# Let's add invasive aspergillosis to the list of influenza complications

Since the 1918 pandemic (H1N1), although the causal agent of influenza was not then known, the main cause of death has been suspected as being from secondary infection. Bacterial pneumonia remains a major complication of influenza. Yet, during the past decade, an unexpected mould, *Aspergillus fumigatus*, has emerged as a potential complication.

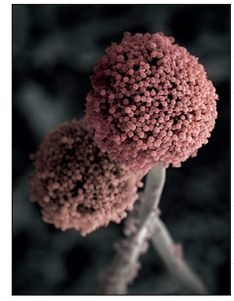
In this issue of *The Lancet Respiratory Medicine*, Alexander Schauwvlieghe and colleagues[1] report a retrospective cohort study assessing patients admitted to seven intensive care units between Jan 1, 2009, and June 30, 2016, in Belgium and in The Netherlands. They found that invasive pulmonary aspergillosis occurred in 19% of patients with severe influenza requiring admission to the intensive care unit (ICU). Invasive pulmonary aspergillosis also occurred in patients without predisposing host factors according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definition.[2] The incidence of invasive pulmonary aspergillosis was significantly higher in non-immunocompromised patients with severe influenza (influenza case group; 14%) than in a control group of influenza-negative patients with community-acquired pneumonia (5%), supporting the view that invasive pulmonary aspergillosis is a complication of influenza infection.

Several lines of evidence argue in favour of authentic invasive pulmonary aspergillosis rather than a mere pulmonary colonisation with *Aspergillus* in these patients. First, invasive pulmonary aspergillosis had a significant effect on overall mortality. Second, 63% of patients in the influenza cohort with aspergillosis (according to the study criteria) had a positive culture for *Aspergillus* in bronchoalveolar lavage (BAL) fluid. Third, albeit performed only in a subset of patients, a serum galactomannan test was positive in 65% of patients with influenza and aspergillosis. However, the EORTC/MSG definitions of invasive pulmonary aspergillosis were developed for severely immunocompromised hosts and not for patients in the ICU.[2] Of three pillars (host factors, clinical features, mycological) of invasive pulmonary aspergillosis diagnosis, the mycological criterion was the main one used for diagnosis because the clinical and radiological criteria are difficult to assess in a population of patients in the ICU. Therefore, a few invasive pulmonary aspergillosis cases might have been misclassified or possibly overlooked.

In addition to influenza, other viruses—such as cytomegalovirus—are known to increase the risk of invasive pulmonary aspergillosis.[3,4] However, only in the past decade has influenza been identified as a risk factor. Therefore, could invasive pulmonary aspergillosis have a special association with the 2009 H1N1 Pandemic?[5,6] However, in the present study,[1] there was no clear association between invasive pulmonary aspergillosis and the influenza subtype. So why was invasive pulmonary aspergillosis not recognised as a complication of influenza previously in this context? The most probable explanation is the recent appreciation of the pathogenic role of moulds in non-haematological patients, in particular in the ICU population.

In this study corticosteroid therapy within 28 days before admission to the ICU was an independent risk factor for invasive pulmonary aspergillosis.[1] Corticosteroids were administered for a variety of reasons (respiratory infections, including influenza, chronic obstructive pulmonary disease, or respiratory failure). The dose was less than 0·3 mg/kg/day and thus was below the threshold of EORTC/MSG host criterion. Of note, the incidence of invasive pulmonary aspergillosis was 12% for non-immunocompromised patients with influenza who did not receive corticosteroids and 23% in those who did (p=0·055; Schauwvlieghe A, Erasmus MC University Medical Center, personal communication). Short courses of corticosteroid therapy have already been associated with invasive pulmonary aspergillosis even in non-immunocompromised patients.[7] A meta-analysis[8] indicated that corticosteroid therapy increased mortality in patients with influenza. Taken together, these data suggest that the combination of influenza and corticosteroid therapy identifies a patient population at high risk of life-threatening invasive pulmonary aspergillosis.

Innate and adaptive immunity is crucial for host defence against influenza. Although the influenza virus itself depresses the function of macrophages and T cells,



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a strong innate immune defence response triggered by a severe influenza infection might also be detrimental due to the induction of high concentrations of cytokines, including interleukin 10. Interleukin 10 negatively affects innate and adaptive immune responses, which might predispose a patient to invasive pulmonary aspergillosis, with or without the added immunosuppressive effects of corticosteroids.[9,10] Pentraxin 3 (PTX3) is an important component of the innate immune response against *A fumigatus*.[11] Influenza induces the production of PTX3 but some subtypes of influenza, including pandemic H1N1, are resistant to its antiviral activity.[12] Because functional single nucleotide polymorphisms have been associated with the development of invasive pulmonary aspergillosis,[13] PTX3 might provide a potential pathogenic link between influenza and invasive pulmonary aspergillosis. It would be interesting to determine the proportion of patients with influenza, with or without invasive pulmonary aspergillosis, who bear the at-risk PTX3 polymorphisms.

Given the results of the present study[1] and of similar observations,[5,6] it seems reasonable to add invasive pulmonary aspergillosis to the list of influenza complications. The next logical step would then be to investigate prospectively whether the administration of mould-active antifungal prophylaxis reduces the incidence of invasive pulmonary aspergillosis in patients with severe influenza infections.

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FL declares no competing interests. TC declares membership on Advisory Boards for Astellas, Basilea, Cidara, Merck Sharp and Dohme, Abbott, Biocartis, and Sobi, and membership on a data monitoring board for Novartis.

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