

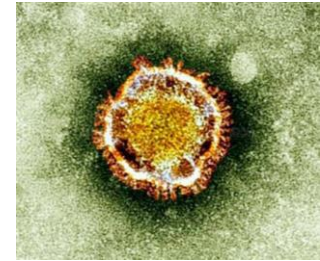
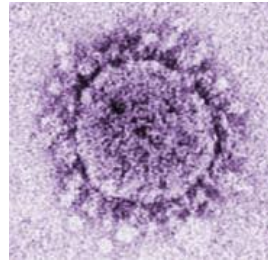


**JNI** 14<sup>es</sup> Journées  
Nationales  
d'Infectiologie

Du mercredi 12 au  
vendredi 14 juin 2013

Polydome, centre d'expositions  
et des congrès

Journée Nationale de Formation  
des infirmier(ère)s en infectiologie  
jeudi 13 juin 2013

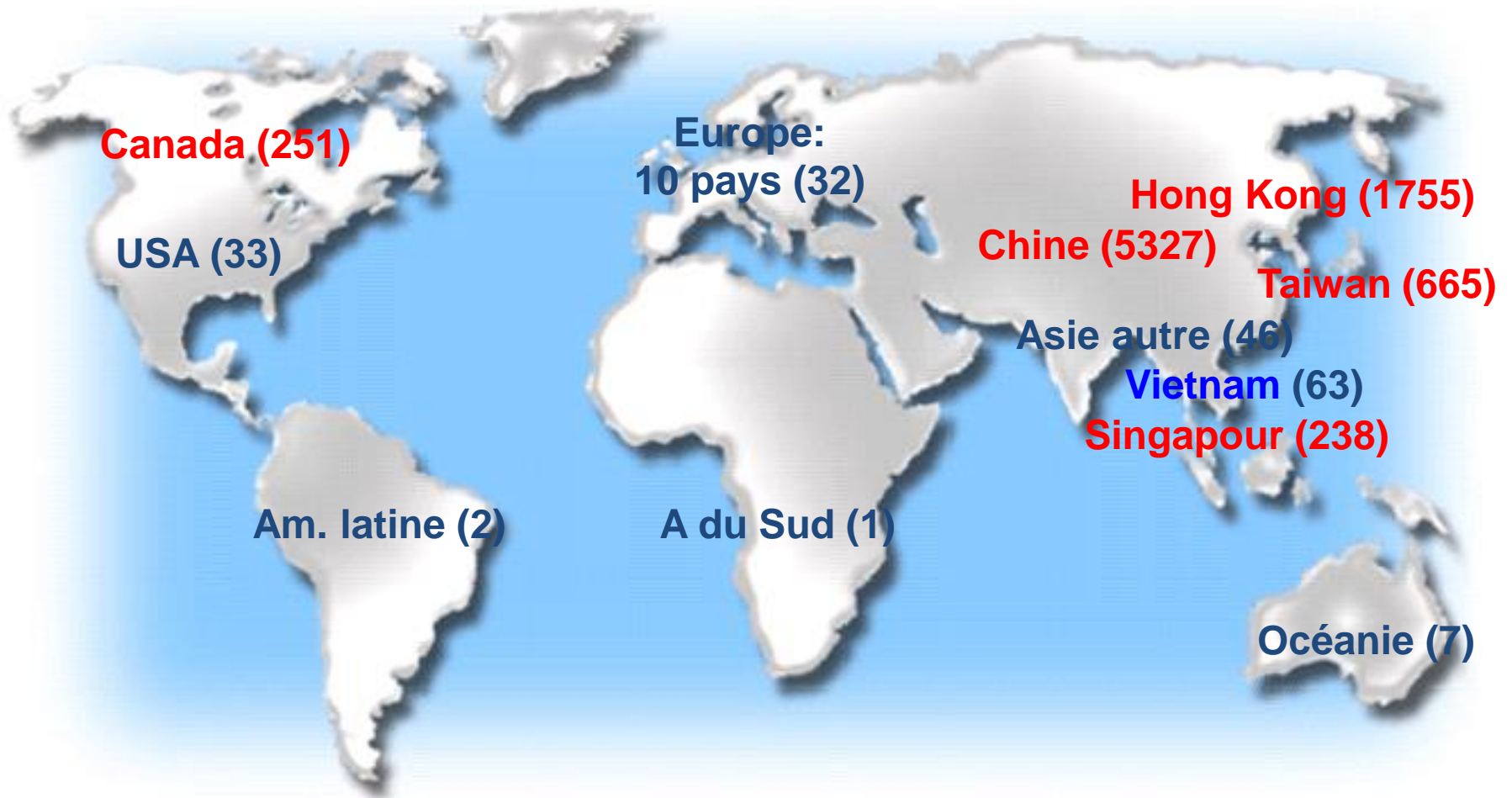
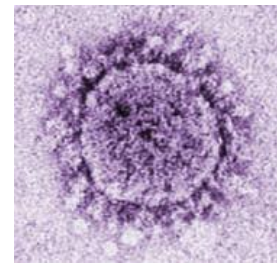


# Comparaison SARS et MERS-CoV

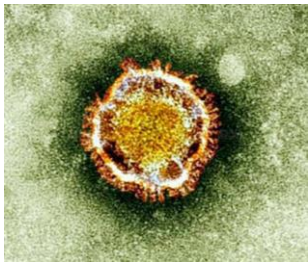
B. Guery  
Maladies Infectieuses  
CHRU Lille

**HISTORIQUE**

# SARS



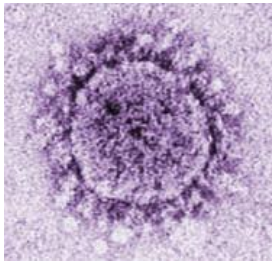
**8422 cas, 916 décès (11%)**



# MERS



**55cas, 31 décès (56%)**

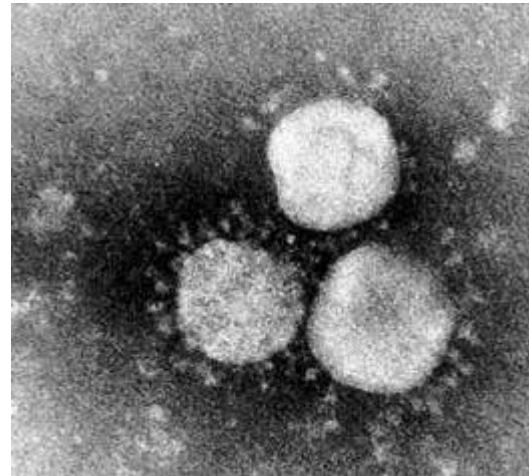


# Historique

- ✓ 16 novembre 2002: 305 cas de pneumonie, Guangdong.
- ✓ 21 février: Cas index, hôtel Métropole
- ✓ 26 février: Début épidémie à l'hôpital Français de Hanoi
- ✓ 12 mars: Alerte mondiale déclenchée par OMS
- ✓ 16 avril: SARS-CoV « authentifié »
- ✓ 5 juillet: Fin officielle de l'épidémie
- ✓ Signalement Avril 2012 WHO
- ✓ 13 Juin 2012: 1 cas en Arabie Saoudite
- ✓ Séquençage du nouveau coronavirus réalisé en Octobre 2012
- ✓ Cas confirmés
- ✓ Jordanie, Qatar, Arabie Saoudite, Emirats Arabes
- ✓ Angleterre, France, Allemagne, Italie, Tunisie
- ✓ .....

# CORONAVIRUS

- ✓ Isolé du poulet (1937)
- ✓ Virus ARN monocaténaire (27-32 kb)
- ✓ 100-150 nm
- ✓ Projections membranaires de 20 nm

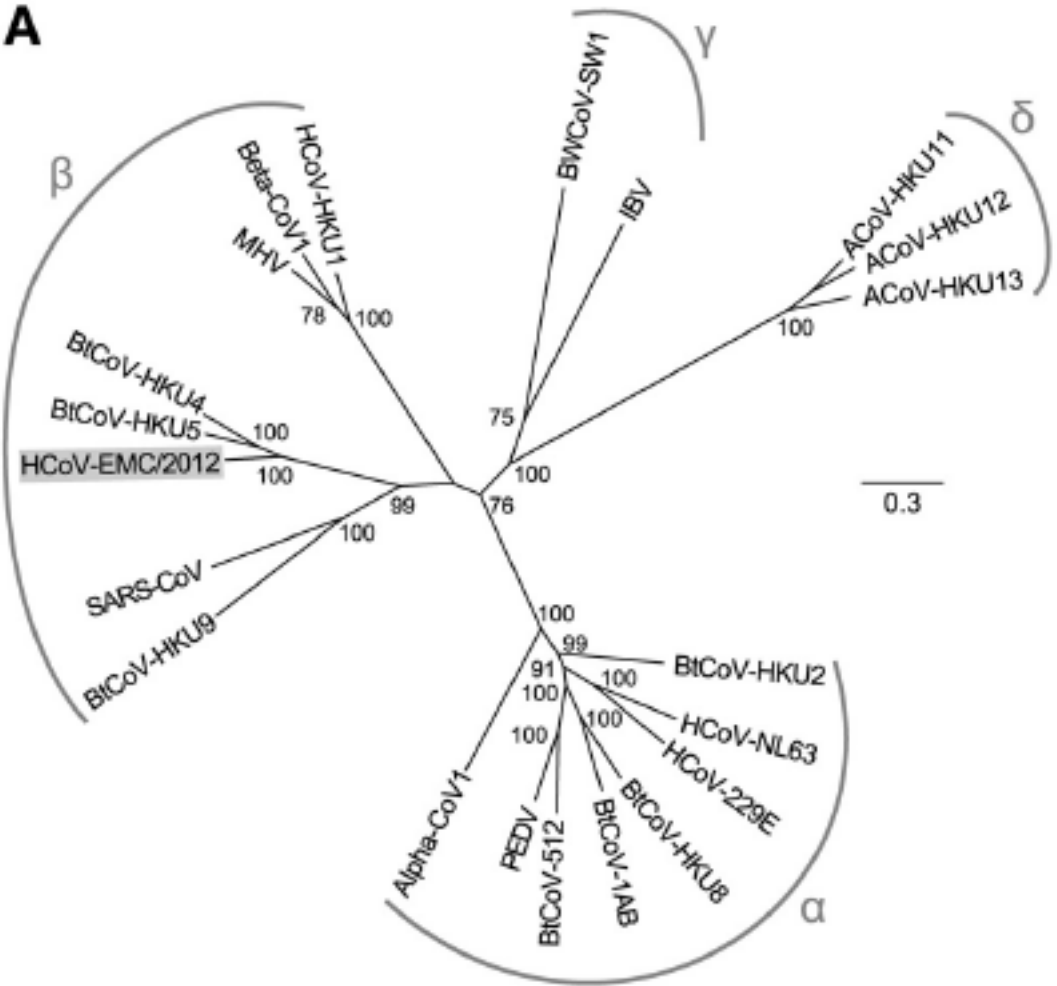




# Genomic Characterization of a Newly Discovered Coronavirus Associated with Acute Respiratory Distress Syndrome in Humans



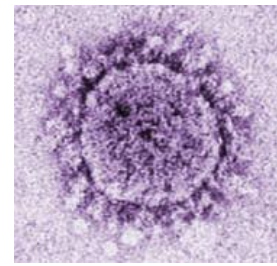
Sander van Boheemen,<sup>a</sup> Miranda de Graaf,<sup>a</sup> Chris Lauber,<sup>b</sup> Theo M. Bestebroer,<sup>a</sup> V. Stalin Raj,<sup>a</sup> Ali Moh Zaki,<sup>c</sup> Albert D. M. E. Osterhaus,<sup>a</sup> Bart L. Haagmans,<sup>a</sup> Alexander E. Gorbalenya,<sup>b,d</sup> Eric J. Snijder,<sup>b</sup> and Ron A. M. Fouchier<sup>a</sup>



**TRANSMISSION**



# SARS



## ✓ Gouttelettes

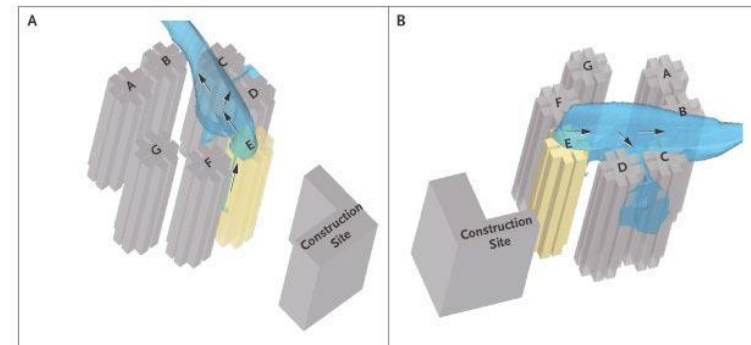
- Contact rapproché (soignants, famille,..)
- Dynamique de l'épidémie : 2.7 infections secondaires par cas au début de l'épidémie (Riley et al, Science)

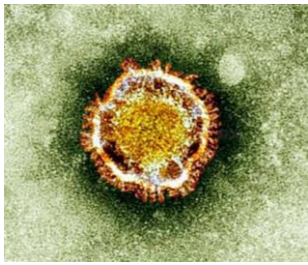


## ✓ Contact: Foyer Amoy Garden

- 321 résidents contaminés sur 15 blocs

## ✓ Air (Yu et al, N Engl J Med 2004)





# MERS

Estimation R0: 0.7-0.8

✓ **Renal transplantation immunosuppressed**

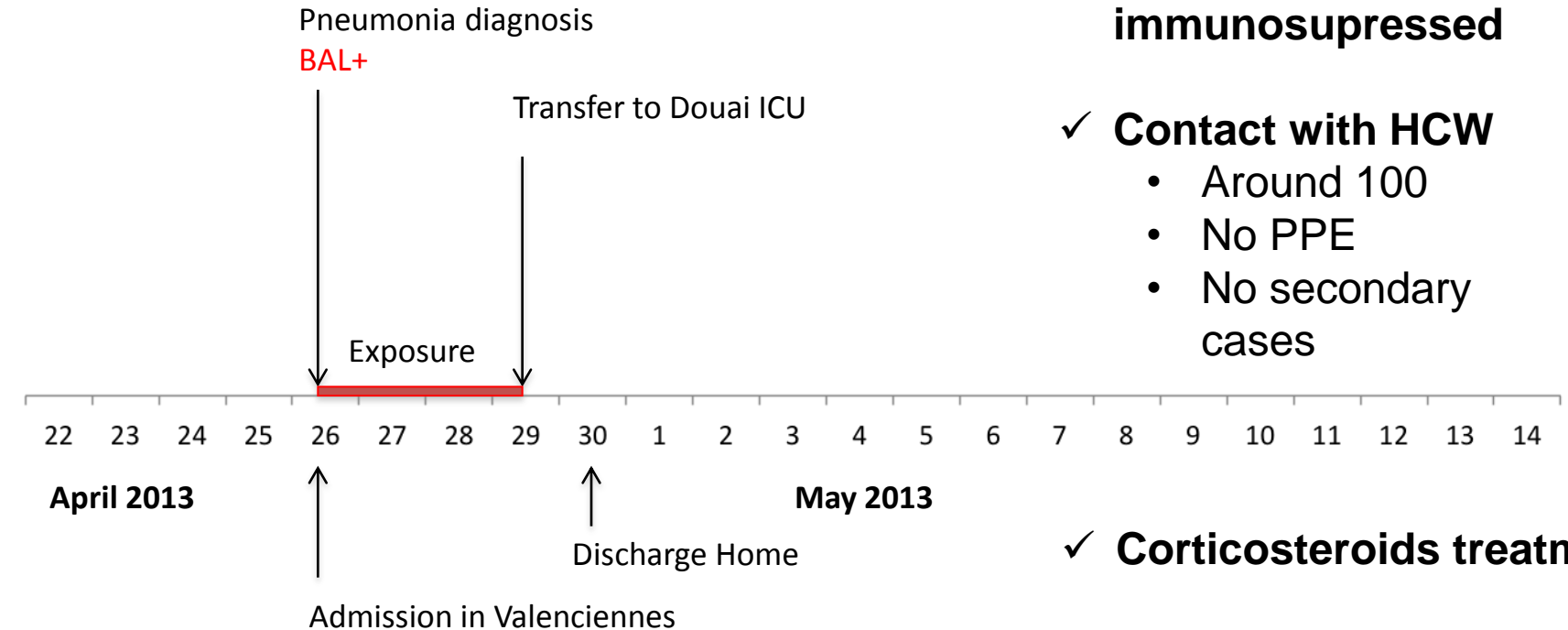
✓ **Contact with HCW**

- Around 100
- No PPE
- No secondary cases

✓ **Corticosteroids treatment**

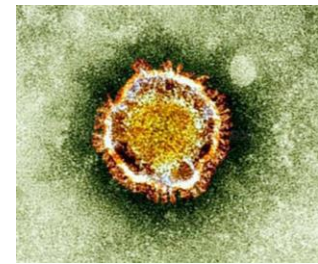
✓ **40 contacts (home)**

- No PPE
- No secondary cases



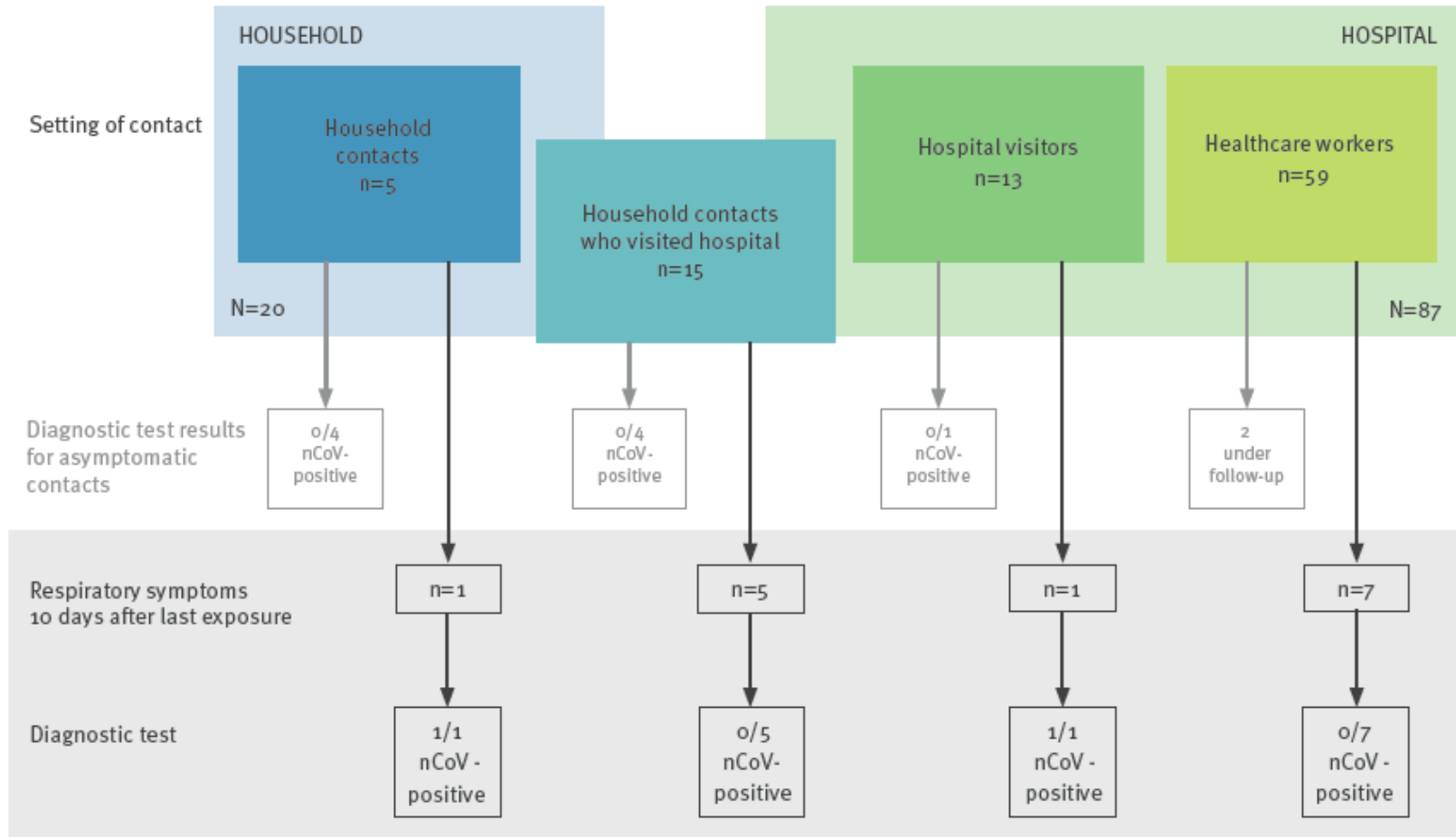
- ✓ The room was 20 m<sup>2</sup>, and 1.5 m separated the two patients' beds.
- ✓ Both patients shared the same bathroom.

# Evidence of person-to-person transmission within a family cluster of novel coronavirus infections, United Kingdom, February 2013

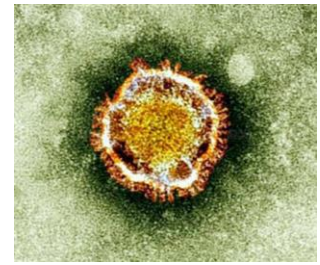


The Health Protection Agency (HPA) UK Novel Coronavirus Investigation team (Richard.Pebody@hpa.org.uk)<sup>1</sup>

1. The members of the team are listed at the end of the article

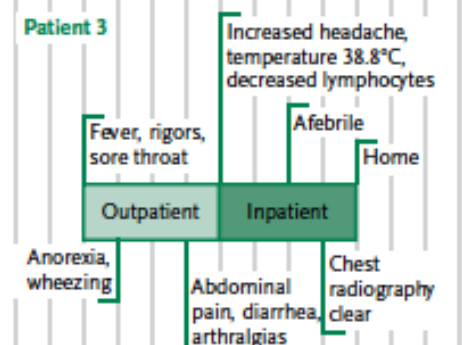
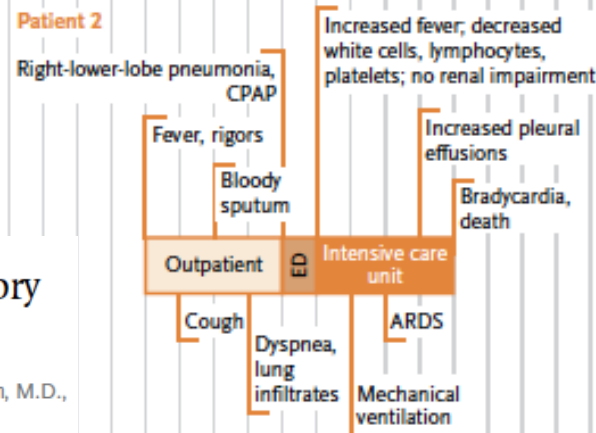
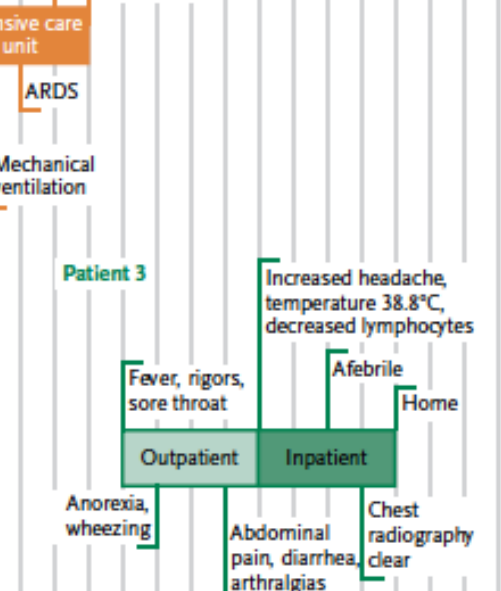
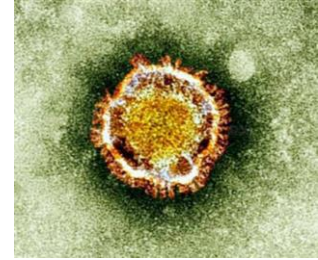
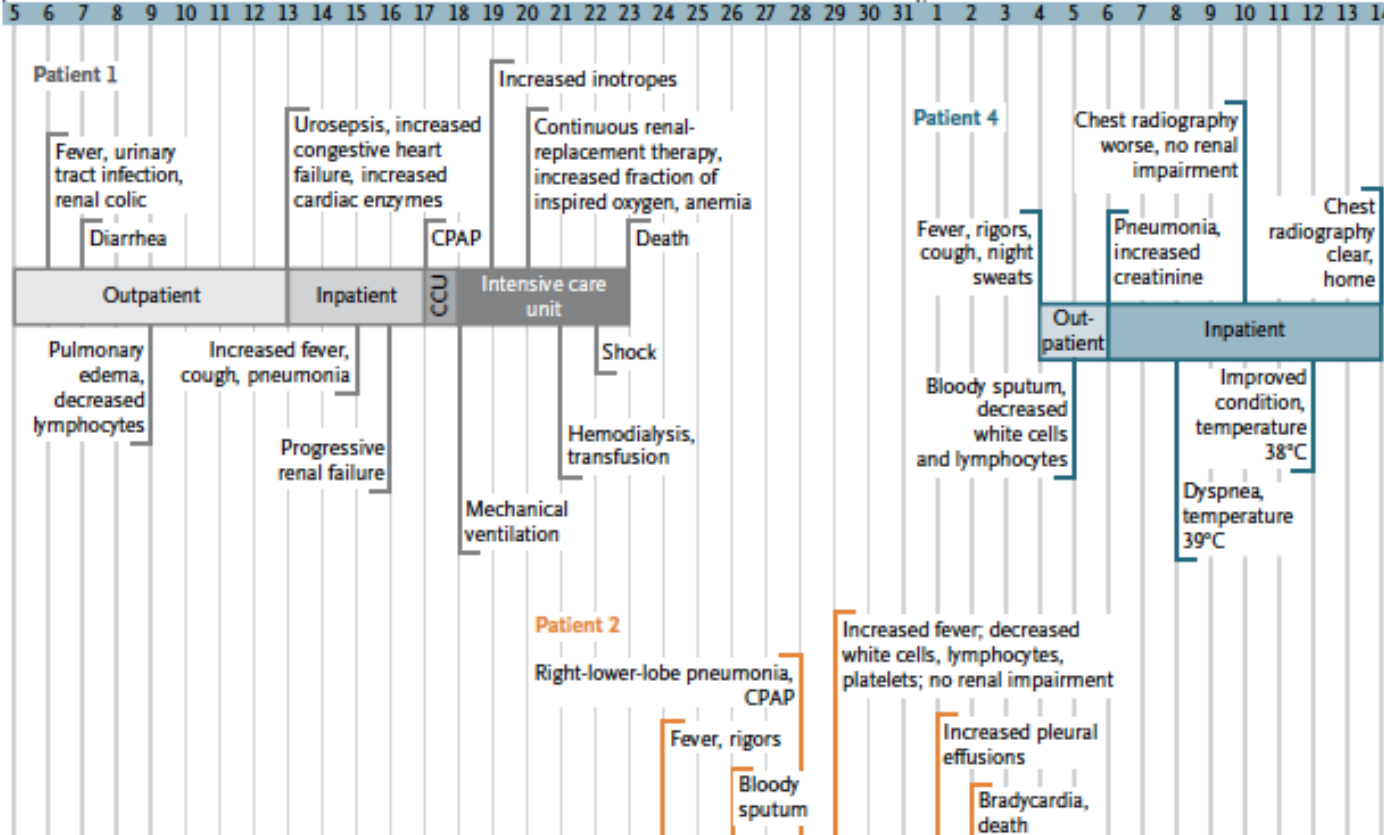


# Contact investigation of a case of human novel coronavirus infection treated in a German hospital, October-November 2012



U Buchholz (buchholzu@rki.de)<sup>1,2</sup>, M A Müller<sup>3,2</sup>, A Nitsche<sup>1,2</sup>, A Sanewski<sup>4,2</sup>, N Wevering<sup>5</sup>, T Bauer-Balci<sup>6</sup>, F Bonin<sup>5</sup>, C Drosten (drosten@virology-bonn.de)<sup>3</sup>, B Schweiger<sup>1</sup>, T Wolff<sup>1</sup>, D Muth<sup>3</sup>, B Meyer<sup>3</sup>, S Buda<sup>1</sup>, G Krause<sup>1</sup>, L Schaade<sup>1</sup>, W Haas<sup>1</sup>

- ✓ October 2012, ARDS transferred from Qatar to Germany.
- ✓ Late diagnosis on 20 November: 123 identified contacts
- ✓ 85: serological test
- ✓ 9 had performed aerosol-generating procedures using PPE rarely or never. Serology negative for all nine.
- ✓ 76 other hospital contacts negative,
- ✓ The contact investigation ruled out transmission to contacts after illness day 20.

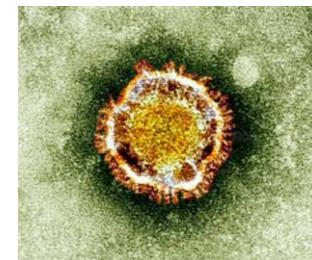


## Family Cluster of Middle East Respiratory Syndrome Coronavirus Infections

Ziad A. Memish, M.D., Alimuddin I. Zumla, M.D., Ph.D., Rafat F. Al-Hakeem, M.D., Abdullah A. Al-Rabeeh, M.D., and Gwen M. Stephens, M.D.

N Engl J Med 2013.  
DOI: 10.1056/NEJMoa1303729

# Family Cluster of Middle East Respiratory Syndrome Coronavirus Infections



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Abdullah A. Al-Rabeeh, M.D., and Gwen M. Stephens, M.D.

**Table 1.** Level of Contact among Family Members of Patients with MERS-CoV Infection before and after Hospital Admission.\*

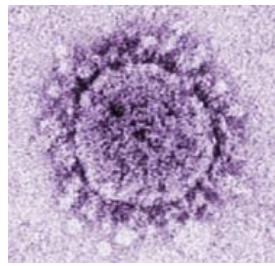
| Family Member     | Close Contact with Patient 1 before Admission | Close Contact with Patient 1 after Admission | Close Contact with Patient 2 before Admission | Close Contact with Patient 4 before Admission | Clinical Diagnosis of MERS-CoV Infection |
|-------------------|---|--|---|---|--|
| Wife of Patient 1 | Frequent                                      | No   | Infrequent                                    | Infrequent                                    | No                                       |
| Patient 2         | Frequent                                      | Frequent                                     | NA  | Frequent                                      | Yes                                      |
| Wife of Patient 2 | No  | No   | Frequent                                      | No  | No                                       |
| Patient 3         | Infrequent                                    | Infrequent                                   | Frequent                                      | Frequent                                      | Yes                                      |
| Patient 4         | Frequent                                      | Frequent                                     | Frequent                                      | NA  | Yes                                      |
| Wife of Patient 4 | No  | No   | No  | Frequent                                      | No                                       |

- ✓ Twenty-four other family members living in the same household and 124 attending staff members at the hospitals did not become ill.

**INCUBATION**



# Incubation

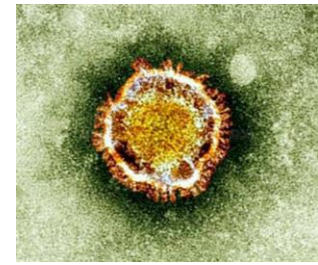


## ✓ SARS

- Toronto (144 patients): 6 jours (3 à 10) (Booth et al. JAMA 2003)
- Hong Kong (57 patients à contagé daté parmi 1425): 6,4 jours (Donnelly et al. Lancet 2003)
- En moyenne à 6 jours variant de 1 à 11 jours

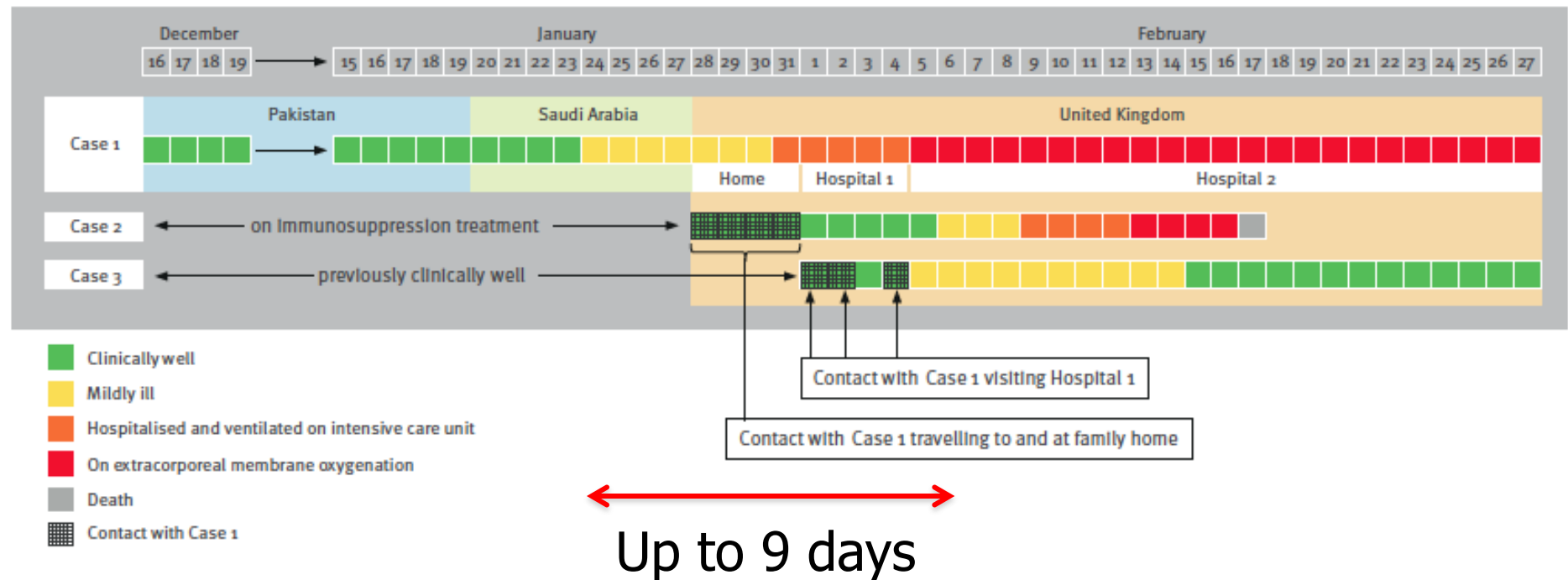


# Incubation

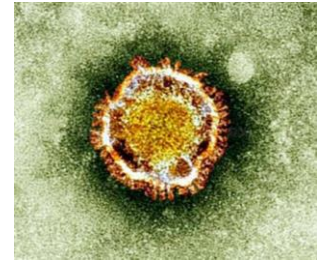


✓ MERS

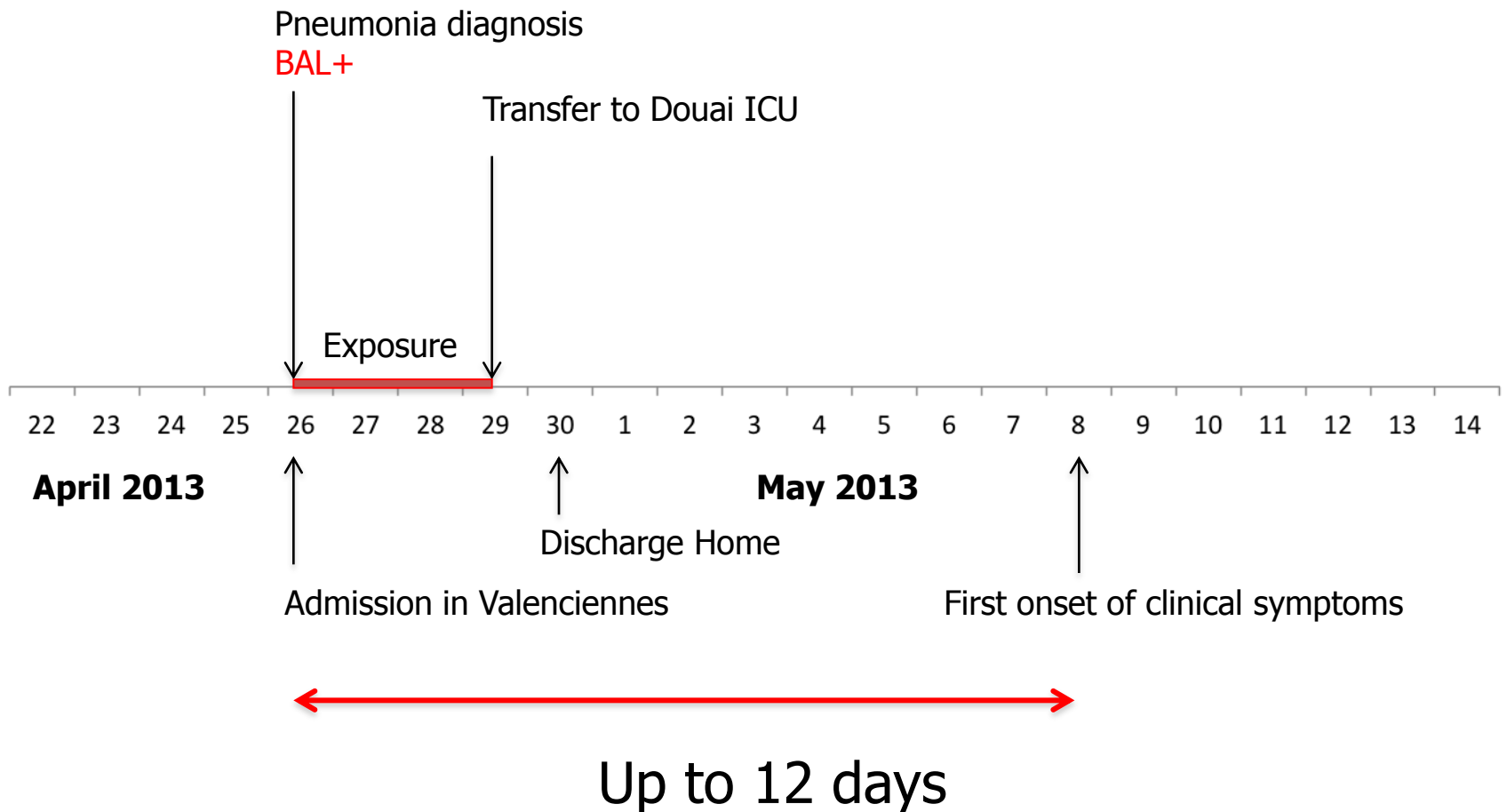
Timeline of three novel coronavirus cases, United Kingdom, December 2012 to February 2013



# Incubation

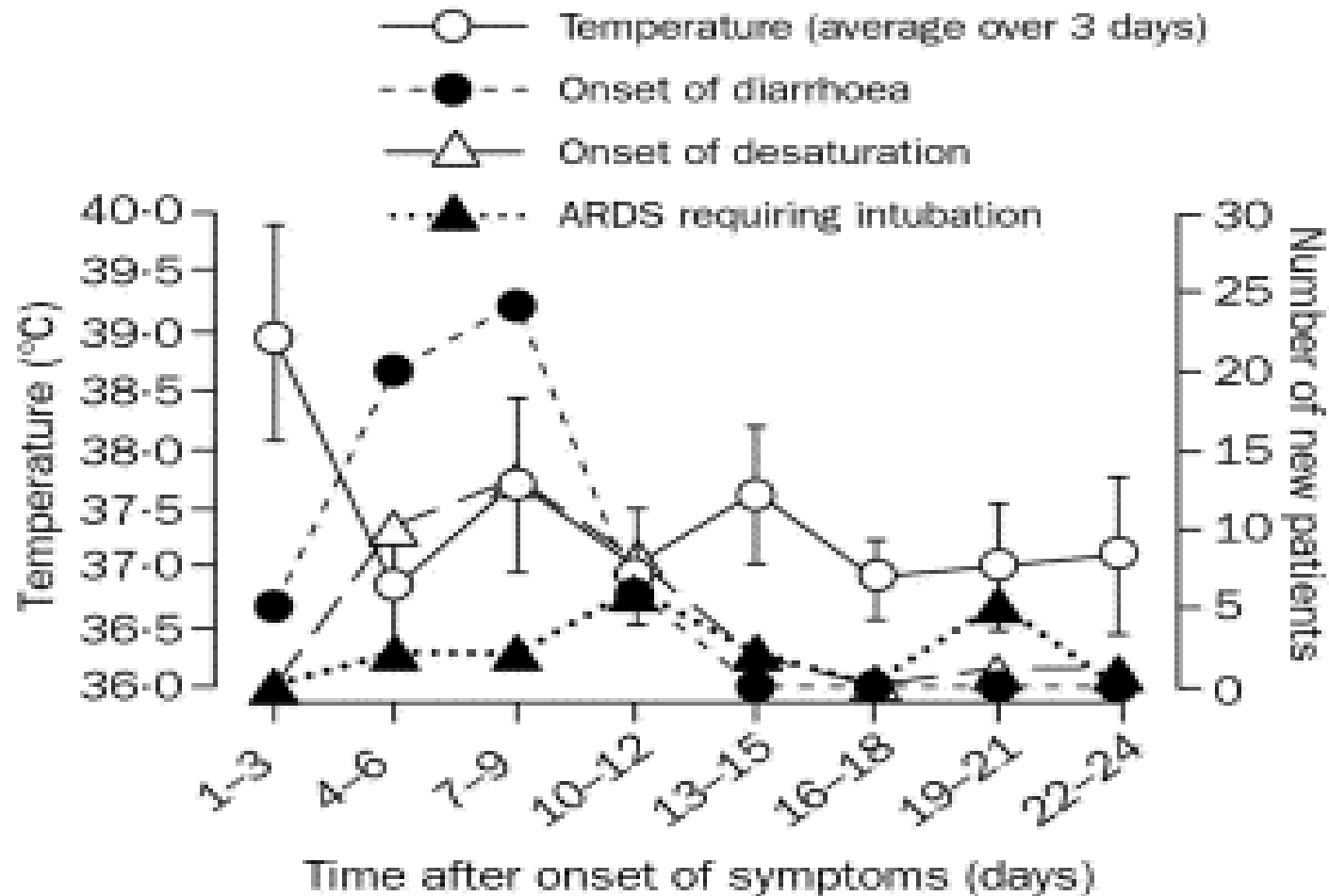
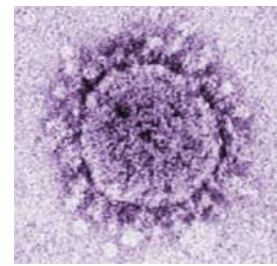


✓ MERS

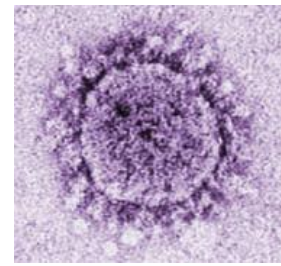


**CLINIQUE**

# SARS



# SARS

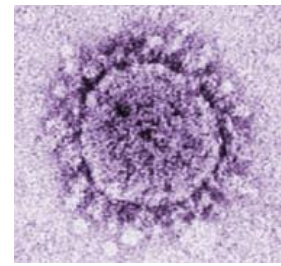


| <b>Signes Cliniques</b> | <i>Lee et al<br/>n= 138</i> | <i>Peiris et al<br/>n= 50</i> | <i>Donnelly et al<br/>n&gt;1250</i> | <i>Booth et al<br/>n= 144</i> |
|-------------------------|-----------------------------|-------------------------------|-------------------------------------|-------------------------------|
| <i>Fièvre</i>           | <b>100</b>                  | <b>100</b>                    | <b>94</b>                           | <b>99</b>                     |
| <i>Frissons</i>         | 73                          | 74                            | 65                                  | 28                            |
| <i>Toux</i>             | 57                          | 62                            | 50                                  | 69                            |
| <i>Myalgie</i>          | 61                          | 54                            | 51                                  | 49                            |
| <i>Malaise</i>          |                             | 50                            | 64                                  | 31                            |
| <i>Rhinorrhée</i>       | 23                          | 24                            | 25                                  | 2                             |
| <i>Pharyngite</i>       | 23                          | 20                            | 23                                  | 12                            |
| <i>Dyspnée</i>          |                             | 20                            | 31                                  |                               |
| <i>Diarrhée</i>         | 20                          | 10                            | 27                                  | 24                            |
| <i>Céphalées</i>        | 56                          | 20                            | 50                                  | 35                            |

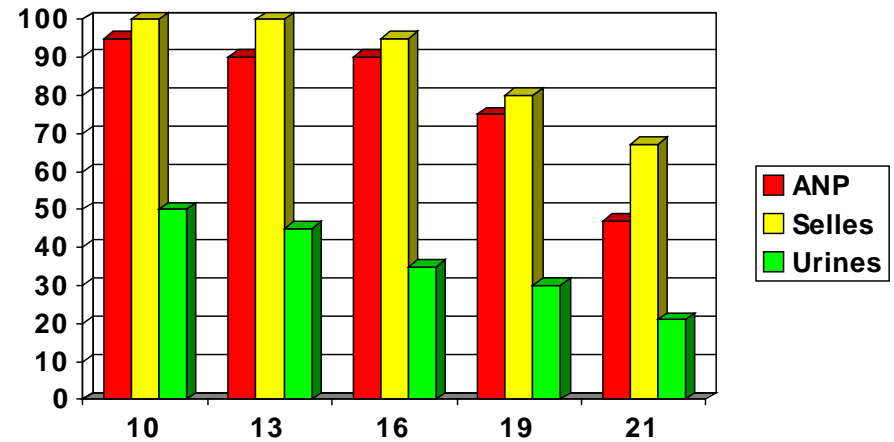
**EXCRETION VIRALE**



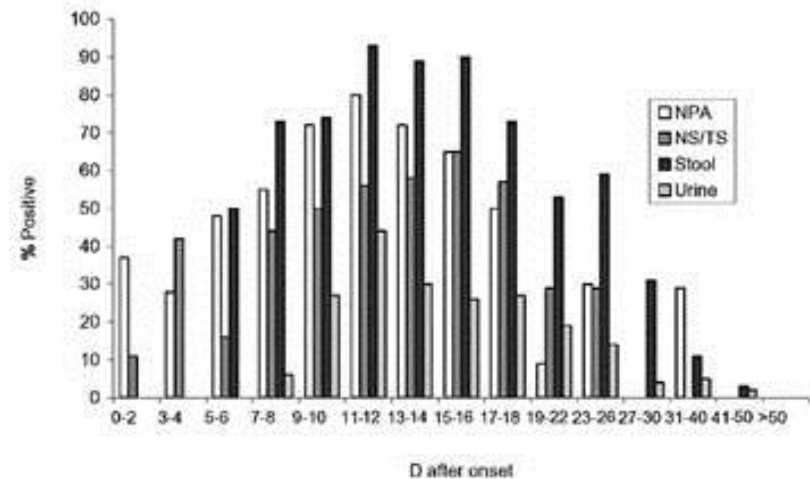
# SARS



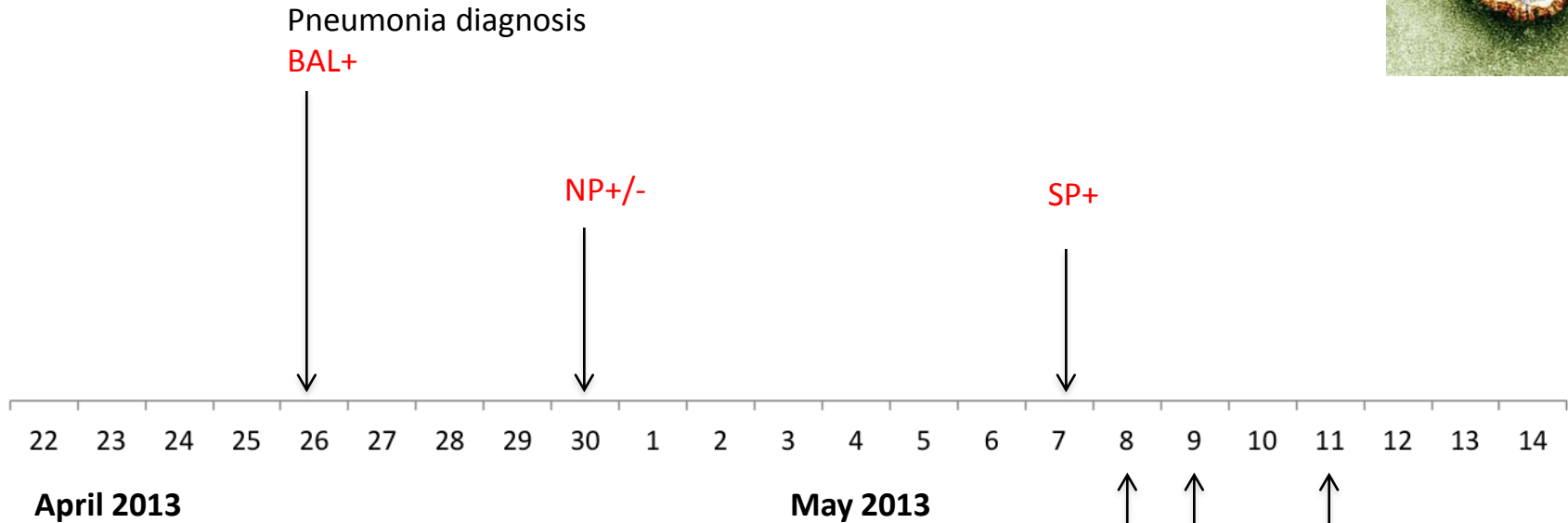
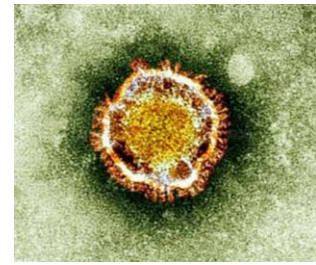
- ✓ Peiris, Lancet 2003 (n=75)
  - ARN coronavirus en RT-PCR: 32% à l'admission, et 68% à J14
    - Selles: 97%, 14,2 jours après le début des symptômes
  - Chez 20 patients à PCR positive à J1:



- ✓ Chan, EID 2004 (n=332)



# MERS



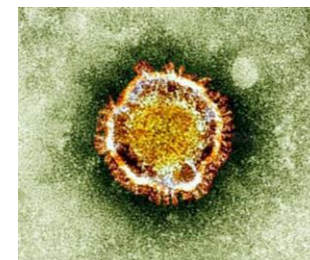
- ✓ For possible or suspect cases, especially when presenting **early after the onset of symptoms**, clinical samples from the LRT should be obtained for confirmation of infection.
- ✓ Confirmation of an initially negative result on another sample taken **a few days later** should be recommended before exclusion of possible cases.
- ✓ LRT > URT

First onset of clinical symptoms

SP+  
NP inc

Admitted for pneumonia  
In Lille Infectious Diseases  
NP+/-

# MERS



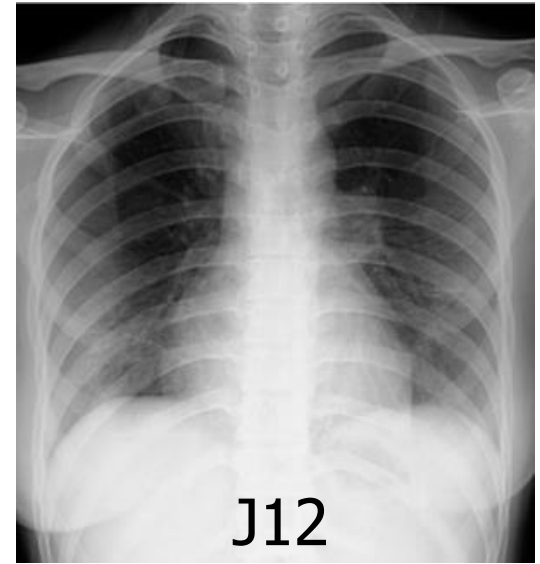
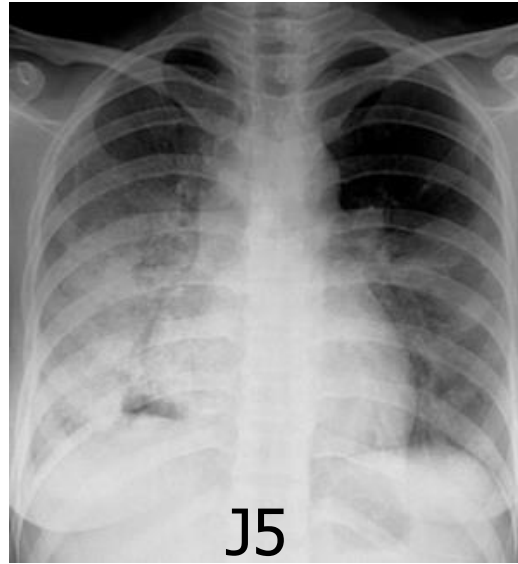
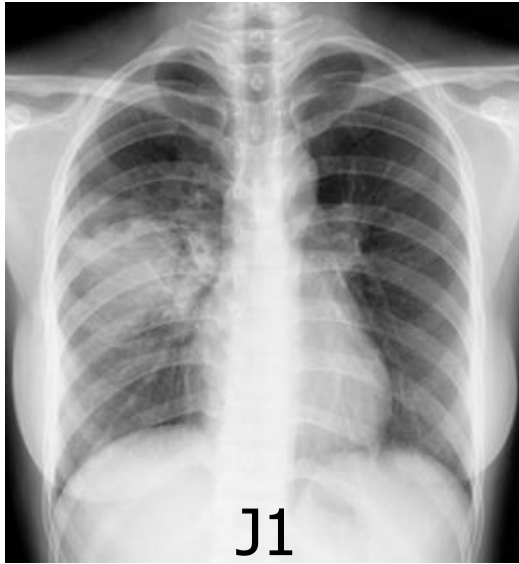
| Echantillon            | Date prelevement | Orf1a | UPE   |
|------------------------|------------------|-------|-------|
| Asp nasale et pharyngé | 30/04/2013       | 40    | 40    |
|                        |                  | 40    | 37,21 |
| Liq broncho alvéolaire | 26/04/2013       | 23,88 | 22,78 |
| Expectoration          | 07/05/2013       | 27,21 | 28,77 |
| sang total EDTA        |                  | 35,23 | 35,91 |
| urines                 | 14/05/2013       | 34,65 | 34,49 |
| trachéal               | 14/05/2013       | 25,5  | 24,17 |
| Plasma                 | 09/05/2013       | 38,78 | 40    |
| sang total EDTA        |                  | 28,85 | 28,1  |
| Pharyngé               | 14/05/2013       | 35,79 | 35,21 |
| sang total EDTA        |                  | 33,24 | 33,66 |
| urines                 | 16/05/13         | 35,72 | 35,78 |
| Pharyngé               | 16/05/13         | 34,76 | 34,71 |
| trachéal               | 16/05/13         | 28,26 | 26,67 |
| sang total EDTA        | 21/05/2013       | 32,07 | 29,18 |
| urines                 | 21/05/2013       | 33,26 | 31,73 |
| Pharyngé               | 21/05/2013       | 33,63 | 32,49 |
| Trachéal               | 21/05/2013       | 28,42 | 27,24 |
| Pharyngé               | 24/05/2013       | 40    | 40    |
| urines                 | 24/05/2013       | 38,1  | 37,42 |
| Trachéal               | 24/05/2013       | 35,31 | 34,49 |
| sang total EDTA        | 24/05/2013       | 31,81 | 31,73 |
| Trachéal               | 23/05/2013       | 36,03 | 36,52 |
| Pharyngé               | 23/05/2013       | 38,47 | 38,29 |
| urines                 | 23/05/2013       | 31,49 | 32,32 |

| Echantillon            | Date prelevement | Orf1a | UPE   |
|------------------------|------------------|-------|-------|
| Asp nasale et pharyngé | 09/05/2013       | 40    | 37,05 |
| crachat induit         |                  | 23,85 | 22,5  |
| ECB trachéal           | 14/05/2013       | 28,8  | 26,35 |
| Trachéal               | 17/05/2013       | 25,83 | 23,28 |
| Trachéal               | 20/05/2013       | 26,82 | 24,72 |
| Trachéal               | 24/05/2013       | 30,51 | 28,62 |
| Trachéal               | 23/05/2013       | 34,48 | 34,9  |
| Trachéal               | 31/05/2013       | 29,82 | 28,76 |
| Trachéal               | 03/06/2013       | 36,41 | 36,17 |
| urines                 | 03/06/2013       | neg   | neg   |
| selles                 | 03/06/2013       | neg   | neg   |

# ICONOGRAPHIE

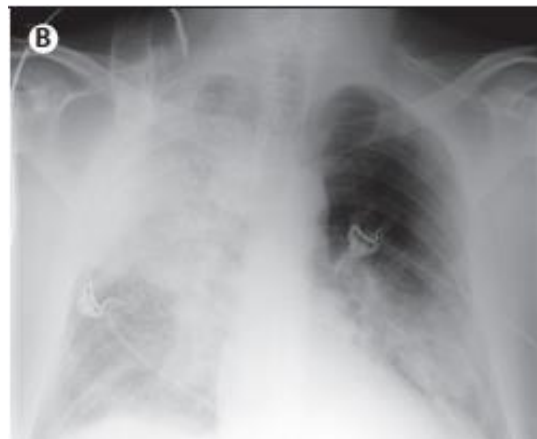
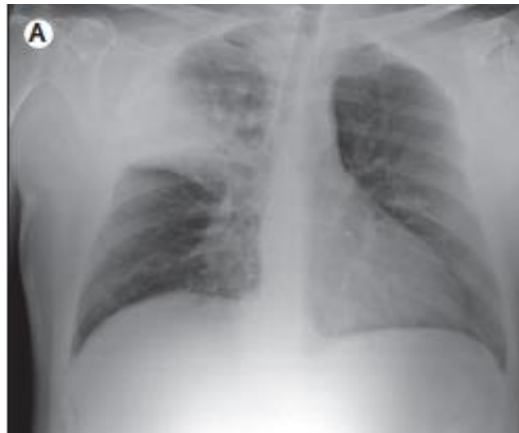
# Chest X Ray

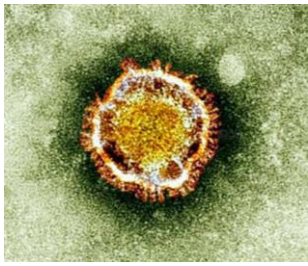
✓ SARS



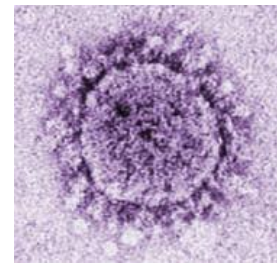
(Wong et al, Radiology 2003)

✓ MERS



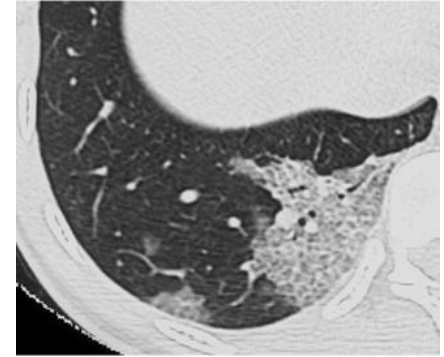


# CT Scan of the lungs



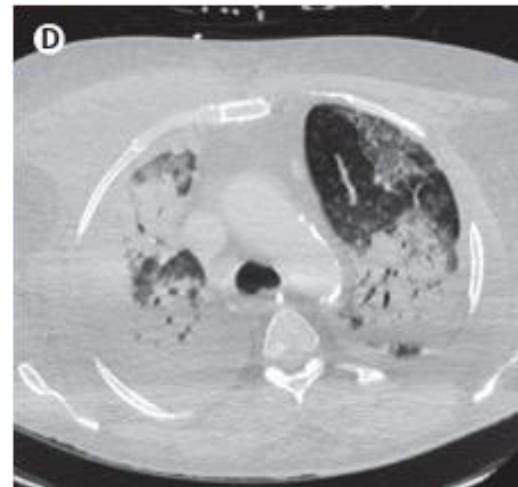
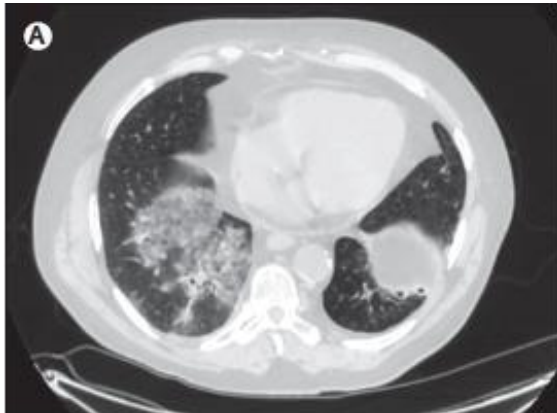
## ✓ SARS

- 24 patients
- Anomalies parenchymateuses 96%
- Aspect de fibrose pulmonaire chez 15/24 (62%)



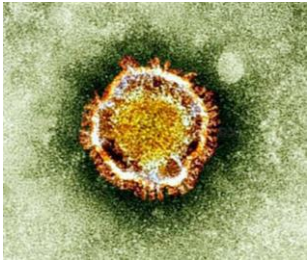
Antonio et al, Radiology 2003

## ✓ MERS

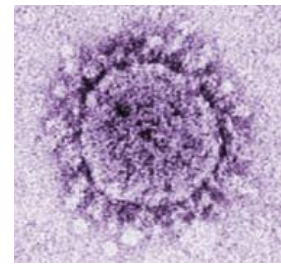


**THERAPEUTIQUE**





# Ventilation



## ✓ SARS

- ARDS
- Pneumothorax (Gommersall et al, Int Care Med 2004)

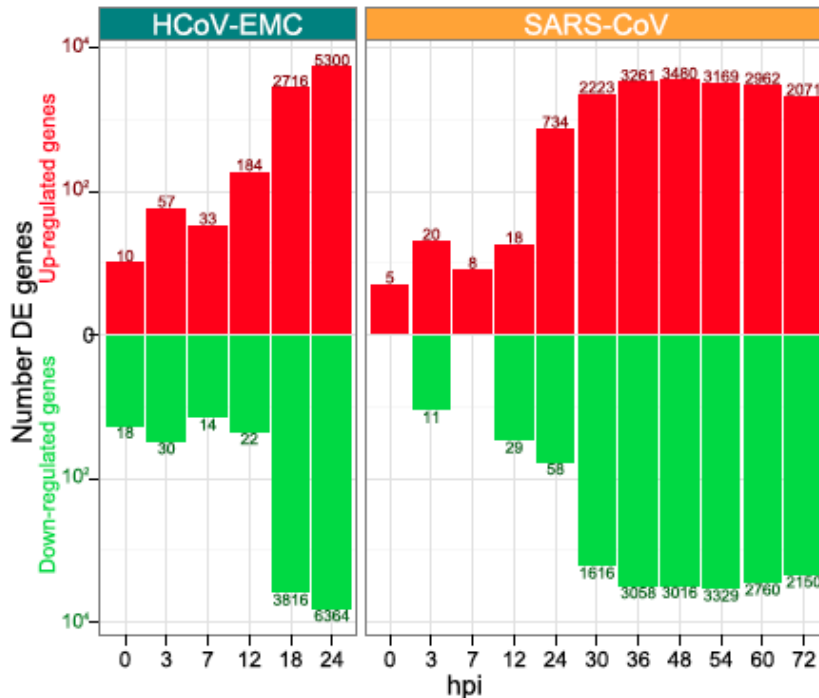
## ✓ MERS

- Compliance conservée avec altération majeure de l'oxygénation
- Indication plus précoce de l'ECMO?



# Cell Host Response to Infection with Novel Human Coronavirus EMC Predicts Potential Antivirals and Important Differences with SARS Coronavirus

Laurence Josset,<sup>a</sup> Vineet D. Menachery,<sup>b,c</sup> Lisa E. Gralinski,<sup>b,c</sup> Sudhakar Agnihothram,<sup>b,c</sup> Pavel Sova,<sup>a</sup> Victoria S. Carter,<sup>a</sup> Boyd L. Yount,<sup>b,c</sup> Rachel L. Graham,<sup>b,c</sup> Ralph S. Baric,<sup>b,c</sup> Michael G. Katze<sup>a</sup>



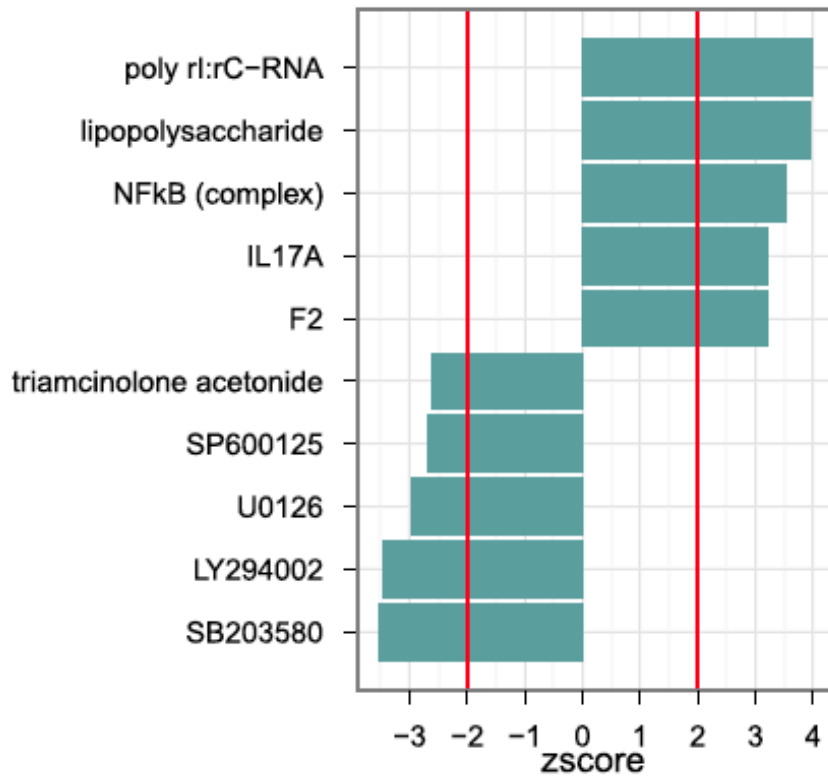
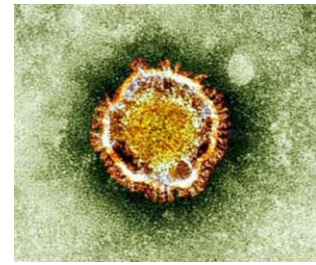
- ✓ HCoV-EMC infection, with 6,532 DE genes at 18 hpi and 11,664 genes at 24 hpi
- ✓ SARS-CoV induced changes of only 792 genes at 24 hpi with maximum changes at 48 and 54 hpi of 6,496 and 6,498 genes,



- ✓ HCoVEMC induced drastic changes in the host transcriptome with 12,392 DE genes at 18 hpi and/or 24 hpi

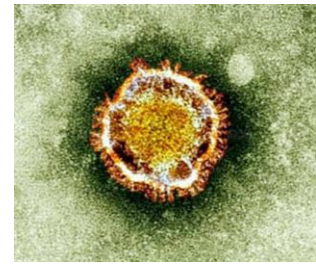
# Cell Host Response to Infection with Novel Human Coronavirus EMC Predicts Potential Antivirals and Important Differences with SARS Coronavirus

Laurence Josset,<sup>a</sup> Vineet D. Menachery,<sup>b,c</sup> Lisa E. Gralinski,<sup>b,c</sup> Sudhakar Agnihothram,<sup>b,c</sup> Pavel Sova,<sup>a</sup> Victoria S. Carter,<sup>a</sup> Boyd L. Yount,<sup>b,c</sup> Rachel L. Graham,<sup>b,c</sup> Ralph S. Baric,<sup>b,c</sup> Michael G. Katze<sup>a</sup>



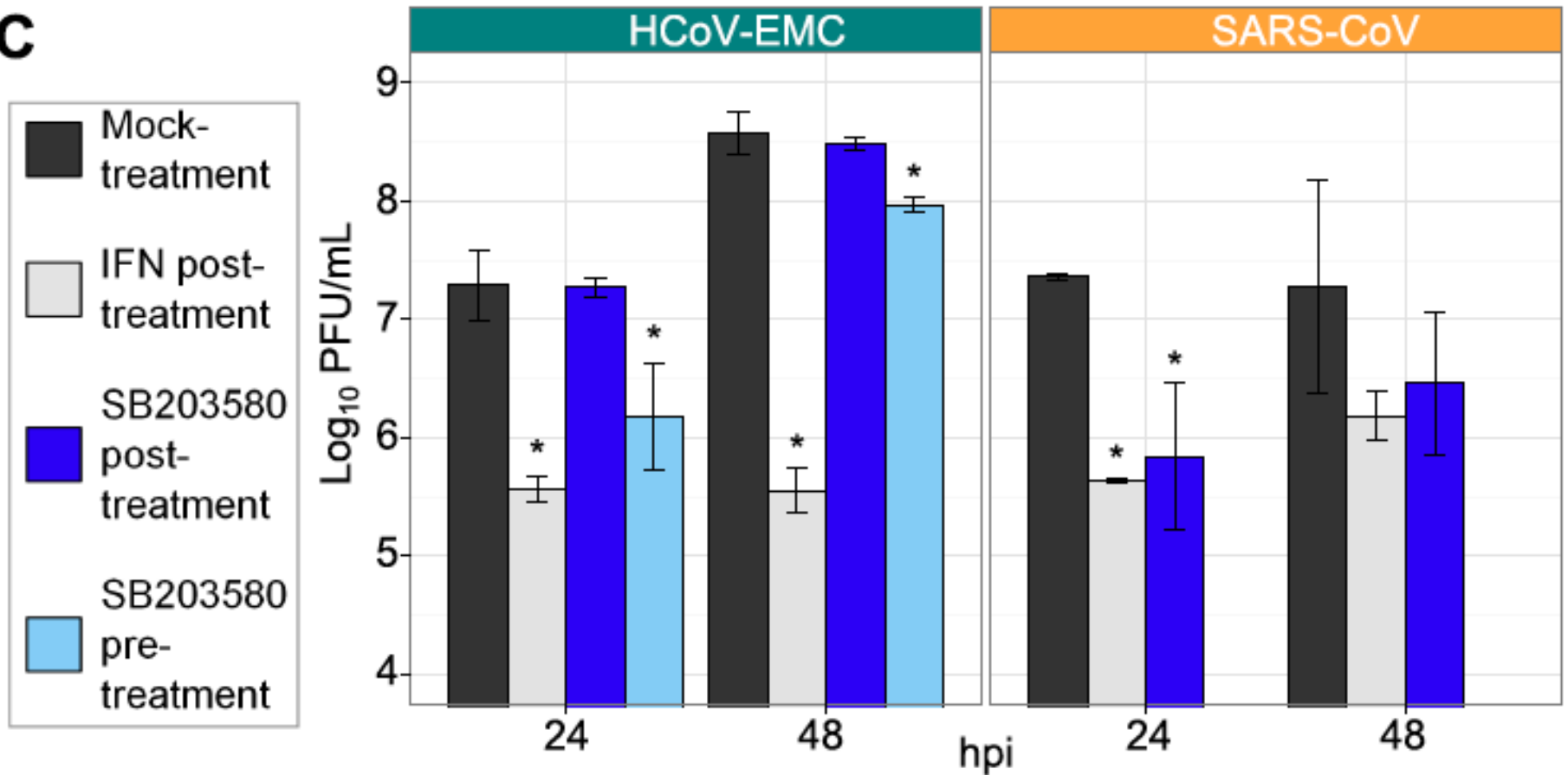
- ✓ Top 5 activated upstream regulators and top 5 inhibited upstream regulators of the early signature.
- ✓ The prediction of activation state is based on the global direction of changes of the 207 genes throughout infection with HCoV-EMC.
- ✓ Red lines depict the limit of significance

# Cell Host Response to Infection with Novel Human Coronavirus EMC Predicts Potential Antivirals and Important Differences with SARS Coronavirus



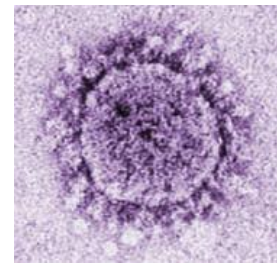
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**C**



SB203580, an inhibitor of p38 MAPK,

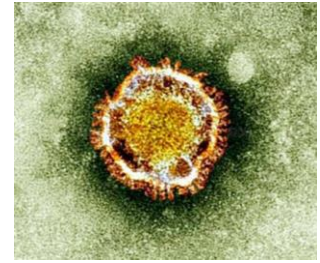
# SARS



- ✓ Corticoïdes: Modulation de la réponse inflammatoire
  - Patients en aggravation secondaire
  - Bolus si SDRA
- ✓ Lopinavir-Ritonavir
  - A 30j, moins de DC ou SDRA à 21 J (2,4 vs 28,8%) (*Chu et al, Thorax, 2004*)
- ✓ Plasma convalescent-Immunoglobulines (*HK Med J 2003*)
- ✓ Chloroquine (*Davidson et al, Curr Op Inf Dis 2003*)
- ✓ Glycyrrhizin: bon effet in vitro, non toxique, mécanisme inconnu
- ✓ Interféron
  - Interféron alpha pégylé (*Nature Medicine 2004*)
  - Interféron alfacon-1+corticoïdes



# MERS



## ✓ Antiviral activity

- Ribavirin
- Lopinavir
- Interferon
- Cyclosporin A
- Associations
- Protease inhibition
- Monoclonal antibodies

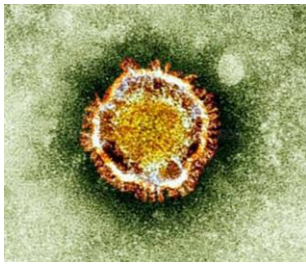
## ✓ Host response modulation

- Immunoglobulins/convalescent plasma
- Glucocorticoids
- Kinase inhibitors

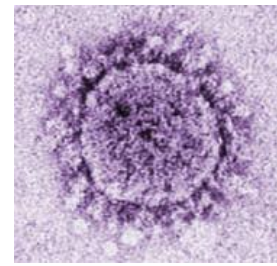
# MERS: Food for thoughts

- ✓ Compare Ribavirin+IFN vs either Riba or IFN alone
  - Ribavirin 10mg/kg/8h IV
  - IFN  $\alpha$ 2b 5 M IU/kg/16h SC or PEG-IFN
- ✓ Monoclonal antibodies: Dutch and English
- ✓ Convalescent plasma if available
- ✓ Consider may be steroids very early in the disease as well as cyclosporin
  - based on the host response profile
  - Associated to IFN for replication?





# Les leçons du SARS



- ✓ Nous sommes vulnérables
  
- ✓ Mots clés:
  - Coopération
  - Communication en temps réel
  - Planification internationale & nationale
  - Prévention
  - Eveil de la communauté médicale et infectiologique
  - Systèmes d'alerte sensibles mais les plus spécifiques possibles
  - Réponse coordonnée et rapide

- ✓ CH Valenciennes
  - N. Ettahar, Didier Caparros, Laurence Vrigneaud, Delphine Labatut, Thomas Quemeneur, Anne-Adélaïde Cracco
- ✓ CH Douai
  - Loubna El Mansouf, Xavier Lemaire, Caroline Séjourné, Claire Boule, Anne Guaguere, Chloé Rousselin, Eric Lefebvre, Philippe Morel, Benjamin Kowalski, Thierry Coppin, Sylvie Hendricx
- ✓ Maladies Infectieuses Lille/Tourcoing
  - Benoit Guery, Fanny Vuotto, Karine Faure, Eric Senneville, Hugues Melliez
- ✓ Virologie Lille
  - Anne Goffard
- ✓ SAMU
  - Roch Joly, Patrick Goldstein
- ✓ CCV Lille
  - André Vincentelli, Natacha Rousse
- ✓ Réanimation Lille
  - Julien Poissy, Daniel Mathieu, Raphael Favory, Aurore Palud, Erika Parmentier-Decrucq, Marie Kauv
- ✓ CNR
  - Sylvie van der Werf, Sylvie Behillil, Vincent Enouf, Mathilde Benassaya, David Briand, Marie Lazzerini, Clio Socratous
- ✓ CIBU
  - Jean Claude Manuguerra, Valérie Caro, Frédéric Fichenick
- ✓ Antenne Régionale CCLIN
  - Karine Blanckaert
- ✓ InVS
  - Alexandra Mailles, Didier Che
- ✓ InVS Lille
  - Pascal Chaud, Marie-Claire Paty
- ✓ ARS, Nord Pas de Calais
  - Jean-Philippe Legendre, and Sandrine Segovia-Kueny, Daniel Lenoir