Relevant knowledge of coronaviruses before the COVID-19 pandemic: virology and vaccines

Bart Haagmans, Viroscience department, Erasmus MC, Rotterdam
Coronaviruses are found in many different animal species and humans

- 4 human CoVs normally cause a common cold
  - HCoV-NL63
  - HCoV-229E
  - HCoV-OC43
  - HCoV-HKU-1
- 2 zoonotic CoVs cause severe respiratory infections
  - SARS-CoV
  - MERS-CoV

_Corman et al., Adv Virus Res. 2018_
Bat CoV SHC014 replicates to similar titers compared to SARS-CoV

(Menachery et al., Nat Med 2015)
The species *Severe acute respiratory syndrome-related coronavirus*: classifying 2019-nCoV and naming it SARS-CoV-2

Coronaviridae Study Group of the International Committee on Taxonomy of Viruses

History of coronavirus naming during the three zoonotic outbreaks in relation to virus taxonomy and diseases caused by these viruses. According to the current international classification of diseases, MERS and SARS are classified as 1D64 and 1D65, respectively.
SARS
- Rivers’ modified Koch’s postulates -

1. Virus isolation
2. Virus propagation
3. Filtration
4. Disease in macaques
5. Re-isolation & PCR of virus
6. Specific immune response

Fouchier et al., Nature 2003
Kuiken et al., Lancet 2003
Gross pathology in SARS-CoV infected macaques aged macaques

Smits et al. Plos Path 2010
Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model (Rockx et al., Science 2020)

→ Similar lesions observed in SARS-CoV and SARS-CoV-2 infected NHP
Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction

RNA controls made available through the European Virus Archive platform
Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR

→ RNA controls made available through the European Virus Archive platform
Rapid communication

Laboratory readiness and response for novel coronavirus (2019-nCoV) in expert laboratories in 30 EU/EEA countries, January 2020

Chantal B.M. Reusken1,2, Eva K. Broberg3, Bart Haagmans3, Adam Meijer3, Victor M. Cormann3, Anna Papas4, Remi Charrel5, Christian Drosten3, Marion Koopmans5, Katrin Leitmeier6, on behalf of EVD-LabNet and ERLI-Net5

1. Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
2. Viroscience department, Erasmus MC, Rotterdam, the Netherlands
3. European Centre for Disease Prevention and Control, Solna, Sweden
4. Charité - Universitätsmedizin Berlin Institute of Virology, Berlin, Germany
5. German Centre for Infection Research (DZIF), Berlin, Germany
6. Department of Microbiology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
7. Unit des Virus Emergents (Aix-Marseille Univ-IRD 590-Inserm 1207-Méditerranée Infection), Marseille, France
8. The participating members of EVD-LabNet and ERLI-Net are acknowledged at the end of the article

Correspondence: Chantal Reusken (chantal.reusken@rvm.nl)

Figure 2
Status of availability of molecular diagnostics for novel coronavirus (2019-nCoV) in EU/EEA countries as at 29 January 2020 (n = 46 laboratories)

* One laboratory of the 47 included in the current study did not indicate when its molecular diagnostics would be available.

Diagnostics available 29 January
Rapid communication

Laboratory readiness and response for novel coronavirus (2019-nCoV) in expert laboratories in 30 EU/EEA countries, January 2020

Chantal B.E.M. Reusken1,3, Eva K. Broberg1,2, Bart Haagmans2, Adam Meijer3, Victor M. Corman4, Anna Papa5, Remi Charrel1, Christian Drosten6, Marion Koopmans7, Katrin Leitmayr3, on behalf of EVD-LabNet and ERLI-Net8

1. Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands
2. Viroscience department, Erasmus MC, Rotterdam, the Netherlands
3. European Centre for Disease Prevention and Control, Salma, Sweden
4. Charité – Universitätsmedizin Berlin Institute of Virology, Berlin, Germany
5. German Centre for Infection Research (DZIF), Berlin, Germany
6. Department of Microbiology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
7. Unité des Virus Emergents (Aix-Marseille Univ-IRD 190-Inserm 1207-IHU Méditerranée Infection), Marseille, France
8. The participating members of EVD-LabNet and ERLI-Net are acknowledged at the end of the article

Correspondence: Chantal Reusken (chantal.reusken@rivm.nl)

Letter to the editor: Plenty of coronaviruses but no SARS-CoV-2

Philippe Colson1, Bernard La Scola1, Vera Esteves-Vieira1, Laetitia Ninove2, Christine Zandotti1, Marie-Thérèse Jimeno1, Céline Gazin1, Marielle Bedoto1, Véronique Filosa1, Audrey Giraud-Gatineau1,2, Hervé Chaudet1,2, Philippe Brouqui3, Jean-Christophe Lagier1,2, Didier Raoult1,2

1. Institut Hospitalo-Universitaire (IHU) Méditerranée Infection, Marseille, France
2. Aix-Marseille University, Institut de Recherche pour le Développement (IRD), Assistance Publique - Hôpitaux de Marseille (AP-HP), Microbes Evolution Phylogeny and Infections (MEPIH), France
3. Unité des Virus Emergents (UVE), Aix-Marseille University, IRD 190, Inserm 1207, IHU Méditerranée Infection, Marseille, France
4. Service de l’Information Médicale, Hôpital de la Timone, Marseille, France
5. Aix-Marseille University, Institut de Recherche pour le Développement (IRD), Assistance Publique - Hôpitaux de Marseille (AP-HP), Vecteurs – Infections Tropicales et Méditerranéennes (VITROME), Marseille, France
6. French Armed Forces Center for Epidemiology and Public Health (CESPI), Service de Santé des Armées (SSA), Marseille, France

Correspondence: Didier Raoult (didier.raoult@gmail.com)

Article submitted on 03 Feb 2020 / accepted on 11 Feb 2020 / published on 11 Feb 2020

Figure 2

Status of availability of molecular diagnostics for novel coronavirus (2019-nCoV) in EU/EEA countries as at 29 January 2020 (n = 46 laboratories)

* One laboratory of the 48 included in the current study did not indicate in its molecular diagnostics test availability.
Laboratory readiness and response for novel coronavirus (2019-nCoV) in expert laboratories in 30 EU/EEA countries, January 2020

Thus, it is surprising to see that all the attention focused on a virus whose mortality ultimately appears to be of the same order of magnitude as that of common coronaviruses or other respiratory viruses such as influenza or respiratory syncytial virus, while the four common HCoV diagnosed go unnoticed although their incidence is high. In fact, the four common HCoV are often not even identified in routine diagnosis in most laboratories, although they are genetically very different from each other [7] and associated with distinct symptomatology [8].
Spike protein: binding to receptor

S1^B (RBD) binds DPP4 (Raj et al., Nature 2013).
Use of coronavirus spike protein to detect virus specific antibodies

Sera from the first three French patients and German cluster in Bavaria

<table>
<thead>
<tr>
<th>% AA pairwise identity to MERS-CoV</th>
<th>S1</th>
<th>S2</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha-CoV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>229E</td>
<td>5</td>
<td>30</td>
<td>21</td>
</tr>
<tr>
<td>NL63</td>
<td>8</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td><strong>Beta-CoV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC43</td>
<td>16</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>HKU1</td>
<td>17</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>SARS</td>
<td>15</td>
<td>39</td>
<td>45</td>
</tr>
</tbody>
</table>
Use of coronavirus spike protein to induce virus neutralizing antibodies
## Candidate SARS Vaccines

<table>
<thead>
<tr>
<th>Developer</th>
<th>Type</th>
<th>Funding</th>
<th>Location</th>
<th>Human trials, target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinovac/CAMS</td>
<td>Inactivated virus</td>
<td>China</td>
<td>China</td>
<td>March 2004</td>
</tr>
<tr>
<td>Univ. of British Columbia</td>
<td>Inactivated virus</td>
<td>Canada</td>
<td>Canada</td>
<td>December 2004*</td>
</tr>
<tr>
<td>Univ. of Toronto</td>
<td>Recombinant</td>
<td>Canada</td>
<td>Canada</td>
<td>December 2004*</td>
</tr>
<tr>
<td>McMaster Univ.</td>
<td>Adenovirus</td>
<td>Canada</td>
<td>Canada</td>
<td>December 2004*</td>
</tr>
<tr>
<td>Aventis Pasteur</td>
<td>Inactivated virus</td>
<td>NIAID contract</td>
<td>France</td>
<td>Late 2005</td>
</tr>
<tr>
<td>Baxter Healthcare</td>
<td>Inactivated virus</td>
<td>NIAID contract</td>
<td>Austria</td>
<td>Late 2005</td>
</tr>
<tr>
<td>Protein Sciences</td>
<td>Recombinant</td>
<td>NIAID contract</td>
<td>U.S.</td>
<td>Late 2005</td>
</tr>
<tr>
<td>U.S. Vaccine Research Center</td>
<td>Plasmid DNA</td>
<td>NIAID</td>
<td>U.S.</td>
<td>December 2004</td>
</tr>
<tr>
<td>Chiron Vaccines</td>
<td>Inactivated virus</td>
<td>Chiron</td>
<td>Italy</td>
<td>Not set</td>
</tr>
<tr>
<td>Univ. of Pittsburgh</td>
<td>Adenovirus</td>
<td>NHLBI/CDC</td>
<td>U.S.</td>
<td>Not set</td>
</tr>
</tbody>
</table>

* Canada will choose one of three candidates for clinical testing after a head-to-head competition in March.

*Marshall and Enserink (Science 2004)*
MERS-CoV vaccine candidates

- Plasmid DNA vaccine (Innovio/GeneOne) → phase 1 data
- Plasmid DNA vaccine (NIAID, VRC)
- Virus like particles (Novavax)
- MVA vaccine (IDT, Sutter) → phase 1 data
- Adenovirus based vectors (Jenner Inst.) → phase 1 data
- Measles virus based vectors (Mühlebach)
- RBD vaccine (Jiang)
Rapid identification and characterization of emerging coronaviruses

- Genetic characterization of viral genomes allows the development of PCR tests, antibody tests and vaccines.
- Earlier basic research on SARS-CoV and MERS-CoV was important in the early COVID-19 response

However rapid assessment of phenotypic characteristics such as pathogenicity, transmission, and antigenicity was more challenging.

→ Further basic virological research needed