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Projekt: Gripeschutz – Commentary on the "Systematic Review of the Efficacy, Effectiveness and Safety of Newer and Enhanced Seasonal Influenza Vaccines" of the ECDC

Dear Ladies and Gentlemen,

as committed doctors and promoters of protection against influenza, we are observing with great interest and excitement the work of the ECDC and the commissioned institutes on the next "Systematic Review of the Efficacy, Effectiveness and Safety of Newer and Enhanced Seasonal Influenza Vaccines". The protocol for this review was recently published, and we would like to share our findings based on our current work over the past years. Please understand this as a contribution to improved influenza protection across Europe.

We are convinced that there is hardly any other vaccination where improvement of vaccines is as urgently needed as for influenza, because the protection rates are low compared to other vaccinations. However, the current vaccine recommendations limit a broad range of vaccines for the population in Germany. This is a growing concern to us: vaccines should always be available promptly for population protection.

For the approval of a vaccine by the EMA, Randomised Clinical Trials (RCT) are the gold standard and essential because they describe the efficacy. However, when recommending a vaccine by a NITAG, the importance given to RCTs should be assessed differently. In our opinion, real world data (RWD) are of great, and sometimes even greater, importance here, because it is about efficacy and benefit in real life, and possibly also of rare side effects that often cannot be captured by RCTs.

In addition, RWD are particularly significant in influenza because circulating influenza viruses mutate unpredictably every year. Although vaccines are also adjusted annually, the protection for influenza varies more than for any other pathogen from season to season and may range between close to 0% to over 70%. Moreover, the protection differs for each influenza subtype, resulting in heterogeneous overall protection rates. RCTs therefore have weaknesses because they often only cover one or a few seasons and thus only represent a small section of reality. RWDs that collectively cover many years are of particular importance in a rapidly mutating viruses such as influenza. They are less susceptible to epidemiological coincidences.

In our view, it is essential for the evaluation and recommendations of vaccines that all available data are included and adequately considered. Specifically, we therefore recommend that RWD should be given a higher priority. At the same time, we support the definition of quality standards for RWD. This is the only way to ensure optimal recommendations with all available information for the best flu protection. The pandemic has shown how essential RWD were for SARS-CoV-2 vaccination recommendations. With the help of RWD, recommendations have been continuously adapted and optimised. This experience should be model for influenza vaccine recommendations.

However, the last ECDC assessment from 2020 emphasises RCTs with considerably higher weight and rates RWD per se as "low evidence". From the minutes of this year's Systematic Review, RWD are again considered as low evidence. The decision to rate RCTs significantly higher than RWDs may have several negative consequences.: For example, even if vaccines have been shown to be more effective by high quality RWD, they may still not receive a recommendation. This prevents or delays the widespread use in the population, which can ultimately cost human lives. This would be different if the efficacy of the already recommended flu vaccines, would be close to 100%, so that other vaccines cannot improve protection. However, this is by far not the case. As a consequence vaccines with good effectiveness might not be recommended or recommendation might be delayed by years.

Influenza vaccination not only protects against a clinical flu, but also protects from complications e. g. cardiovascular diseases such as myocardial infarction and stroke, or bacterial superinfection by pneumococci) These complications cannot be captured if laboratory-confirmed influenza is selected as the target criteria, because these complications occur with a time delay and influenza can no longer be confirmed in the laboratory or is not even considered for differential diagnosis.

We would be pleased if you would take these considerations into account. In this context we demand - also as a signal to European health policy - a new "data culture" in this context for the entire EU. There are already pioneers in the political arena, e. g. MEP Stelios Kympouropoulos, who recently adopted a **Call to Action on the topic of RWD**.

For further questions and exchange of ideas, please feel free to contact us.

Yours sincerely and on behalf of the Project: Gripeschutz



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Projekt: Gripeschutz is an independent initiative of medical professionals with the aim of significantly improving flu protection through flu immunisation of people in Germany.

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