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19.01.2019

**STIKO recommendations for "flu" vaccinations during pregnancy
Request to STIKO dated 19.10.2018. Your letter dated 18.12.2018 to Dr. Jäger**

Dear Prof. Mertens,
Dear Dr. Harder,

Thank you for your reply to the request for "Influenza vaccination in pregnancy".

From your remarks and the sources you cited, we cannot derive the answers to our questions in a scientifically comprehensible way. You essentially refer to position papers or other authorities that support your position that we have questioned.

We therefore take the liberty of coming back to our questions and ask you to take our concerns seriously about the welfare of the pregnant women and children we care for.

1. Information for patients

The question: "Why don't you inform those affected on the basis of scientific evidence?" referred to the materials with the RKI logo which are given to patients, often without well-founded personal information:

- www.impfen-info.de/mediathek/printmaterialien/grippeimpfung/

Even the headings of these texts (with the RKI logo) are not scientifically verifiable: There is no "flu vaccination" (vaccination against "ILI"), but only a vaccination against influenza viruses. The case definition of ILI ("flu") contains no pathogen detection, and the frequency of detection of influenza in "flu" diseases varies seasonally:

- ILI case definition: An acute respiratory infection with: measured fever of $\geq 38\text{ }^{\circ}\text{C}$ and cough with onset within the last 10 days (WHO 2014) - An acute respiratory illness with a measured temperature of $\geq 38\text{ }^{\circ}\text{C}$ and cough, with onset within the past 10 days". (WHO 2018: www.ncbi.nlm.nih.gov/pmc/articles/PMC5791775/pdf/BLT.17.194514.pdf)
- Jefferson, T.: Guest Editorial: Mistaken identity: seasonal influenza versus influenza-like illness. *BMJ Clinical Evidence* 5 October, 2009.

The contents of these brochures do without verifiable information and address emotions. Why don't you instead orient yourself on the criteria "evidence-based patient information"?

- Steckelberg A. et al. (2005): Criteria for evidence-based patient information, medical training. *Agony. Gesundheitswes.* 2005, 99:343–351

2. Evidence

You do not respond to the literature cited in the inquiry, but refer to a publication of the RKI from the year 2016:

- Remschmidt C. et al. (2016): Background paper of STIKO: Evaluation of the existing influenza vaccination recommendation for indication groups and for seniors (standard vaccination from 60 years). Federal Health Gazette 2016, 59:1606-1622

This publication evaluated the vaccination against influenza in pregnant women until 2014. No significant, short-term identifiable risks were found. The more recent publications mentioned to you in the inquiry could not have been considered at that time:

- Ahmed S. et al. (2017): Narcolepsy and influenza vaccination-induced autoimmunity. *Ann Transl Med.* 2017;5(1):25
- Cochrane Review 2018: Demicheli V: Vaccines for preventing influenza in healthy adults. *Coch. Database* 01.02.2018, Jefferson T: Vaccines for preventing influenza in healthy children. *Coch. Database* 01.02.2018
- Doshi P. (2018): Pandemrix vaccine: why was the public not told of early warning signs? *BMJ* 2018;362:k3948
- Canelle Q. et al. (2016): Evaluation of potential immunogenicity differences between Pandemrix™ and Arepanrix™. *Hum Vaccine Immunother.* 2016 12(9):2289-98.
- Gadroen K. (2016): Patterns of spontaneous reports on narcolepsy following administration of pandemic influenza vaccine. *Vaccine.* 2016 22;34(41):4892-7
- Liblau RS (2018): Put to sleep by immune cells. *Nature* 2018, 562(7725):46-48
- Sarkanen T. et al. (2018): Narcolepsy Associated with Pandemrix Vaccine. *Current Neurology and Neuroscience Reports. Curr Neurol Neurosci Rep* (2018) 18: 43 - Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-anal. *Sleep medicine* Volume 38, Pages 177-186
- Stowe J. et al. (2016): Risk of Narcolepsy after AS03 Adjuvanted Pandemic A/H1N1 2009 Influenza Vaccine in Adults: A Case-Coverage Study in England. *Sleep.* 2016 May 1; 39(5): 1051-1057.
- Verstraeten T. et al. (2016): Pandemrix™ and narcolepsy: A critical appraisal of the observational studies. *Hum Vac Immuno* 2016 12(1): 187-193
- Vogel G (2015): Narcolepsy link to pandemrix flu vaccine becomes clearer, *Science* 2015 Vol 349(6243):17

The newer findings, e.g. on the causation of narcolepsy by vaccine Pandemrix™ the pandemic (H1N1) 2009 influenza, are of importance here:

The vaccine was taken off the market (also in Germany) for pregnant women because the adjuvant had been suspected as a possible cause of the serious side effect. Since then, STIKO has only recommended non-adjuvant vaccines for influenza vaccination. In fact, however, the type of antigen preparation at Pandemrix™ seems to have been responsible for the very serious consequences (triggering of an autoimmune disease, directed against cells in the sleep/wake center of the brain carrying hypocretin receptors).

In your reply, you refer further to a WHO position paper of November 2012. An analysis of the degree of evidence from these WHO recommendations

- Donzelli, A. (2019): Influenza vaccination for all pregnant women? So far the less biased evidence does not favor it. *Human vaccines & immunotherapeutics.* / Donzelli, A. (2018): Influenza Vaccinations for All Pregnant Women? Better Evidence Is Needed. *International journal of environmental research and public health* 15 (9). DOI: 10.3390/ijerph15092034.

comes to the following conclusions:

“... evidence from observational studies in pregnancy is subject, among others, to the healthy-vaccinee bias, overestimating the vaccine effectiveness and safety. An USA survey adds new evidence that documents this bias. Therefore, it is essential to assess vaccine effectiveness and safety with RCTs. ... In substantial agreement with the Cochrane reviewers, I think that further RCTs with appropriate study designs are needed for influenza vaccination in pregnancy. They should be carried out by independent bodies and

researchers, and safety concerns should be dispelled before promoting universal seasonal influenza vaccination during pregnancy. Current evidence from valid studies is insufficient and not reassuring.”

The authors of a large CDC study also point to the need for further research into the safety of influenza vaccination in pregnancy:

“.. SAB (spontaneous abortion) was associated with influenza vaccination in the preceding 28 days. The association was significant only among women vaccinated in the previous influenza season with pH1N1-containing vaccine. This study does not and cannot establish a causal relationship between repeated influenza vaccination and SAB, but further research is warranted.”

Donahue J. et al. (2017): Vaccine Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011-12. *Vaccine* 2017, 35(40):5314-5322

3. Unknown unknowns.

With regard to the question of previously unknown effects in the context of complex early childhood brain and immune development, you refer to your own statements seven years ago. However, knowledge about the developmental dynamics of the fetal brain during pregnancy is developing exponentially. It is becoming increasingly clear that serious long-term consequences are caused by disturbances during this time window. Especially with regard to developmental delays in infants and disorders within the autism spectrum:

- Faa G et al. (2016): Fetal programming of neuropsychiatric disorders *Birth Defects Res.* 2016 108(3):207-223
- Cattane N. et al. (2018): Prenatal exposure to environmental insults and enhanced risk of developing Schizophrenia and Autism Spectrum Disorder: focus on biological pathways and epigenetic mechanisms. *Neuroscience and biobehavioral reviews.* DOI: 10.1016/j.neubiorev.2018.07.001.
- Kundakovic, M. et al. (2017): The Epigenetic Link between Prenatal Adverse Environments and Neurodevelopmental Disorders. *Genes* 8 (3). DOI: 10.3390/genes8030104.

In this context, we referred you to a study that investigated the relationship between influenza vaccination and pregnancy:

- Zerbo O. (2017): Association between Influenza Infection and Vaccination during Pregnancy and Risk of Autism Spectrum Disorder *JAMA Pediatr.* 2017;171(1):e16360

Here, too, it was demanded that more meaningful studies than previously with new designs were necessary:

„There was no association between maternal influenza infection anytime during pregnancy and increased ASD risk. There was a suggestion of increased ASD risk among children whose mothers received an influenza vaccination in their first trimester, but the association was not statistically significant after adjusting for multiple comparisons, indicating that the finding could be due to chance. These findings do not call for changes in vaccine policy or practice, but do suggest the need for additional studies on maternal influenza vaccination and autism.“

New bio-physical research regards the brain as rhythm organ of complex oscillating cells

- Buzsáki G. et al. (2018): Time in the Brain. *Opinion Space and Time: The Hippocampus as a Sequence Generator.* *Trends in Cognitive Sciences*, 2018, 22(10):853 http://buzsakilab.com/content/PDFs/Buzsaki_Tingley_2018.pdf

The essential brain rhythms (and their structural bases) stabilize only slowly in the fetal and in the early neonatal period. Damage is easily possible during this time and results in developmental delays that only become apparent years later. The narcolepsy epidemic following Pandemrix™ vaccinations impressively demonstrates that brain rhythm disorders can also occur after vaccination during pregnancy.

At present, no one can guarantee that developmental delays after a vaccination in pregnancy can be ruled out. The knowledge of brain physiological connections during this period is still in its infancy.

We therefore consider it negligent that STIKO does not adhere to the precautionary principle when assuming only moderate benefit (Cochrane 2018): "Do not harm first!"

Yours sincerely

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Signed on behalf of, 19.01.2019

