the timing of intussusception relative to vaccination, a comparison of intussusception rates is not required. Also, the underidentification of intussusception cases would not bias our results unless we selectively missed cases of intussusception immediately after vaccination; we do not believe that this occurred.

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Diagnosis and Management of the Antiphospholipid Syndrome

TO THE EDITOR: In their review article, Garcia and Erkan (May 24 issue)[1] describe current and future therapies in the prevention and treatment of thrombosis in patients with the antiphospholipid syndrome (APS). Direct oral anticoagulant therapy is mentioned as a possible therapeutic approach on the basis of the results of a randomized, controlled trial.[2] However, there is recent evidence that direct oral anticoagulants are less effective than warfarin in the prevention of recurrent thrombosis in patients with a high-risk profile (i.e., those who are triple-positive for lupus anticoagulant, anticardiolipin antibodies, and anti–β_2-glycoprotein I antibodies). We retrospectively observed a higher rate of recurrent thrombosis (particularly arterial thrombosis) among patients who received rivaroxaban than among those who received warfarin (42% vs. 7%).[3] Moreover, an Italian randomized, controlled trial that compared rivaroxaban with warfarin in patients with APS who were triple-positive for lupus anticoagulant, anticardiolipin antibodies, and anti–β_2-glycoprotein I antibodies (Rivaroxaban in Thrombotic Antiphospholipid Syndrome [TRAPS]; ClinicalTrials.gov number, NCT02157272) closed prematurely in January 2018 because of an excess of thrombotic events in the group that received rivaroxaban. Hence, direct oral anticoagulants do not seem to be effective in high-risk patients with APS, and further studies to evaluate alternative therapeutic approaches (e.g., anticoagulant plus antiplatelet agents) are warranted.

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TO THE EDITOR: Garcia and Erkan state that catastrophic APS is difficult to distinguish from other thrombotic microangiopathies. We suggest that catastrophic APS is in fact the coexistence of APS and thrombotic thrombocytopenic purpura (TTP). The coexistence of TTP with other diseases, such as systemic lupus erythematosus, is well recognized.[1,2] Since the recommendation was made to add plasma exchange and rituximab therapy to anticoagulation, mortality among patients with so-called catastrophic APS has decreased.[3,4] Acceptance of the view that TTP is caused by APS would allow physicians to initiate early therapy that could improve the prognosis of both diseases. Are we in fact dealing with an uncommon manifestation of APS or with two different diseases?

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TO THE EDITOR: In their review, Garcia and Erkan refer to the lack of population-based studies on the prevalence of antiphospholipid-antibody positivity. They indicate a prevalence of anticardiolipin-antibody positivity of 10% and a prevalence of lupus anticoagulant of 1% among healthy blood donors but do not provide a cutoff point for antiphospholipid-antibody positivity. This prevalence of antiphospholipid-antibody positivity would be higher than that among women with complications from pregnancy (6%) and similar to that among patients with venous thrombosis (10%) or myocardial infarction (11%). Obviously, the prevalence of antiphospholipid-antibody positivity depends on an appropriate definition. The classification criteria for the antiphospholipid syndrome recommend the use of either 40 GPL (IgG phospholipid) or MPL (IgM phospholipid) units or the 99th percentile of antiphospholipid-antibody titer in a reference group as the cutoff point for positivity.[1] Unfortunately, 40 GPL or MPL units are not equivalent to the 99th percentile for most assays.[2] Cutoff points recommended by manufacturers are often based on underpowered studies. We have shown in a population-based cohort of approximately 5000 participants that 3.2% had at least one antiphospholipid-antibody measurement (i.e., IgG or IgM anticardiolipin antibodies or IgG or IgM anti–β_2-glycoprotein 1 antibodies) above the age-adjusted 99th percentile.[3] Thus, before we discuss the prevalence of antiphospholipid-antibody positivity, we should agree on a uniform definition of this condition.

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THE AUTHORS REPLY: We agree with Ciavarella and Martinelli that, on the basis of the two studies published after our manuscript went to press, direct oral anticoagulants must be considered less effective than warfarin for the prevention of thrombosis in high-risk patients with APS.[1,2] While we would, for now, discourage the use of direct oral anticoagulants as a first-line thrombosis prevention strategy in high-risk patients with APS, we also think that ongoing (and possibly future) clinical trials should be considered before final conclusions are drawn about the role of direct oral anticoagulants in patients with APS. With respect to the comments of Riera-Mestre and Vidaller, we believe that catastrophic APS and TTP have many overlapping features and that both should be included under the umbrella of thrombotic microangiopathies. We agree that for patients with catastrophic APS who present with a TTP-like picture, plasma exchange could be very appropriate as a part of first-line combination treatment. Finally, we agree with Lackner and Müller-Calleja that without a universally accepted definition of antiphospholipid-antibody positivity, the prevalence of this condition in the general population will remain uncertain.

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