

PREPARE response to seasonal influenza in Europe

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Seasonal influenza activity is increasing in northern, southern and western European countries (<http://flunewseurope.org>). Concerns about this season's influenza epidemic have dominated media outlets, particularly in the UK, where health services are struggling to cope with increased demand. An early signal for the impact of this influenza season was provided by ECDC's early risk assessment in December 2017 (ecdc.europa.eu/en/publications-data/risk-assessment-seasonal-influenza-eueea-2017-2018). Current concerns arise, in part, from the severity of influenza A/H3N2 outbreaks in other parts of the world: Australia and the USA in particular. The vaccine efficacy in Australia is reportedly very low.

The Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) is monitoring this situation closely. On 11th January 2018, PREPARE activated an internal trigger to review the threat of this Influenza outbreak to Europe and to consider an appropriate response mode. The PREPARE Outbreak Mode Committee (OMC) met that day and concluded that, based on public health surveillance data, the threat to Europe was limited. There was little indication from the European national Influenza centers that the seasonal influenza season 2018 was more severe than usual. In contrast to Australia and the USA where Influenza A/H3N2 virus represented or currently represents the dominant circulating strain, aggregated data from EU wide surveillance showed co-circulation of influenza B > influenza A/H1N1 > influenza A/H3N2. The influenza A/H3N2 strains were a mix of clades, so far closely related to the vaccine strain. Based on the available information there was no evidence for increased severity, compared to previous years.

Given the dynamics of influenza epidemiology and the possibility that the predominance of circulating viruses in Europe may change, PREPARE has mobilized to outbreak mode 1. This mode is activated for infectious disease outbreaks that present a *limited threat* to Europe and facilitates preparedness by evaluating the ability of active studies in PREPARE to respond (www.prepare-europe.eu/outbreakresponsemodes). Observational and interventional studies that are currently active in PREPARE are orientated towards enrolling patients with acute respiratory infections to answer clinical research questions relevant to understanding disease severity and improving clinical management of these patients. As a result, active PREPARE studies are automatically including patients with influenza and this forms a good basis for an outbreak response from PREPARE, if required.

A summary of relevant studies is as follows:

The **PREPARE MERMAIDS ARI** studies (www.prepare-europe.eu/About-us/Workpackages/Workpackage-3) aim to identify host and pathogen related determinants of severity of community acquired acute respiratory infections (ARI), including influenza, in adults and children. MERMAIDS ARI is currently recruiting patients presenting with symptoms of acute respiratory infections in 35 sites across 8 EU countries. As of 29th January, 839 adult patients have been recruited to these studies.

The **PREPARE ALIC⁴E** trial (www.prepare-europe.eu/About-us/Workpackages/Workpackage-4) is an adaptive platform trial evaluating the clinical and cost effectiveness of oseltamivir in over 200 primary care sites across 15 EU countries. The trial is currently recruiting patients presenting to primary care practices with Influenza-like Illness. To date, 2350 patients with influenza-like illness have been recruited to these studies. Data on over 340 participants recruited and randomised so far this winter into the ALIC⁴E Trial suggest that the severity of influenza like illness in those consulting in primary care is no worse now than in the previous two winters, but with the caveat that many of those recruited so far this season have come from Catalonia, and that influenza generally becomes more widespread in Eastern Europe after it does in the West. ALIC⁴E is the only primary care study that is currently randomizing patients to receiving antiviral treatment or not. Patients in the study are followed up for a month in order to gather critical data about complications and recovery and data will be analyzed once follow up is complete and data is cleaned. Results should be able to inform care by next winter. A press release with further details of this study has been issued: www.phc.ox.ac.uk/news/should-flu-symptoms-be-treated-with-antivirals-in-primary-care.

The **PREPARE REMAP-CAP** trial (www.prepare-europe.eu/About-us/Workpackages/Workpackage-5) is an adaptive platform trial evaluating multiple treatment options for critically ill adult patients with Community Acquired Pneumonia admitted to the Intensive Care Unit. Multiple sites across Europe are currently obtaining regulatory approvals and will be opened shortly. One site is already actively recruiting patients; however there has been no increase in influenza-related admissions to this ICU.

As part of PREPARE's Mode 1 activities, PREPARE will assess the capacity and operational readiness of its networks to escalate to a higher mode, if required. We continue to monitor this situation closely and will periodically provide further updates when this situation changes.

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