Rationale for the provisional classification of the SARS-CoV-2 virus as a risk group 3 biological agent and recommendations for non-targeted activities (laboratory diagnostics) and targeted activities with SARS-CoV-2

Committee on Biological Agents (ABAS) Decision 1/2020 of 27 March 2020 (amended on 26.05.2020)

Background

Cases of a new type of respiratory disease were reported for the first time in the Chinese city of Wuhan (Hubei Province, People's Republic of China) in December 2019. All patients were reported of having previous contact to a food market in Wuhan where fish, marine and other wild animals were marketed. During the course of infection, some patients developed severe pneumonia. On 11 February 2020, the disease was officially designated “Coronavirus Disease 2019” (COVID-19) by the WHO. Based on available data, it was estimated that approximately 2 % of infected people died. By sequencing the virus genome upon isolation from patients, the pathogen has been identified as a new member of the Coronaviridae family and has been assigned to the subgenus Sarbecovirus (subfamily Orthocoronavirinae, genus Betacoronavirus) by the International Committee on Taxonomy of Viruses (ICTV). The sequence data showed more than 85 percent sequence identity to SARS-like coronaviruses previously detected in bats (Bat-SL-CoVZC45, Bat-SL-CoVZXC21). Based on this information, the novel human coronavirus was classified as type 2 of SARS-CoV (Severe acute respiratory syndrome-related coronavirus, SARS-CoV-2).

SARS-CoV-2 was recognized as the causative agent of a systemic infection often manifested as severe pneumonia. In addition, it was shown that SARS-CoV-2 infection could be associated with endothelial dysfunction, deep venous thrombosis and microinfarctions in blood vessels of the renal and coronary system. High amounts of SARS-CoV-2 have been detected in the respiratory system of infected patients. Particularly in non-ventilated rooms and building areas, rapid human-to-human transmission has been observed to occur by droplets and aerosols. Furthermore, SARS-CoV-2 can be transmitted before onset of Covid-19 symptoms (fever, cough, and pneumonia) and as well as by individuals with asymptomatic infection. Some SARS-CoV-2 infected individuals develop only mild symptoms of a common cold, which are not recognized as COVID-19 by the affected individuals or third persons. Thereby, efficient spreading of the infection occurred and resulted in the current pandemic. On May 22th, more than 5 million of infected people had been diagnosed and registered worldwide. Among the infected individuals, 333 489 had died resulting in a case fatality rate of 6.5 % (Johns-Hopkins-University). In European countries case fatality rates ranging from 3.9 % (Austria), 4.6 % (Germany) and 6.2 % (Switzerland) up to 12.9 % (The Netherlands), 14.2 % (Italy) and 14.3 % (United Kingdom) were
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determined (further details and data is provided by Johns-Hopkins-University, USA, and Robert-Koch-Institut, Berlin, Germany).

Rationale for a classification in risk group 3

SARS-CoV-2 is similar to SARS-CoV-1, a member of the subgenus Sarbecovirus, which is pathogenic to humans and had triggered the 2002/3 SARS epidemic (mortality rate 9.6 percent). Albeit to a lesser extent, similarities of SARS-CoV-2 to MERS-CoV were observed. MERS-CoV is the causative agent of the Middle East respiratory syndrome, a severe lung disease (mortality rate 34 percent) reported from citizens of the Arabian Peninsula states. SARS-CoV-1 and MERS-CoV are both classified as risk group 3 agents. At present, no antiviral therapy and preventive vaccines are available for SARS-CoV-2. Therefore, also SARS-CoV-2 is assigned to risk group 3 (RG3). This assignment is further supported by epidemiological data indicating a high potential for human-to-human transmission.

Classification of SARS-CoV-2 in risk group 4 is not justified according to definition and criteria laid down in the national guideline TRBA 450. In this context, it is mandatory to consider the severity of the disease caused by the respective biological agents. Assignment to RG4 is reserved to biological agents causing severe disease in almost all infected individuals independent of age and gender. In general, infections by RG4 viruses are associated with high fatality rates of 30 % and higher. These criteria are met with all virus species causing hemorrhagic fever (e.g. ebola virus, south-american hemorrhagic fever virus) or variola (pox virus, meanwhile eradicated by vaccination). With SARS-CoV-2, the situation is different:

(I) Only distinct groups of SARS-CoV-2 infected individuals are reported to develop severe courses of the disease. Data provided by the Robert-Koch-Institute demonstrate that the majority of fatal cases (86 %) is observed with infected patients above 70 years of age, although this age group represents only 19 % of all registered patients diagnosed for COVID-19. Mean age of deceased patients is 81 years. Similar data is published in the federal state of Bavaria, where compared to the national situation most SARS-CoV-2 infections have been recorded as of 26 May 2020 (Landesamt für Gesundheit und Lebensmittelsicherheit, LGL Bayern).

(II) As expected for patients of advanced age, almost all deceased COVID-19-patients suffered from co-morbidities, i. e. obesity, coronary heart disease, asthma, diabetes mellitus type 2, peripheral artery disease and neurodegenerative disorders.

(III) Furthermore, first data demonstrate that a significant number of SARS-CoV-2 infected individuals do not develop symptoms or that symptoms are transient, mild and similar to diseases known as “common cold” (cough, sneezing etc). Based on the detection of SARS-CoV-2 specific antibodies, a study initiated in North Rhine Westphalia (Heinsberg) demonstrates that the number of persons with prior SARS-CoV-2–infection exceeds that of individuals diagnosed and registered for acute infection by a factor of ten. Similar data is obtained from still ongoing studies on the prevalence of SARS-CoV-2 specific antibodies in the population of the Oberpfalz region in Germany (personal communication, Prof. Dr. B. Schmidt, University of Regensburg). Therefore, it is highly probable that a significant number of SARS-CoV-2 infected individuals are asymptomatic und do not develop a severe form of Covid-19.
This recent data confirms and justifies the assignment of SARS-CoV-2 to risk group 3 of biological agents. As opposed to this, neither epidemiological nor clinical data requires and justifies an assignment to risk group 4. On the other hand, classification in risk group 2 could be reconsidered in the future if protective vaccines or antiviral therapies become available.

**Non-targeted activities in the context of laboratory diagnostics for SARS-CoV-2 detection**

Non-targeted activities for laboratory diagnostics of SARS-CoV-2, based on biological specimen like sample preparation, sample processing, virus inactivation for molecular biology (PCR), as well as use of positively confirmed samples (without virus multiplication or enrichment) as reference material for investigating alternative SARS-CoV-2 detection methods, can be performed under protection level 2 conditions. Yet, the use of inactivated samples is highly recommended. All activities that may lead to a release of SARS-CoV-2, like opening sample tubes containing respiratory material (throat swabs, sputum, BAL, etc.), must be performed in a class 2 biosafety cabinet, and a protective gown and gloves must be worn. Respiratory protection (at least FFP2 masks) and protective glasses or face shields are recommended for primary diagnostics, and are mandatory for subsequent use of positively confirmed specimen as reference material for alternative SARS-CoV-2 detection methods. Activities have to be carried out by experienced employees, who have been instructed in safe handling of wearing personal protective equipment. After workflow completion, potentially contaminated surfaces, materials or personal protective equipment must be disinfected or disposed of in a way that SARS-CoV-2 carryover and exposure of employees or third parties can be ruled out. To reserve a biosafety cabinet or workspaces exclusively for SARS-CoV-2 diagnostics can be a prudent approach in this regard.

The recommendations of the Robert Koch-Institute on infection protection must be considered separately.

**Targeted activities** as defined in section 5 of the Biological Agents Ordinance (BiostoffV) involving SARS-CoV-2, such as virus propagation, use of enrichment techniques with active, infectious SARS-CoV-2, use of SARS-CoV-2 infected cell cultures and of samples containing enriched SARS-CoV-2, must be performed in protection level 3 laboratories as before.

**International recommendations**

Recommendations for targeted and non-targeted activities with contact to SARS-CoV-2 have been published by administrations of several countries including the USA, Canada and Australia. In all cases, SARS-CoV-2 has been assigned to RG3 and recommendations for activities involving virus cultivation and diagnosis are identical to those published by the German administration.

**References**

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