

Editorial Focus

Can vaccination for common respiratory viruses decrease the incidence of venous thromboembolism?

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Thrombotic events initiated on the arterial side of the vasculature have been separated conceptually from those arising on the venous side, and, consequently, the well-documented risk factors for arterial thrombosis, such as metabolic syndrome, have not been viewed as primary contributors to venous thrombosis. Rather, venous thrombosis is classically characterised by alterations in Virchow's triad, namely, altered blood flow, hypercoagulability, and vascular wall perturbation. In recent years studies have demonstrated an interesting overlap of risk factors for arterial thrombosis with those associated with the onset of venous thrombosis (1–3). These risk factors are incompletely characterised, and some, such as diabetes and metabolic syndrome, are themselves complex. Thus, caution should be exercised in assuming that shared risk factors imply common underlying pathogenic mechanisms. Furthermore, the increasing frequency of cardiovascular risk factors in the general population may severely compromise our ability to clearly define the role these factors play in the development of venous thromboembolism (VTE).

Risk factors for VTE are characterised as genetic (4), transient, and/or chronic in nature (5). One identified risk factor, acute infection, induces a hypercoagulable state that has been reported to increase the risk for both arterial and venous thrombosis (6, 7), and specific mechanisms are currently under investigation. Cytomegalovirus has been identified as the causative agent in a case of diffuse superficial thrombophlebitis and deep-vein thrombosis (8). A recent study in *Thrombosis and Haemostasis* demonstrated differential platelet signalling and granule release in response to thrombotic platelet-activating stimuli as compared to platelets activated by immune stimuli (9). In a recent retrospective analysis of thrombotic events in septic patients, pulmonary tissue was identified as a common primary infection site for patients with thrombotic events, and VTE accounted for 25 of 87 identified events (10). Viral infections of the upper respiratory tract result in increased platelet P-selectin expression and ADP-induced platelet aggregation (11). Infection with the influenza virus increases the procoagulant activity of endothelial cells and monocytes *in vitro* (12, 13), and an *in vivo*

procoagulant effect of influenza infection has been demonstrated in a murine model (14). Potential links between common respiratory infections and venous thrombotic events must be further defined. If a causal link exists, it is reasonable to hypothesise that decreasing respiratory infections may subsequently reduce the incidence of VTE.

In the current issue of *Thrombosis and Haemostasis*, Zhu et al. report findings of a case-controlled study aimed at investigating the potential protective effect of influenza vaccination in reducing VTE (15). Vaccination was associated with a 26% reduction overall in VTE and a 48% reduction in subjects younger than 52 years of age. The underlying mechanism for this protective effect, as acknowledged by the authors of the study, remains unknown. Importantly, the mechanism may be unrelated to modulation of respiratory illness.

Chronic inflammation, or repeated bouts of acute inflammation, may contribute to the development of VTE. A reduction in the overall exposure of the vascular wall to inflammatory stimuli, including those elicited by viral respiratory infections, may decrease the incidence of VTE. However, we cannot draw conclusions about the role of influenza infection or vaccination if the infectious burden of the patient population is not known, particularly over time. Vaccination status in the study was based on participant recall, a weakness acknowledged by the authors of the study. Interpretation is further limited by the lack of data on occurrence of respiratory illnesses, caused by influenza virus or other pathogens, during the study period. The reported IL-6 levels were not statistically different between the controls and patients with VTE. Therefore, it is unlikely that patients with VTE were suffering from the acute phase of a respiratory infection. However, the temporal link between respiratory illness and VTE is not clearly defined at this time. The efficacy of the influenza vaccine varies annually, partially as a function of how well the vaccine antigenically matches the seasonal virus. The Centers for Disease Control report an efficacy range as wide as 48% to 90% in healthy adults. Clearly there is a need for studies extending beyond one vaccination cycle. Additionally, VTE events in the study were distributed evenly across the year, while influenza is a seasonal disease.

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The potential for routine preventative measures, like influenza vaccination, to reduce VTE is certainly of public health significance and warrants further investigation. The work by Zhu et al. paves the way for additional studies that are needed to define

the mechanism(s) responsible for the putative protective effect of influenza vaccination and to investigate the distinct possibility that factors common to the vaccinated group, but unrelated to influenza infection status, are responsible for the effect.

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