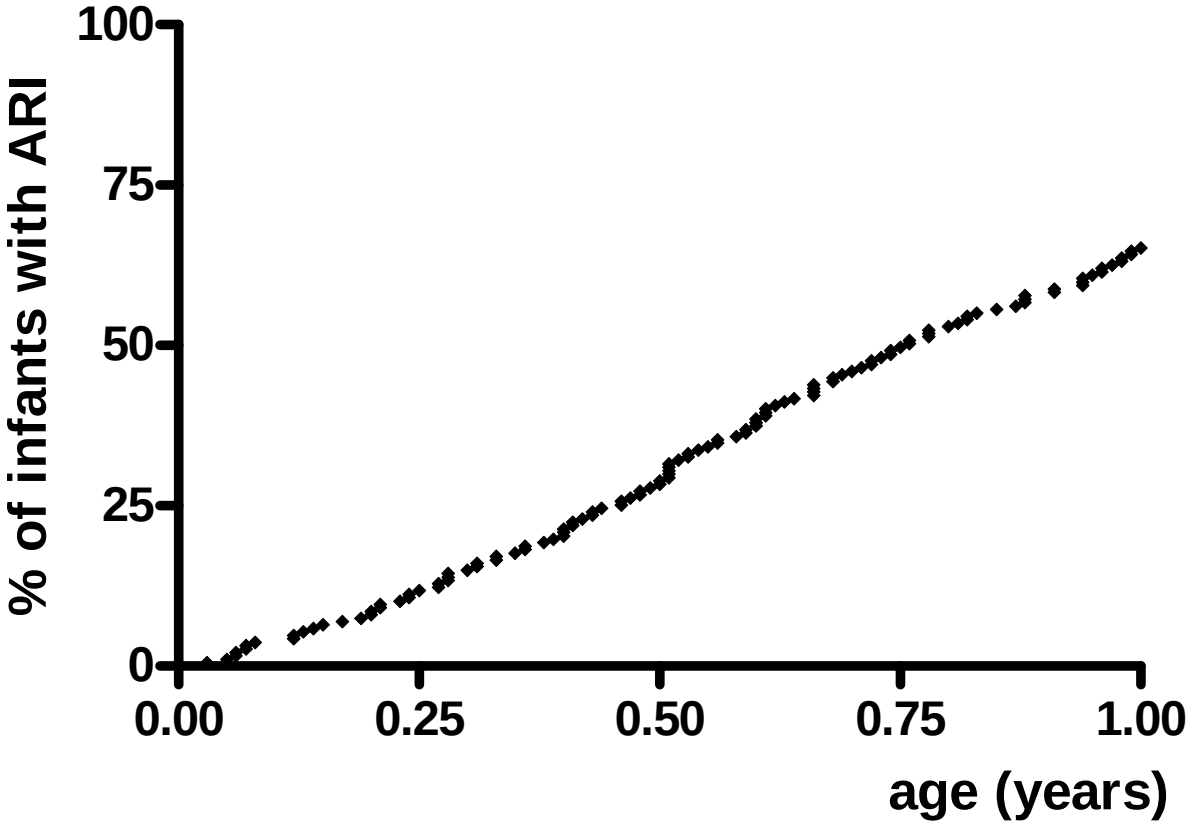


http://virologie.hug-ge.ch



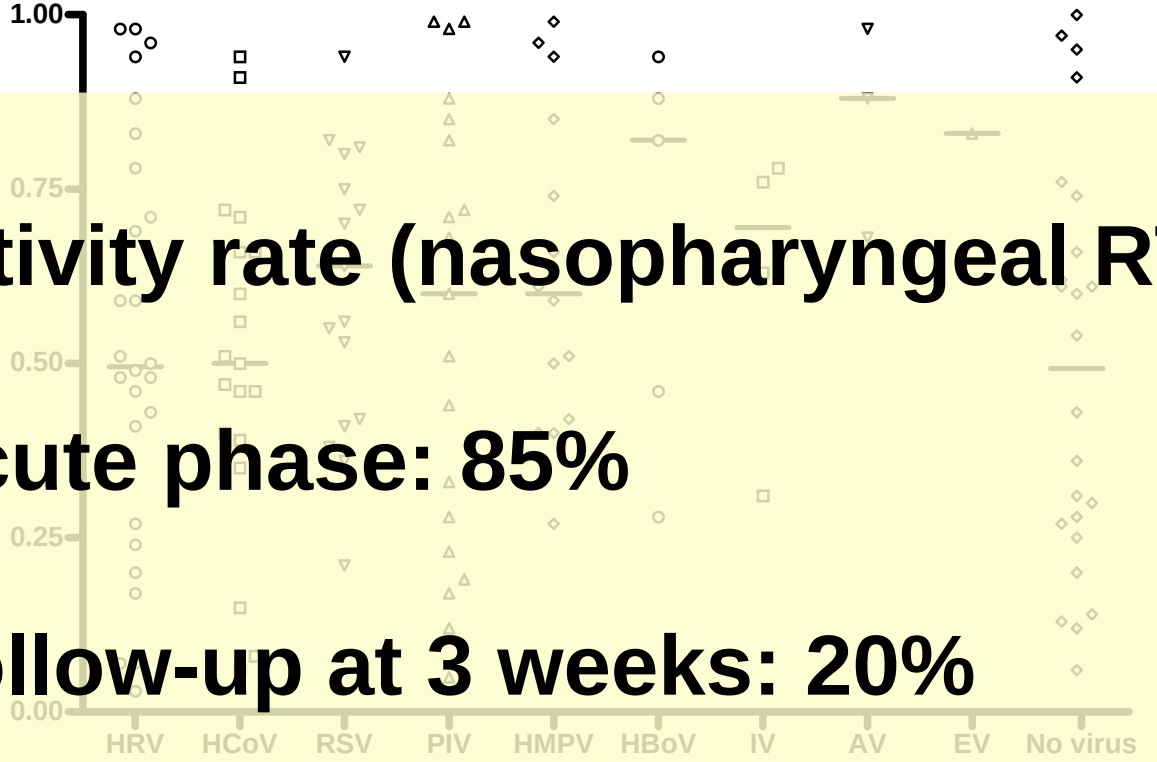

Dépistage des virus respiratoires dans les prélèvements respiratoires : janvier 2011 (jusqu'à la semaine 5)
VRS
Picorna
Para2
Para1+3
MPVh
Influenza B
Influenza A
Influenza A H1N1
Adeno
Négatif
Nombre
250
200
150
100
50
0
Semaine
1
2
3
4
5
Total

Viral aetiology of acute respiratory infections in infancy



N Regamey et al. PIDJ 2005

Viral aetiology of acute respiratory infections in infancy



Positivity rate (nasopharyngeal RT-PCR)

Acute phase: 85%

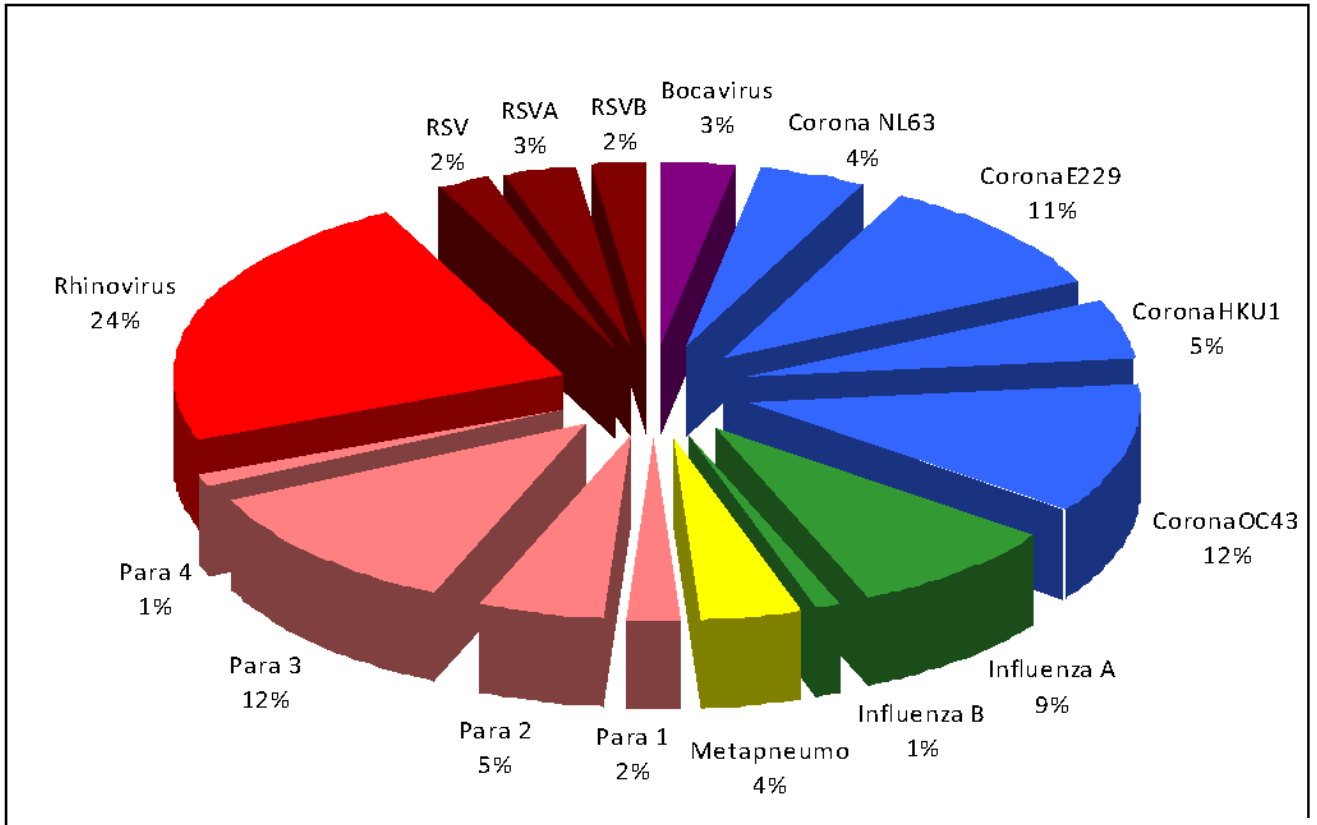
Follow-up at 3 weeks: 20%

Botanique vs. impact clinique?

- **Enfants: bronchiolite chez l'enfant et autres infections resp. inférieures sérieuses = RSV et parainfluenza 3**
  - **Metapneumovirus**
  - **Rhinovirus**
  - **H1N1**
  - **….**
  - **Doubles infections (?)**

Respiratory viruses in bronchoalveolar lavage: a hospital-based cohort study (n=522)

17.4% of cases positive



J Garbino et al. Thorax 2009

Clinical features

TABLE 4: CLINICAL PREDICTORS OF RESPIRATORY VIRUS AT THE TIME OF BRONCHOALVEOLAR LAVAGE

Predictors	OR (CI 95%)	p-value
Baseline Conditions		
No immunosuppress		
HIV		
Other immunosuppr		
Lung transplantatior		
Other transplantatio		
Signs or symptom		
New radiologic infil		
Treated with antibio		
Sputum		
Opportunistic infect		
Cough	[illegible]	[illegible]
Respiratory infection suspected	1.5 (0.7 – 3.2)	0.26
Dyspnea	0.7 (0.4 – 1.3)	0.29
Fever	1.5 (0.7 – 3.3)	0.26
Flu-like illness	1.2 (0.6 – 2.7)	0.57
Rhinoparyngitis	0.9 (0.5 – 2.0)	0.89

(*mixed logistic regression model, clustered on patient)**antibiotic treatment targeting a respiratory tract infection

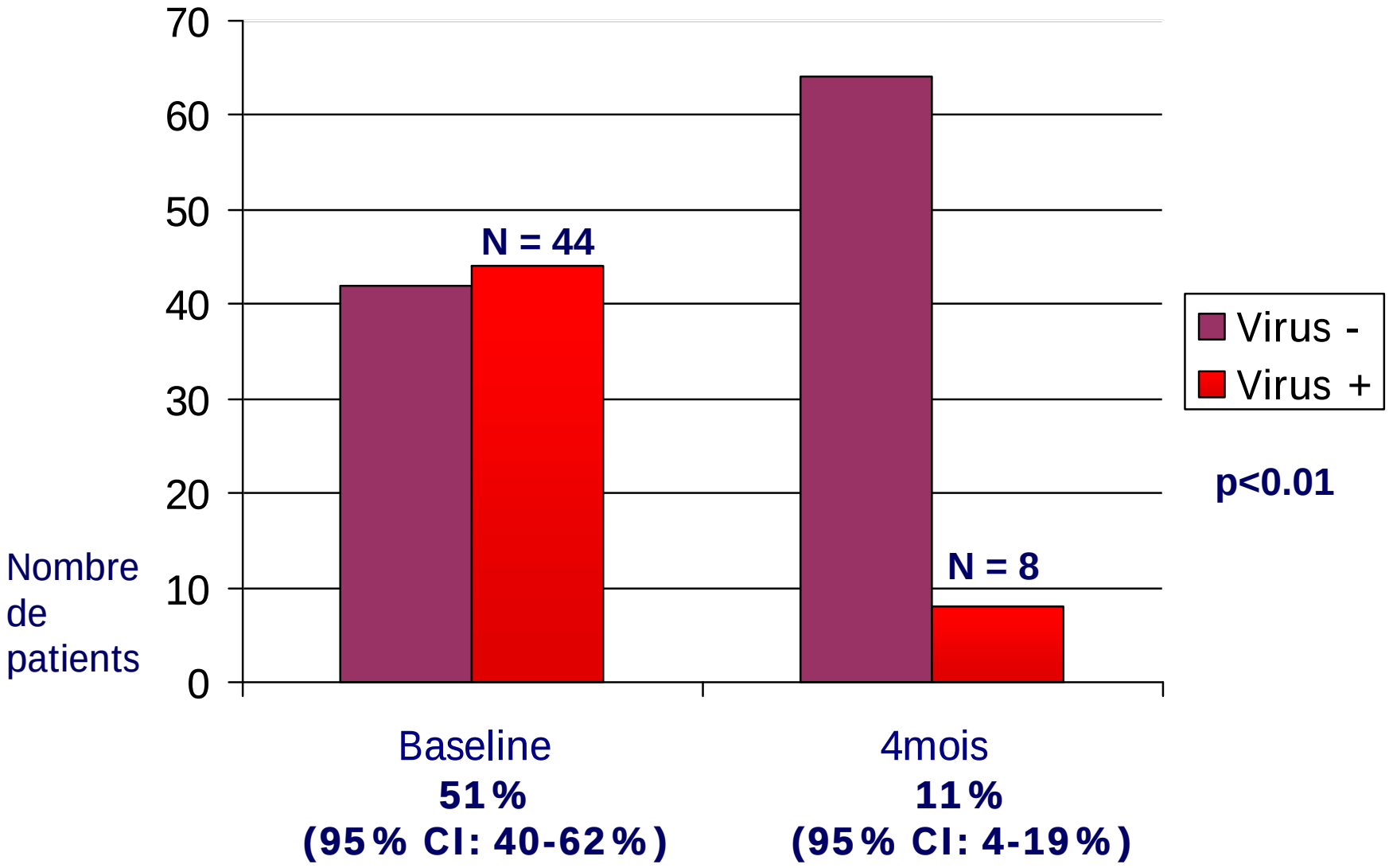
- **Positivity rate: similar across all subgroups**
- **Association with previous antibiotic treatment & lack of new radiological infiltrate**

Upper viral respiratory infection, biomarkers and chronic obstructive pulmonary disease (COPD) exacerbations

Omar Kherad, Laurent Kaiser, Pierre-Olivier Bridevaux, François Sarasin, Yves Thomas, Jean-Paul Janssens and Olivier T. Rutschmann

Chest; Prepublished online April 30, 2010;
DOI 10.1378/chest.09-2225

Résultats virologiques

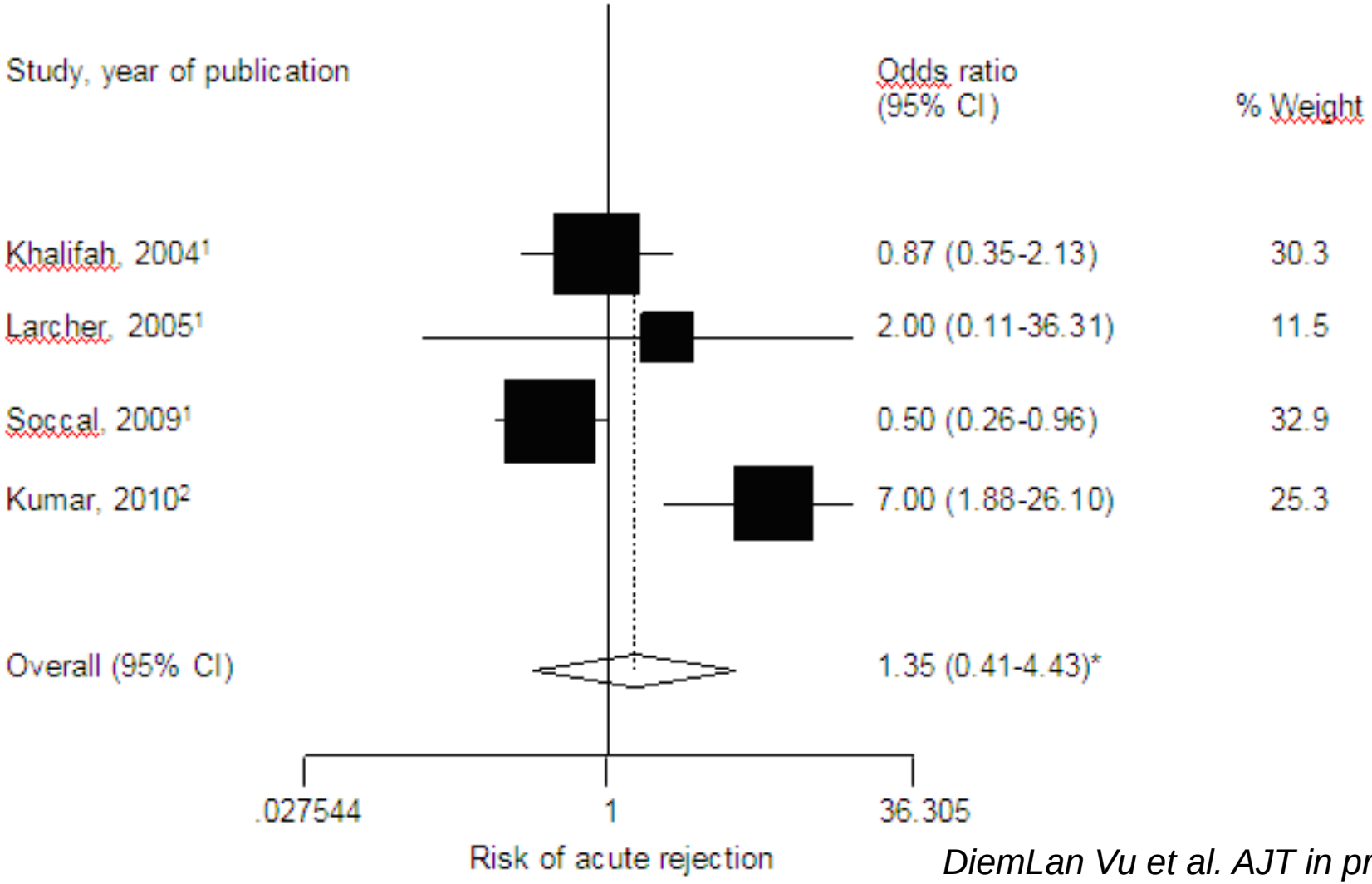


Transplantés pulmonaires

- La greffe est directement exposée au virus
- Absence de
  - Réponse immune
  - Réflexe de toux
  - Drainage lymphatique

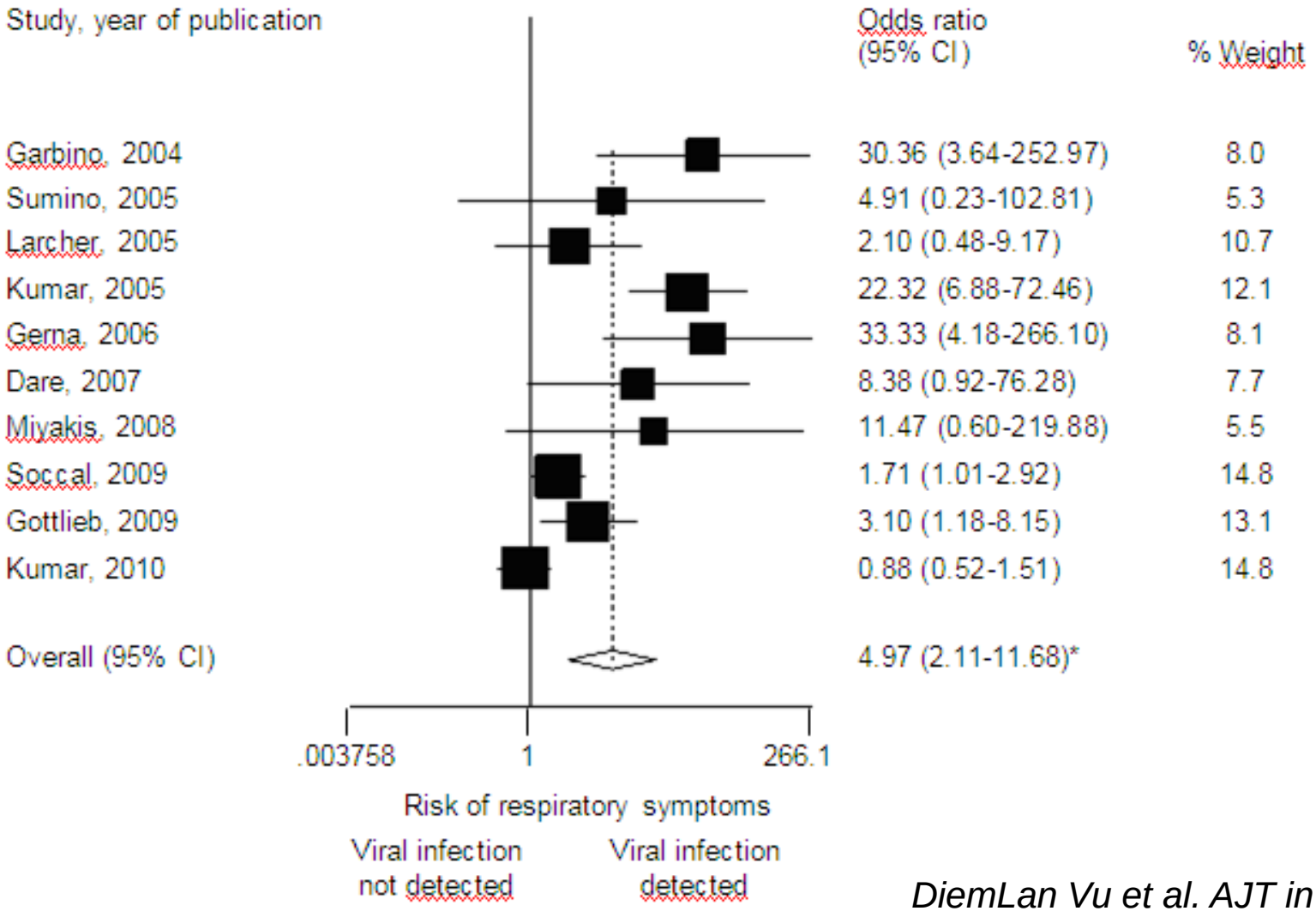
Les infections virales favoriseront le rejet aigu et chronique/BOS

Lung Transplant Recipients: rejection



DiemLan Vu et al. AJT in press

Lung Transplant Recipients Respiratory symptoms

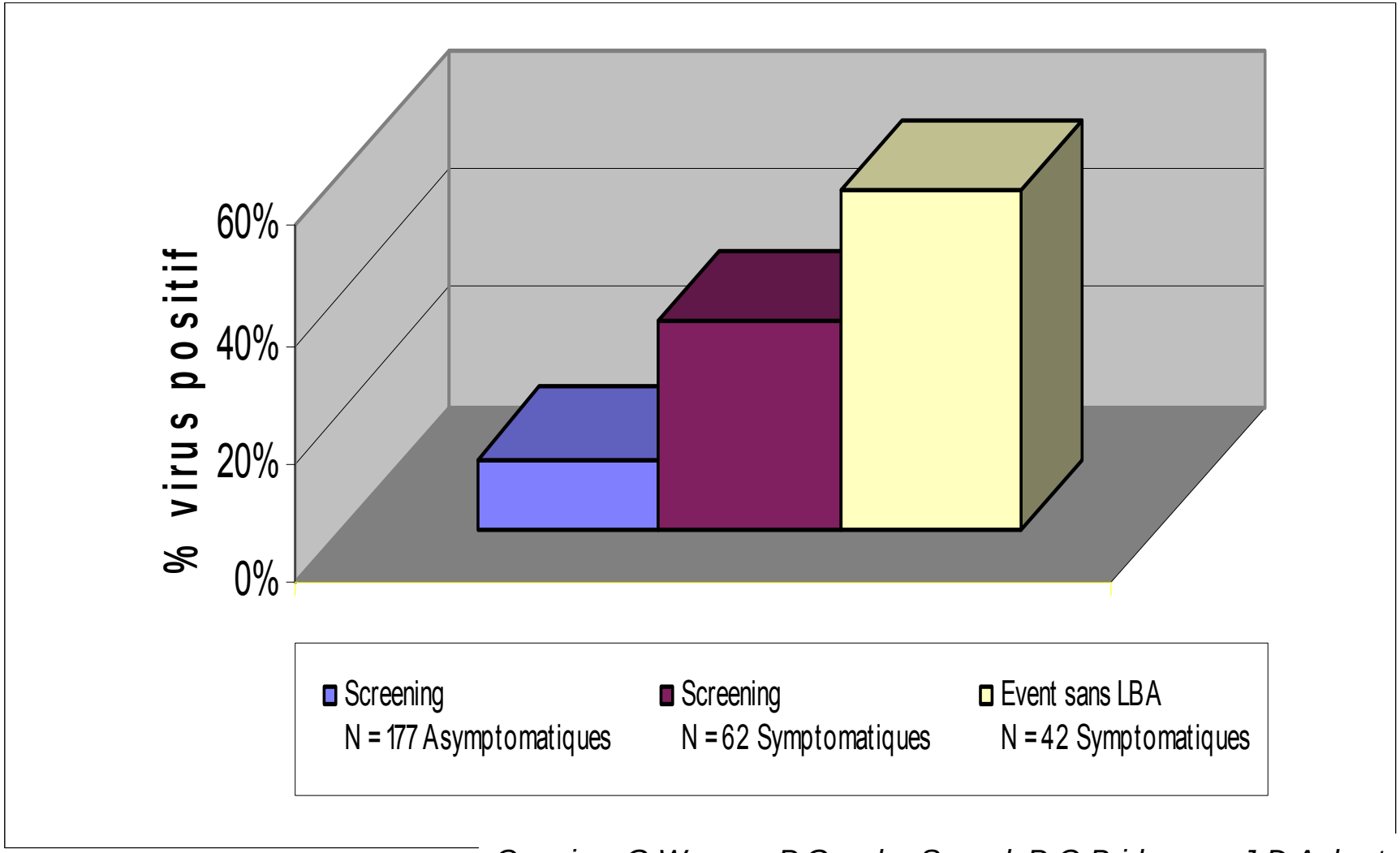


DiemLan Vu et al. AJT in press

Transplantés pulmonaire (Lausanne-Genève) n=106

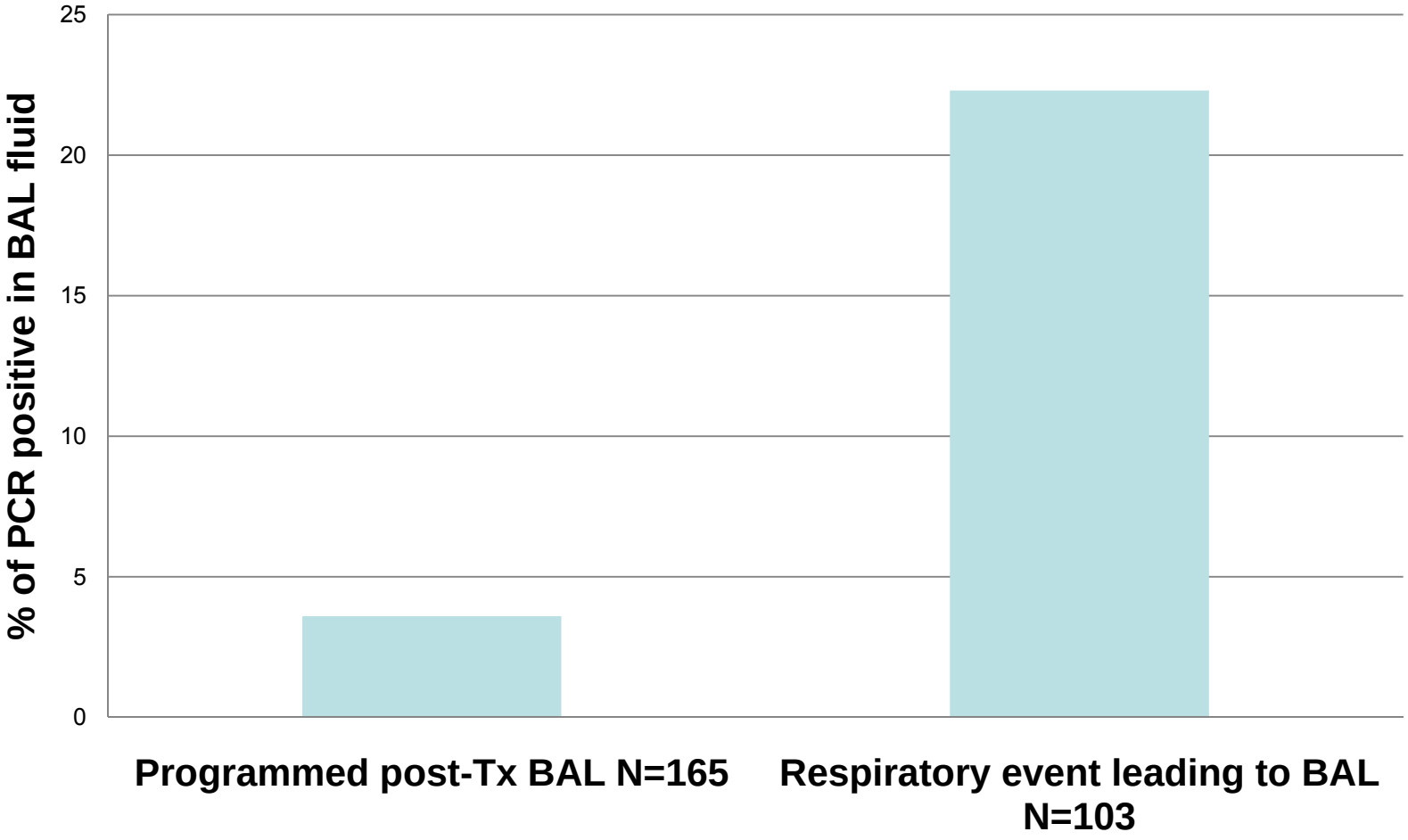
- Etude de cohorte prospective visant à évaluer l'impact des virus respiratoires
  - Juin 2008 – en cours
  - Screening systématiques: 3 périodes par an en l'absence de symptômes
  - Evènements cliniques respiratoires motivant une consultation « avec ou sans » LBA

Proportion de PCR virales positives en fonction de la situation clinique: étude prospective CHUV-HUG



Ongoing: G Wagner, P Gasche-Soccal, P-O Bridevaux, J-D Aubert et al.

Respiratory virus positivity rate in BAL according to the clincial condition



Ongoing: G Wagner, P Gasche-Soccal, P-O Bridevaux, J-D Aubert et al.

Swiss TPH

Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

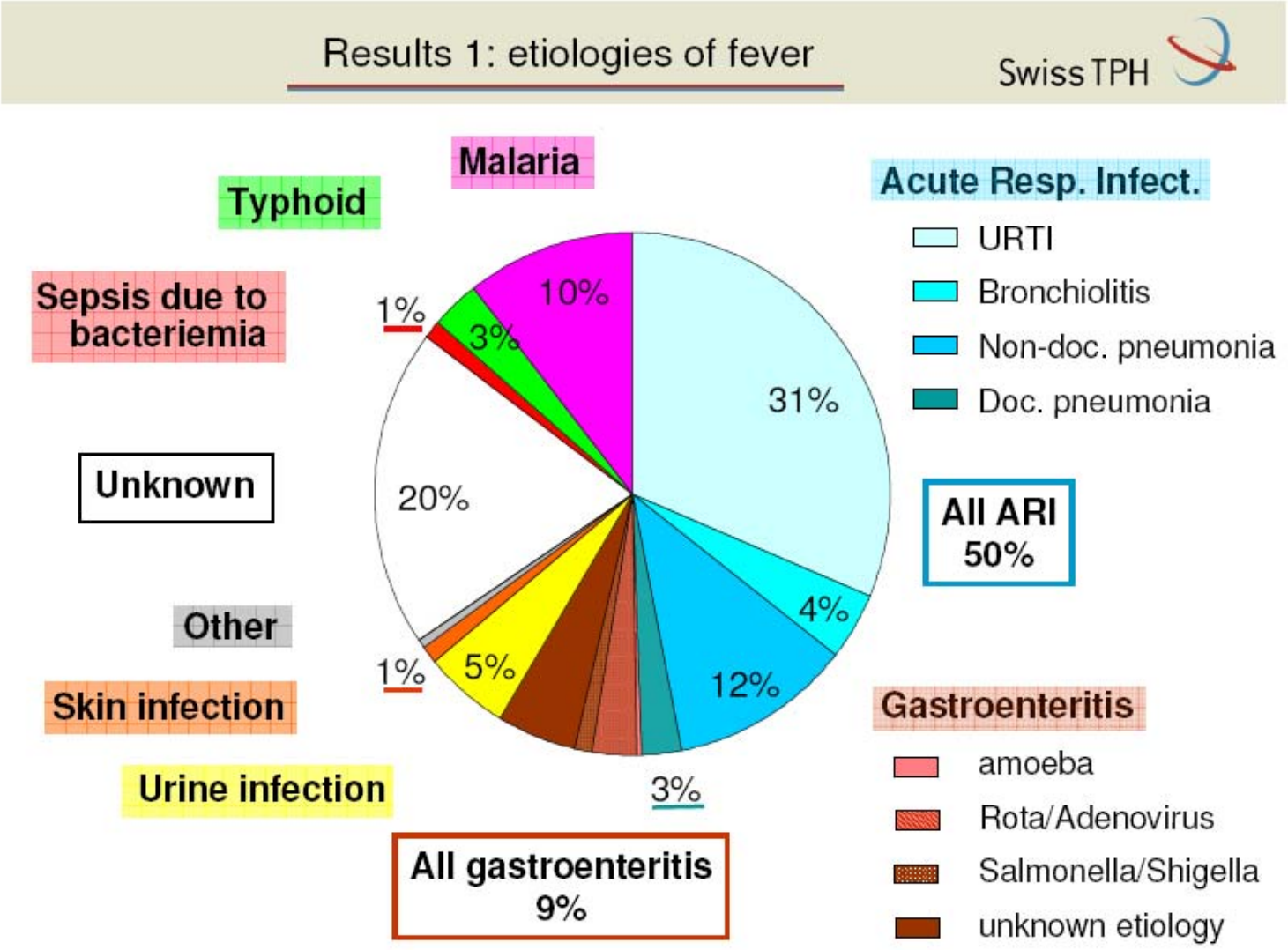
HUG
Hôpitaux Universitaires de Genève

Policlinique Médicale Universitaire

Influenza and other respiratory viruses among febrile children with or without acute respiratory symptoms in Tanzania

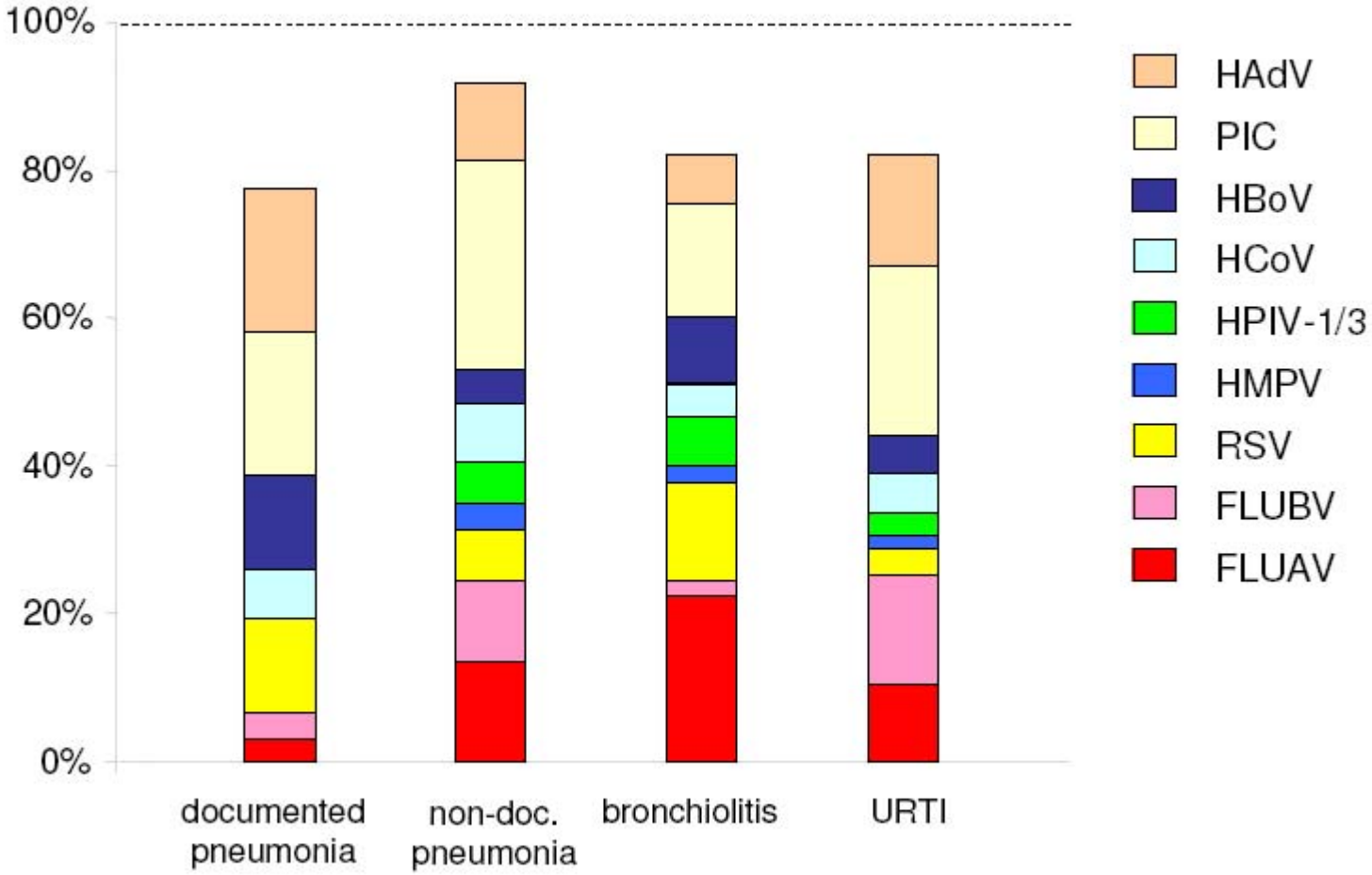
V. D'Acremont, P. Cherpillod, M. Kilowoko, E. Kyungu, S. Philipina, W. Sangu, J. Kahama-Maro, Y. Thomas, L. Alamo, C. Lengeler, B. Genton, L. Kaiser

1005 Tanzanian children with fever



Results 5: distribution of viruses by type of ARI

Swiss TPH



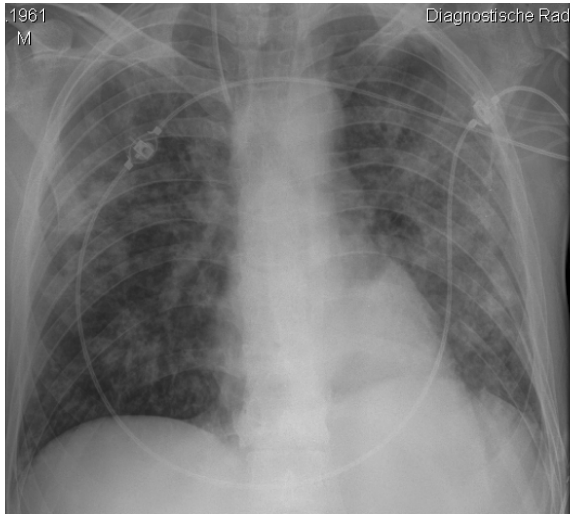
(positive X-ray)

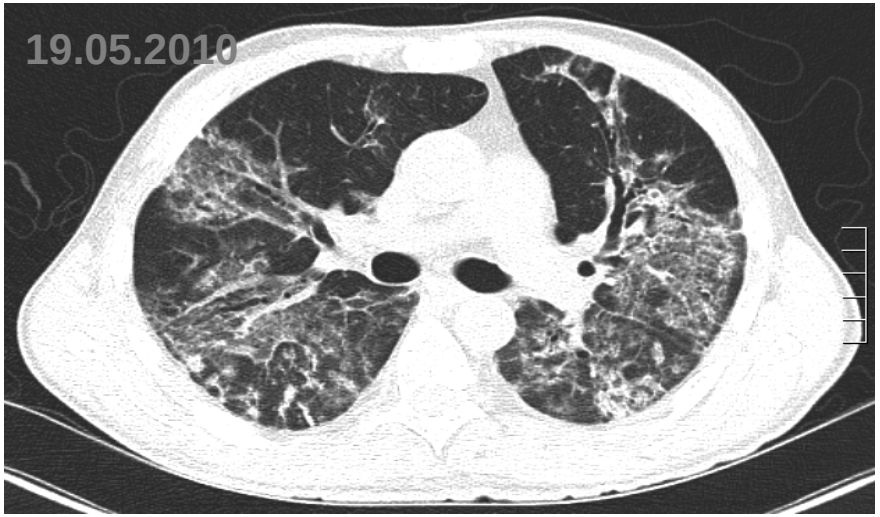
Antiviraux: RSV et influenza

47 Year Old Man with Multiple Myeloma

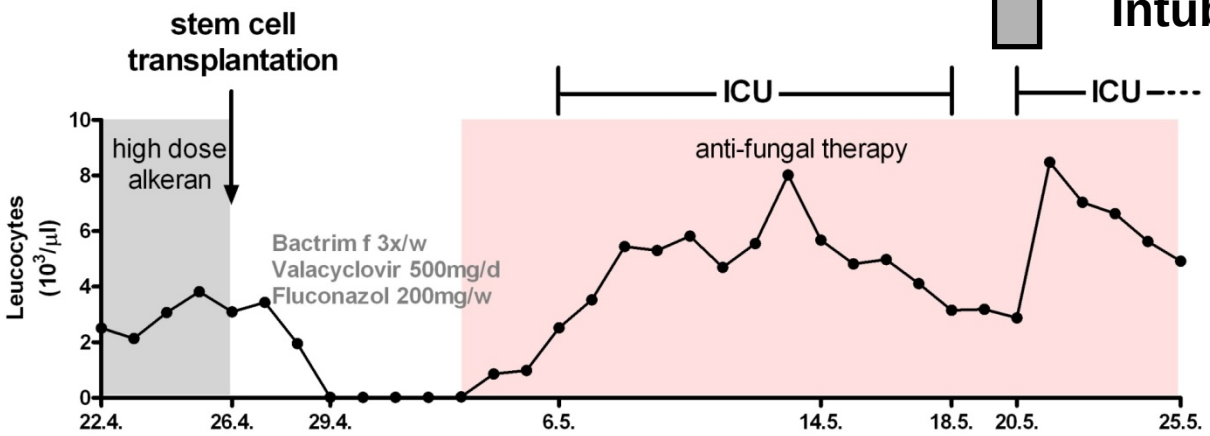
- **2008: Multiple myeloma IgG kappa: initial stage III with multiple bone manifestations**
  - 11/2008: chemotherapy and autologous stem cell transplantation
- **2009**
  - 09/2009: Disease progression with significant increases of paraprotein and total IgG
  - 2 cycles of chemotherapy
  - 04/2010: partial remission and second HSCT

Current Illness





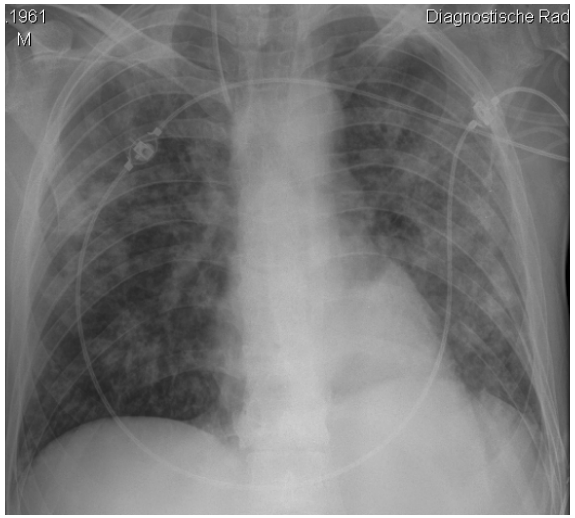
Acute dyspnea
Intubation



Broncho Alveolar Lavage

Microscopy/Cult.: negative for bacterias and fungi

Aspergillus Antigen (Galactomannan): negative



	Blood (ETDA)	Throat (Swab)
CMV DNA	negative	negative
EBV DNA	negative	(positive)
HSV-1	negative	negative
HSV-2	negative	negative
RSV-A	negative	negative
RSV-B	negative	**positive**

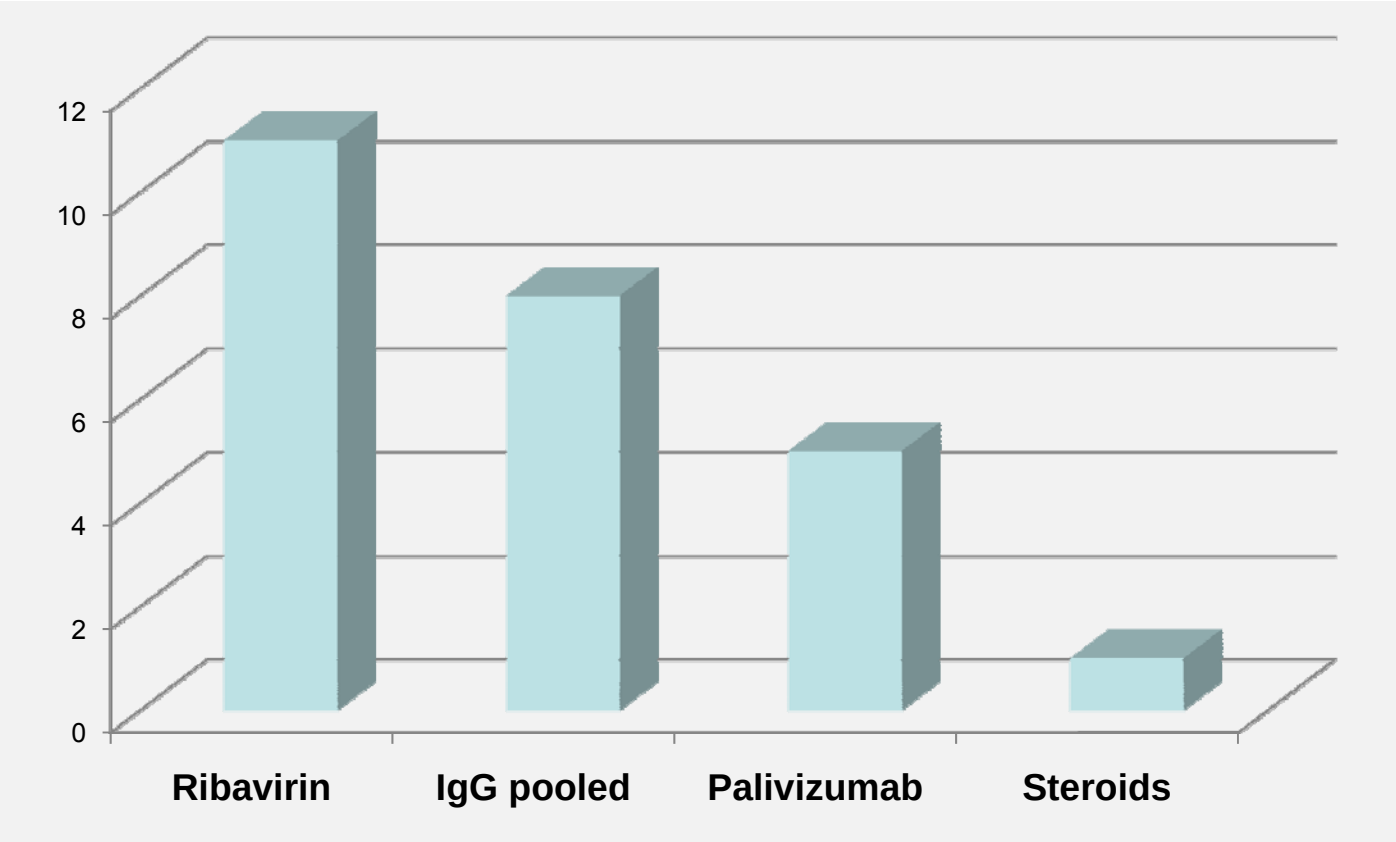
RSV pneumonia in an allogeneic HSCT patient recently transplanted: which treatment?

1. Ribavirin
2. Immunoglobulins
3. Ribavirin and immunoglobulins
4. Nothing
5. Don’t know

Immunoglobulins?

1. Substitution by conventional polyclonal immunoglobulins
2. Weight adapted specific anti-RSV IgG (palivizumab)
3. No immunoglobulins
4. I don't know

11 selected Swiss and international specialists: what would you use in case of RSV pneumonia in HSCT recipients?



RSV complications in Allo-HSCT recipients: conclusions

- Rate of progression from the upper to the lower respiratory tract
  - 0% to 60% (?), average ~ 30%
  - Higher when additional immunosupressive conditions are present
- Established RSV LRTI or pneumonia
  - High mortality rate, ≥ 30% (?)
- Respiratory dysfunction (?) *V Erard et al JID 2006*

Aerosolized ribavirin: HSCT patients treated early (« upper respiratory stage ») versus late

Risk of lower respiratory tract infection:

Treated early (n=44): 25% (n=11), 0-32%

Late treatment (n=116): 47% (n=54), 27-100%

P value < 0.01

Mortality:

Treated: 50% (28/56), 33-88%

Not treated: 89% (8/9), 50-100%

P value = 0.04

MCHUMOR.COM by T. McCracken

Full course of aerosolized ribavirin

- 6 gr aerosolized over 18 hours each 24 hours periodes over 10 days.
  - Adapted to real-life: 2g over 2h., 3 times/day

- Geneva: ~ 23’000.- for 5 days.

Intravenous or oral ribavirin

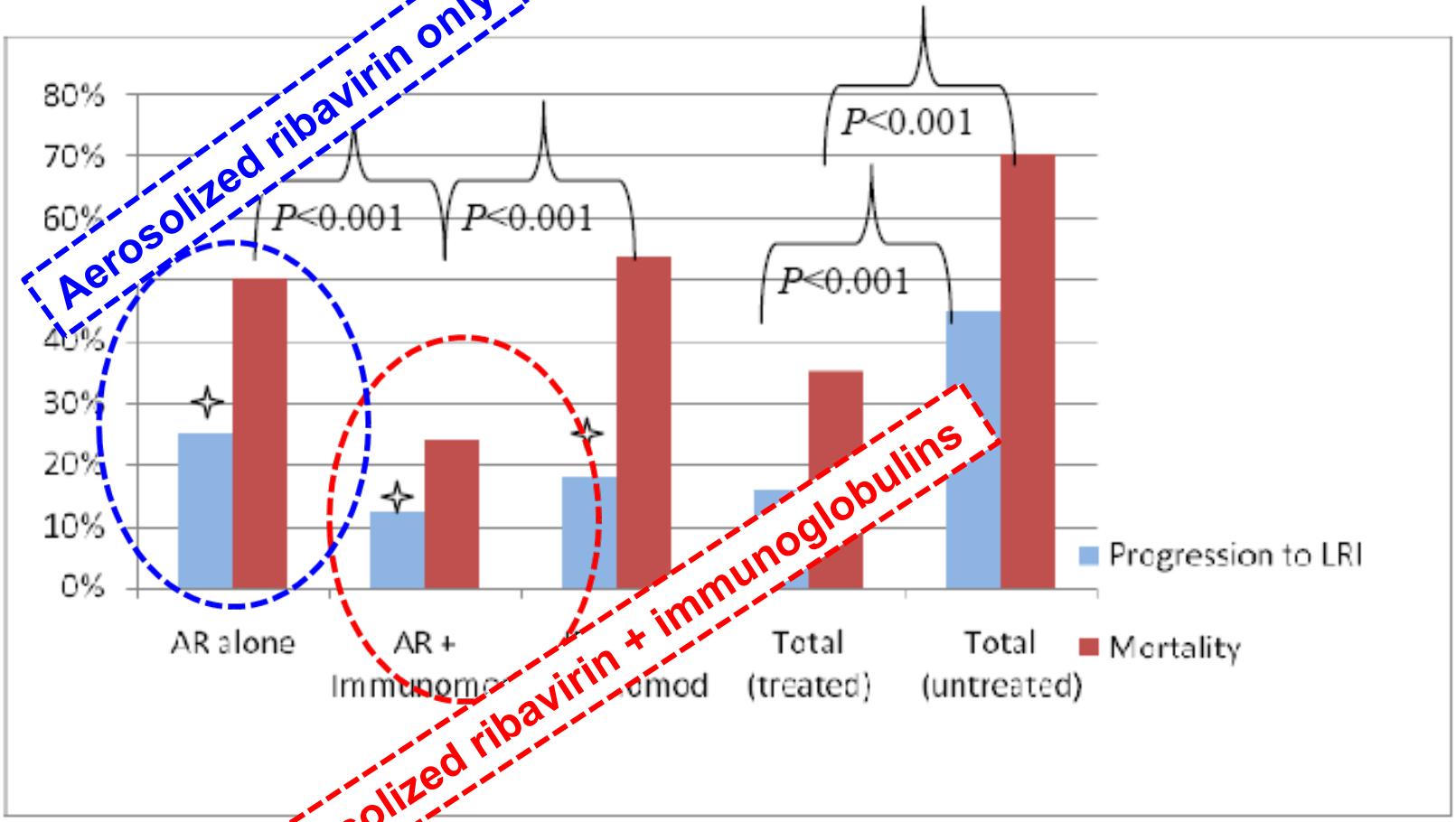
- iv: loading dose 35 mg/kg in 3 doses for one day then 25 mg/kg in 3 doses every 8 hours for 6 days. ~ 15'000.-

- Oral:15 to 20 mg/kg/day in 3 divided dose for 10 days. ~ 430.-

Biology of Blood and Marrow Transplantation 7:11S-15S (2001)
J Heart Lung Transplant 2009;28:67-71.

Palivizumab (?)
Humanized monoclonal antibody directed againts the RSV F protein

Figure: Summary of outcome data by type of regimen received

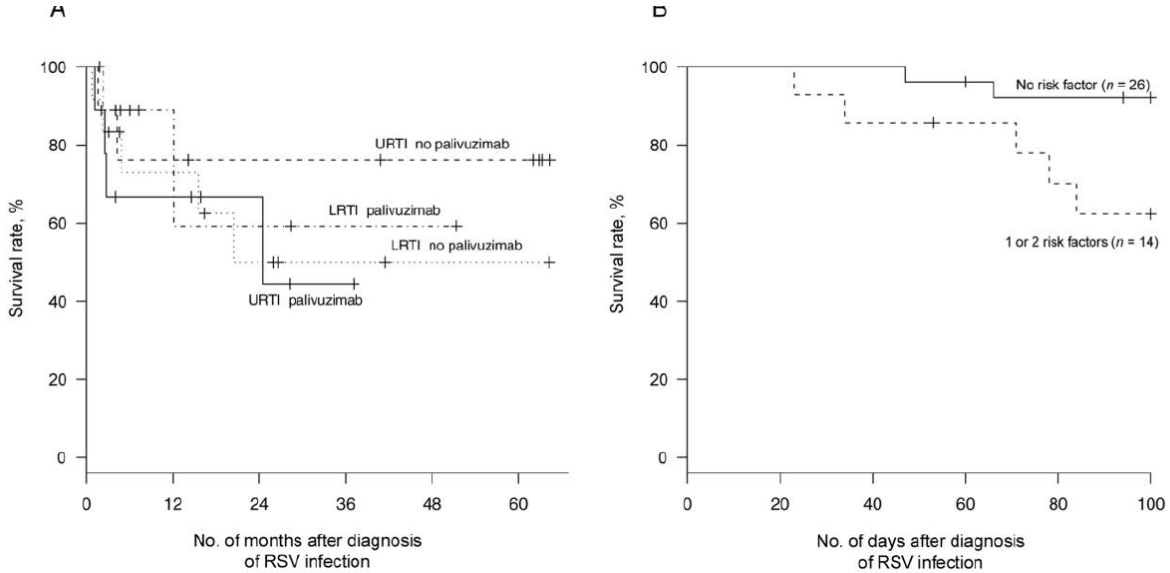


✧ For progression to LRI: AR alone vs. AR plus immunomodulators or IR or OR with or without immunomodulators; P=0.13.

Management of RSV infections in adult recipients of hematopoietic stem cell transplant: review of the literature

Jharna N. Shah and Roy F. Chemaly

Palivizumab in 40 Allo-HSCT recipients, Paris 1999-2006. F Sicre de Fontbrune et al. CID 2007:45:1019



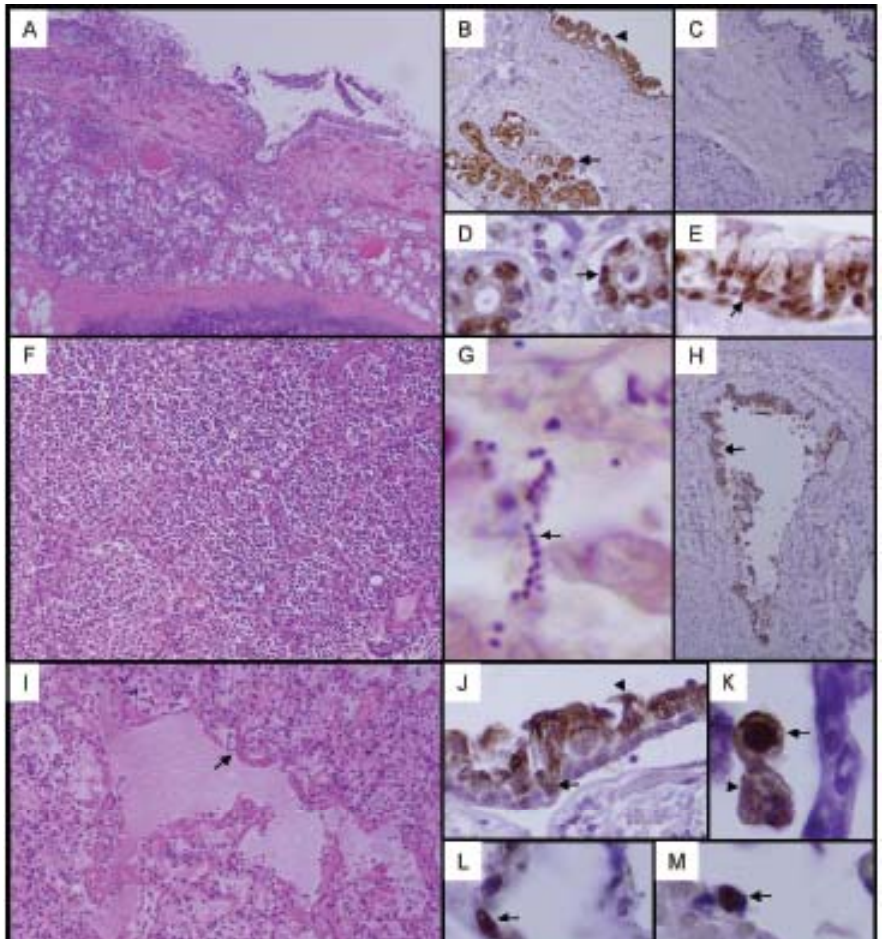
tract disease). Palivizumab did not prevent progression to lower respiratory infection and had no impact on the overall survival rate.

- Pooled IgG did not improve survival. Garret et al. *Biology of Blood and Marrow Transplantation 2001:7:11S-15S*
- Steroids: not supported by any published study.

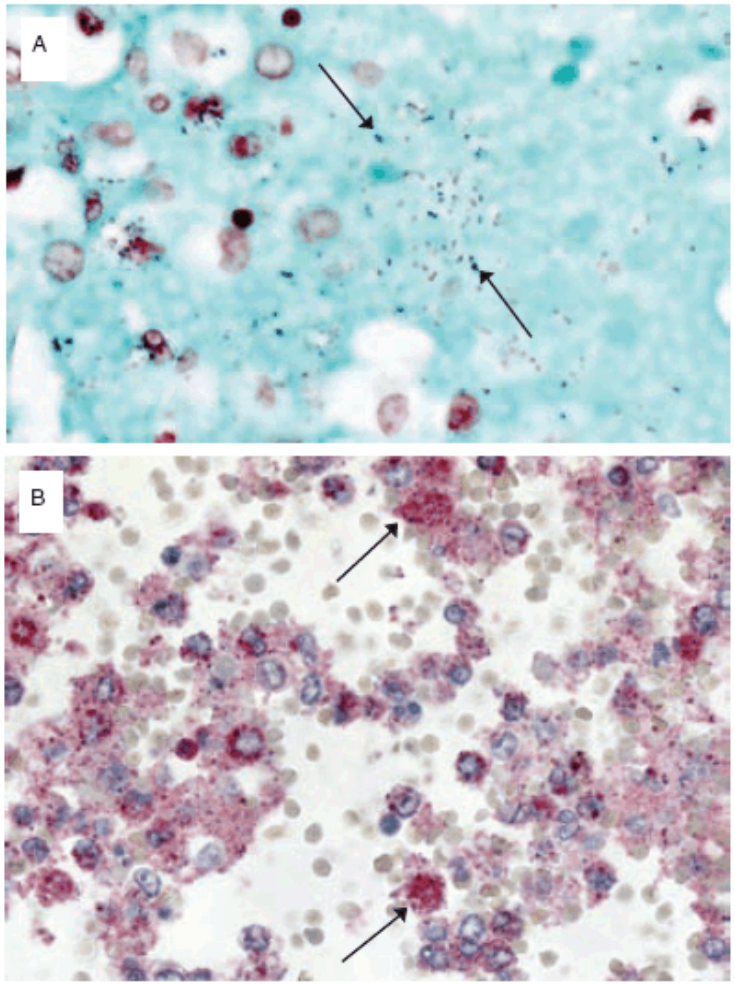
Palivizumab in HSCT: recommendations

- Palivizumab :
  - Evidence: insufficient to support a recommendation
  - Should generally not be used for treatment
- Consider only in highly selected cases
  - 15 mg/Kg for 3-4 weeks
  - Cost: ≥ 16’000.- for one injection

Could antiviral therapy prevent H1N1 complications?



Diffuse alveolar damage
Necrotizing bronchiolitis
Hemorrhagic component



Bacterial pneumonia: infrequent

Influenza A/H1N1 Viral Infection—Gill et al

Arch Pathol Lab Med—Vol 134, February 2010

Could antiviral therapy prevent complications?

- « No » randomized study that has explored the ability of oseltamivir to prevent hospitalizations and serious complications as a primary end-point
- Pooled/meta-analyis of existing randomized studies in which lower respiratory tract complications / antibiotic use / hospitalizations could be analyzed

Could antiviral therapy prevent complications?

- Meta-analysis (2000-2009): oseltamivir prevent lower respiratory tract complications « *Level of evidence: II or weak* »
- These studies were used to support WHO / CDC / and other National Guidelines

Retrospective or case series: oseltamivir in pandemic H1N1

- Early oseltamivir treatment associated with
  - Decreased risk of hospitalization
  - Decreased risk of pneumonia
  - Decreased risks of ICU or death in severely ill
    - Pregnant women: ICU admission and mortality
    - SOT recipients: hospitalization and ICU death
  - Decrease viral load

Cao et al., NEJM 9 Dec 09; Li et al., Chest 137:759, 2010; Yu et al., Options abst P-208; Kumar et al., Lancet ID 9 July 2010; Siston et al., JAMA 303:1517, 2010; Yang et al., J Infect 2010; Jain et al., NEJM 8 Oct 09

Virus respiratoires: conclusions

- Capacité « infinie » à persister et se transmettre dans l'espèce humaine (rhinovirus)
- Morbidité:
  - Du rhume à l'exacerbation de maladies pulmonaires chroniques.
  - PCR positive « = » symptômes.
  - Infections chroniques % transplantés.
- Stratégies diagnostiques et thérapeutiques réservées aux patients hospitalisés ou à risque
  - nombreuses incertitudes et limitations

Remerciements

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Influenza: Translating Basic Insights. Washington, DC December 2-4, 2010.
Poster #P1.35

HARVARD School of Public Health

Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of ten randomized clinical trials

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Models of Infectious Disease Agent Study
MIDAS

Center for Communicable Disease Dynamics

Background

Kaiser and colleagues (*Arch Int Med* 2003; 163:1667) found that oseltamivir reduces the risk of influenza-related lower respiratory tract complications requiring antibiotics by 55%. This conclusion has been questioned by a recent Cochrane review (Jefferson et al. *BMJ* 2009; 339:b5106).

After the appearance of the Cochrane review, we were approached by Roche and asked to perform an independent analysis of the data from the 10 trials in the Kaiser paper. We agreed to do so because we believed that the question of oseltamivir's effects was of considerable public health importance, particularly in the context of a recent influenza pandemic. The agreement specified that we receive complete access to the data from those trials, assistance from Roche statisticians in answering questions regarding the data, complete freedom to publish any results, without restriction by Roche. Neither we nor our institution received any funding for this work from Roche.

Methods

We re-analyzed the 10 placebo-controlled, double-blind randomized trials described by Kaiser et al. Eligibility criteria:
- Patients presented within 36 hours of symptom onset
- Fever ≥37.8°C if aged<65 years; ≥37.5°C if aged ≥65 years plus at least 1 respiratory symptom (cough, sore throat, or coryza) and 1 constitutional symptom (headache, myalgia, chills/sweats, or fatigue).

Patients were randomized to receive oseltamivir (75 mg twice daily) or placebo for 5 days.

Primary endpoint for our analysis: Lower respiratory tract complications (LRTC) requiring antibiotics (Abx). This was reconstructed retrospectively from the database.

Our approach had 3 key differences from that of Kaiser et al. (2003):
- Fixed effects meta-analysis of results from 10 trials (following a negative test for heterogeneity using the bootstrap Q statistic), rather than pooling the 10 trials. *Rationale*: both the distribution of risk factors for the outcome and the probability of assignment to oseltamivir varied across studies, possibly leading to confounding.
- Inclusion of all endpoints diagnosed during the first two days after randomization, rather than excluding the first two days. *Rationale*: consistent with classical intention to treat (ITT) analysis.
- Sensitivity analysis on those patients who deviated from protocol or withdrew from the study early, rather than excluding them. *Rationale*: consistent with classical ITT analysis.

Acknowledgments

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Disclosures

ML received consulting income in 2007-8 from the Avian/Pandemic Flu Registry, a project of Outcome Sciences (Cambridge, MA), which was sponsored by Roche. MH declares no conflict of interest. Neither the authors nor their institution received funding from Roche for this work.

Results

	Oseltamivir	Placebo	Meta-analytic Risk Ratio (95% CI)
N	1969	1501	
LRTC treated with antibiotics (LRTC-abx)	120	171	0.70 (0.56,0.88) p (heterogeneity)=0.26
LRTC-abx in first 2 days	28	21	
Confirmed influenza at baseline	1313	1033	
LRTC-abx among confirmed influenza	74	117	0.61 (0.47, 0.81) p (heterogeneity)=0.13
No confirmed influenza at baseline	656	468	
LRTC-abx among pts *without* confirmed influenza	46	34	1.05 (0.69,1.62) p (heterogeneity)=0.95

For LRTC in general, the risk ratio for oseltamivir versus placebo was 0.74 (0.60, 0.91; P-value for heterogeneity 0.17) in all patients, 0.69 (0.54, 0.88; P-value for heterogeneity 0.31) in influenza-infected patients, and 0.94 (0.63, 1.40; P-value for heterogeneity 0.92) in non-influenza-infected patients.

Had we performed a pooled analysis for the primary LRTC-Abx endpoint, we would have found RR=0.50 (0.38, 0.66). If we had further ignored events during the first 2 days of follow-up, the risk ratio would have been 0.45 (0.33, 0.61), reproducing the findings of Kaiser et al.

Sensitivity analyses showed modest impacts of loss to follow-up or noncompliance.

Conclusion

Our re-analysis confirms that oseltamivir reduces the risk of LRTC treated with antibiotics among patients with flu symptoms or with confirmed influenza. The 24-day risk reduction was about 30% overall and 40% in patients with influenza infection. No risk reduction was observed in patients without influenza. The effect estimates changed little even under unrealistic scenarios that classified a disproportionate number of missing outcomes as endpoints occurring in the oseltamivir group.