ZKBS
The Central Committee on Biological Safety

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Recommendation by the ZKBS on the risk assessment of poliovirus as a donor or recipient organism according to § 5 para. 1 GenTSV

General Information

Poliomyelitis is a disease that has been known for a long time, the pathogen for which was described in 1909 and was identified later as the poliomyelitis-virus (poliovirus, PV) [1]. Because children under five years of age are primarily affected, poliomyelitis is also known as an infantile paralysis.

The virus belongs to the *Picornaviridae* family (genus *Enterovirus*). Based on extensive sequence match with other viruses of the species *Enterovirus C*, polioviruses have been assigned to this species since 2017 [2]. PV is approx. 30 nm in size and a non-enveloped virus, the genome of which comprises positively-oriented, single-stranded linear RNA and it is approx. 7.4 kb [3]. The RNA can be subdivided into three regions: (1) A 5' *non translated region* (NTR), to which the viral-coded *viral protein genome-linked* (VPg-protein) is covalently bound, (2) an open reading frame that codes for the 220 kDa surrounding viral polyprotein, comprising three regions (P1 - structural protein, P2 - and P3 - non-structural proteins), as well as (3) a 3' NTR followed by polyadenylation. The 5' NTR is 742 nucleotides long and features a complex secondary structure. It possesses functions for RNA replication and also contains the *internal ribosome entry site* (IRES) for the initiation of cap-independent translation. The virus replicates in the cytoplasm of the host cell [3]. The icosahedral capsid of the poliovirus is composed of the capsid proteins VP1-4. Additionally, various neutralising antigens (N-Ags) are located on the virus surface, making possible a differentiation between the three PV-serotypes: PV-1 (Mahoney), PV-2 (Lansing) and PV-3 (Leon) [3].

The poliovirus is relatively stable in the environment and is only slowly inactivated using common disinfectants or low pH values. It remains capable of reproducing over many weeks in waste water and in the environment [4-6]. The natural host is the human, whereby CD155 serves as the receptor. Non-human primates can also be naturally infected to a very small extent. Various monkeys can be infected experimentally if PV is introduced directly into the central nervous system (CNS) [3; 7; 8].

After oral uptake, PV replicates primarily in the nasopharynx, the mucous membranes of the digestive system and in lymphatic tissue (e. g. Peyer's patches, tonsils). The viraemia that follows progresses mostly without symptoms, in 4 – 8 % of infections there are flu-like symptoms and general signs of an infection (fever, gastrointestinal symptoms, headache, muscle pain, general discomfort, infection of the upper respiratory tract) [3]. Only in approx. 5 % of infections do the viruses also attack cells of the CNS and they replicate in particular in motor neurons [9]. 2 – 4 % of affected individual with CNS participation develop symptoms of non-paralytic, aseptic meningitis. Paralytic poliomyelitis, the clinical picture of infantile paralysis, occurs at a rate of approximately 1 %. This is accompanied by paralysis of the extremities and, in the worst case, of the diaphragm. The immobilisation of the respiratory muscles leads to death in 2 – 5 % of children and 15 – 30 % of adults [3]. The symptoms in survivors revert during the course of a year, but not infrequently permanent injury can remain. A post-poliomyelitis syndrome often results after years [9].

The poliovirus is highly contagious and is mainly transmitted by the faecal-oral route as a smear infection. Air-borne transmission is also possible during the primary virus replication in the epithelium of the pharynx [9]. Before the 20th century practically all small children were infected with PV, but they were protected by maternal antibodies. As a consequence of improved hygiene, as of the 20th century children were increasingly infected later on, when there was no more antibody protection from the mother. This resulted in epidemics [3]. In 1955 an inactivated polio vaccine (IPV, Salk, composed of all three wild type serotypes) was approved; in 1960 a trivalent oral vaccine (OPV, Sabin) composed of attenuated polioviruses [6]. In contrast to the IPV, the OPV also confers gastrointestinal immunity that prevents not only the illness but also the transmission. The OPV live vaccine, however, regularly leads to the occurrence of vaccine-derived poliomyelitis; that is, vaccine-derived polioviruses (cVDPV) are generated that become neurovirulent again. This has been established as due to the genetic instability of the attenuation [6; 10]. While therapy continues to take place exclusively symptomatically, the occurrence of PV was greatly contained by the highly effective vaccinations. Poliovirus has been assigned to **risk group 2** to date.

The World Health Organisation (WHO) has set the goal of world-wide PV eradication [11; 12]. PV-1 currently exists only in Afghanistan, Nigeria and Pakistan. Infections with PV-2 have not been described since 1999, and none with PV-3 since 2012. PV2 was declared by the WHO to be eradicated in 2015. Based on the risk of the development of cVDPV, which can lead to polio epidemics, since 2016 the attenuated PV-2 vaccine strain has no longer been normally used worldwide as a live vaccine. In large parts of the world there has been a complete switch to vaccination with IPV. Correspondingly, the population there increasingly has no mucosal protection [11]. In order to minimize the risk of the deliberate release of PV from laboratory populations, the WHO developed a strategy for laboratory containment, established in detail in Global Action Plan III (GAPIII) [13]. Thus, activities with all PV-2 (vaccine viruses and wild type viruses) have been impermissible since 2016, except for central installations with special approval, so-called *poliovirus essential facilities* (PEF). In Germany, no laboratory is seeking approval as a PEF [12].

In 1997, Germany joined the *Global Polio Eradication Initiative* of the WHO and has pledged to support all measures to achieve and maintain freedom from polio. The National Commission for the Eradication of Polio was also set up in this context [14]. In July 2017, polio-lab containment obtained a legal basis in Germany through an amendment to the Infection Protection Law (IfSG). Prospectively, the containment should be expanded to PV-1 and -3 in 2019 [11]. In relation to the GAPIII of the WHO, an EU-wide upgrade of PV-2 (wild type- and vaccine strains) is planned into **risk group 3** (Employee Protection Directive 2000/54/EG). The upgrade has already been implemented in the Technical Regulations for Biological Substances (TRBA) 462 "Classification of viruses into risk groups.“ PV-1 and -3 continue to be assigned to **risk group 2**.

Recommendation

According to § 5 para. 1 GenTSV in conjunction with the criteria in annex I GenTSV, the enterovirus C isolate of poliovirus serotype 1 and serotype 3 remain assigned as donor and recipient organisms for genetic engineering operations to **risk group 2**. The isolate of poliovirus serotype 2 (wild type- and vaccine strains) is assigned to **risk group 3**.

Reasoning

The three serotypes of the poliomyelitis virus are highly infectious and, in approx. 5 % of infections, trigger severe symptoms of aseptic meningitis or poliomyelitis, which lead to paralysis and even to death. There is an efficacious vaccine. The poliomyelitis virus serotype 2 is considered eradicated since 2015. The upgrade of this serotype into risk group 3 should

minimise the number of labs that work with PV-2 and, at the same time, increase safety measures when handling PV-2, so that the risk of deliberate release from lab populations is minimised and maintaining freedom from polio is assured.

Literature

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