

**Update of the recommendation of the ZKBS on the risk assessment of  
novel avian influenza A virus H7N9  
as donor or recipient organism for genetic engineering operations according to  
Article 5 paragraph 1 GenTSV**

Influenza viruses of subtype H7, which possess multiple basic amino acids at the cleavage site of hemagglutinin (HA) and have an intravenous pathogenicity index of at least 1.2 in 6 weeks old chickens, are currently classified as “highly pathogenic” avian influenza viruses (HPAIV) [1]. HPAIV of subtype H7 are assigned to **risk group 3** in accordance with Article 5 paragraph 1 GenTSV. If, however, the cleavage site of the HA is monobasic, they are low-pathogenic avian influenza viruses (LPAIV), which according to Article 5 paragraph 1 GenTSV are assigned to **risk group 2**.

In March 2013, a novel influenza A virus of subtype H7N9 was detected in three patients in China with acute progressive lung failure [2]. It was the first time this subtype, which differs from H7N9 viruses hitherto circulating in birds, was detected in humans. Sequence analysis of the viral genome revealed that it is a reassortant virus in which the RNA segments for HA and neuraminidase (NA) are derived from influenza viruses of subtypes H7N3 and H11N9 or H7N9, respectively, while the six internal segments originate from an avian influenza virus of the subtype H9N2 [2,3]. The reassortant H7N9 has a monobasic cleavage site in the HA. In addition, the virus has genetic markers indicating (a beginning) adaptation to replication in mammals, such as various mutations in HA leading to increased binding to the human receptor type ( $\alpha$ 2,6-linked sialic acid) and the E627K substitution in the polymerase subunit PB2, which was found only in the human H7N9 isolates and is associated with higher replication efficiency in mammals [2,3].

The distribution area of the novel avian influenza A virus H7N9 is currently limited to China, meanwhile, several provinces are affected [4]. In addition, a first case has been reported from Taiwan, which is, however, related to travel to China of the affected patient [5]. In addition to human infections, the virus has been detected in chickens, pigeons, ducks and environmental samples [6]. Of more than 68,000 samples however, only 46 (equivalent to 0.07%) were positive for the novel virus. Little is known about the size and nature of the animal reservoir. In accordance with the genetic characterisation as LPAIV, the virus triggers mild symptoms in infected birds at best, but disease symptoms can also be completely absent [7,8]. Infected livestock are therefore not recognized by increased morbidity and mortality.

There is also little information available on the routes of transmission of the novel influenza virus. It is suspected that close contact between humans and infected poultry enables transmission of the virus [9]. In the ferret model, some human H7N9 isolates can be efficiently transferred through the air [10,11]. In contrast, human-to-human transmission seems far less efficient. In the case of four of 135 confirmed infections to date, this cannot be completely ruled out, as several people from the same household fell ill. However, only in one of these cases a transmission could be confirmed by molecular biology, while in the other cases infection at a

common source of infection is also conceivable [9,12-14]. In addition, there were no signs of asymptomatic or subclinical H7N9 infection in other individuals who had close contact with the patients and were medically or molecular biologically examined [9,14]. Therefore, a human-to-human transmission seems very unlikely at this stage.

In most of the human cases described so far, infection with the novel H7N9 virus led to a severe respiratory disease associated with fever, cough, pneumonia and acute progressive lung failure [2,8]. Only a few cases showed a mild progression [8,9]. Of the 135 laboratory-confirmed human infections up to date, approx. 32% have been fatal (as of 13.08.2013) [4]. A vaccine against the novel H7N9 virus is currently not available. Initial analyses indicate that some of the isolates are sensitive to the neuraminidase inhibitors oseltamivir and zanamivir [3,6], but this has yet to be confirmed by appropriate studies.

## Recommendation

According to Article 5 paragraph 1 GenTSV in conjunction with the criteria in Annex I GenTSV, novel avian influenza A virus H7N9 is assigned to **risk group 3** as donor and recipient organism for genetic engineering operations.

## Reasoning

The novel avian influenza A virus H7N9 is an avian influenza A virus with a monobasic cleavage site in HA, which can cause severe disease in humans that can be fatal in up to 32% of the cases. Transmission is believed to occur through close human contact with infected poultry. A human-to-human transmission of the novel virus is unlikely at this time. Prophylaxis or therapy with proven effectiveness is not available.

## Notes

Genetic engineering operations using the novel avian influenza A virus H7N9 as donor or recipient organism will be evaluated by the ZKBS on a case-by-case basis. As a precaution, it is pointed out that genetic engineering operations aimed at increasing the airborne transmission of the novel avian influenza A virus between mammals and the handling of the viruses thus produced are to be assigned to **biosafety level 4** in accordance with Article 7 para. 1, para. 3 no. 4 and para. 4 GenTSV in conjunction with Article 7 para. 1a GenTG.

For genetic engineering operations with the aforementioned influenza virus of **risk group 3**, the use of respiratory protection (FFP3 mask or comparable respiratory protection) is recommended in addition to the safety measures of **level 3**.

## References

1. Stellungnahme der ZKBS zur Risikobewertung hochpathogener aviärer Influenzavirus-A-Stämme der Subtypen H5 und H7 und davon abgeleiteter Laborstämme gemäß § 5 Absatz 1 GenTSV. (Az.: 6790-05-02-34) März 2007
2. Gao, R., Cao, B., Hu, Y., *et al.* (2013). Human infection with a novel avian-origin influenza A (H7N9) virus. *N Engl J Med* **368**:1888-1897.
3. Kageyama, T., Fujisaki, S., Takashita, E., Xu, H., Yamada, S., Uchida, Y., Neumann, G., Saito, T., Kawaoka, Y., and Tashiro, M. (2013). Genetic analysis of novel avian A(H7N9) influenza viruses isolated from patients in China, February to April 2013. *Euro Surveill* **18**(15) doi:pii: 20453.

4. The World Health Organization (2013). Human infection with avian influenza A(H7N9) virus – update [http://www.who.int/csr/don/2013\\_08\\_11/en/index.html](http://www.who.int/csr/don/2013_08_11/en/index.html)
5. Chang, S.Y., Lin, P.H., Tsai, J.C., Hung, C.C., and Chang, S.C. (2013). The first case of H7N9 influenza in Taiwan. *Lancet* **381**:1621.
6. Centers for Disease Control and Prevention (2013). Morbidity and mortality weekly report. Emergence of avian influenza A(H7N9) virus causing severe human illness - China, February - April 2013. 01 May 2013
7. Guan, Y., Farooqui, A., Zhu, H., Dong, W., Wang, J., and Kelvin, D.J. (2013). H7N9 incident, immune status, the elderly and a warning of an influenza pandemic. *J Infect Dev Ctries* **7**:302-327.
8. European Centre for Disease Prevention and Control (2013). Updated rapid risk assessment - Severe respiratory disease associated with a novel type A influenza virus, A(H7N9) – China <http://ecdc.europa.eu/en/publications/Publications/influenza-A%28H7N9%29-China-rapidrisk-assessment-4-april-2013.pdf>
9. Li, Q., Zhou, L., Zhou, M., *et al.* (2013) Preliminary report: epidemiology of the avian influenza A (H7N9) outbreak in China. *Lancet* [Epub ahead of print].
10. Zhang Q., Shi J., Deng G. *et al.* (2013) H7N9 influenza viruses are transmissible in ferrets by respiratory droplet. *Science* **341**(6144):410-4.
11. Belser J.A., Gustin K.M., Pearce M.B. *et al.* (2013) Pathogenesis and transmission of avian influenza A (H7N9) virus in ferrets and mice. *Nature* doi: 10.1038/nature12391. [Epub ahead of print]
12. The World Health Organization (2013). Human infection with avian influenza A(H7N9) virus in China - update 23 April 2013 [http://www.who.int/csr/don/2013\\_04\\_23/en/index.html](http://www.who.int/csr/don/2013_04_23/en/index.html)
13. The World Health Organization (2013). WHO risk assessment; human infections with influenza A (H7N9) virus. 13 April 2013 [http://www.who.int/influenza/human\\_animal\\_interface/influenza\\_h7n9/RiskAssessment\\_H7\\_N9\\_13Apr13.pdf](http://www.who.int/influenza/human_animal_interface/influenza_h7n9/RiskAssessment_H7_N9_13Apr13.pdf)
14. Qi X., Qian Y.H., Bao C.J. *et al.* (2013) Probable person to person transmission of novel avian influenza A (H7N9) virus in Eastern China, 2013: epidemiological investigation. *BMJ* **347**:f4752.