

**Follow-up theory of cases with a clinical picture of thrombocytopenia, bleeding and thrombosis and occurring 7-10 days after vaccination with the AZ vaccine:**

Some of the case stories including the Danish case, involve primarily younger, previously relatively healthy women (and two men) who developed thrombocytopenia, bleeding and thrombosis all within 7-10 days of vaccination with the AZ vaccine. A theory has now been raised that the mechanism behind the clinical presentation could be similar to what is seen in cases of heparin induced thrombocytopenia (HIT), except that the immunological response could be triggered by the AZ vaccine rather than heparin.

Heparin induced thrombocytopenia occurs very rarely and it is not possible to pinpoint in advance which patients are at increased risk of developing this condition. Heparin triggers an immunological response leading to thrombocytopenia, bleeding and thrombosis. The time to onset is typically 5-7 days. The cases with the AZ vaccine had time to onset of the serious adverse event within 7-10 days in patients with a clinical presentation very similar to that seen with HIT.

Given that the factor(s) involved in the development of thrombocytopenia, bleeding and thrombosis, it is difficult, from quality perspective, to know what to look for. Although, at this stage, it does not seem likely, that the events seen is quality related, this should not be excluded. While it is clear that the AZ vaccine does not contain heparin, the question remains whether something else, related to the quality of the AZ vaccine, could have been involved in causing the events seen. Any possible option should be taken into consideration, such as: possible quality defects, a particular excipient, or a product- or process related impurity, originating from a particular step in the manufacturing process, and which may trigger a similar immunological response as seen in cases of HIT. It should also be considered if batches involved in the currently reported events is from a particular drug substance- or drug product site.