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MAJOR ARTICLE

Adenovirus-Based Vaccines and Thrombosis in Pregnancy: A Systematic Review and Meta-analysis

Lauren Pischel,[1,2] Kavin M. Patel,[1] George Goshua,[3,4] and Saad B. Omer[1,2,5,6]

[1]Section of Infectious Diseases, Department of Medicine, Yale School of Medicine, New Haven, Connecticut, USA; [2]Yale School of Public Health, New Haven, Connecticut, USA; [3]Section of Hematology, Department of Medicine, Yale School of Medicine, New Haven, Connecticut, USA; [4]Department of Health Policy and Management, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA; [5]Yale Institute of Global Health, New Haven, Connecticut, USA; and [6]Yale School of Nursing, Orange, Connecticut, USA

Background. Rare cases of thrombosis and thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]) have been associated with 2 coronavirus disease 2019 adenovirus vector vaccines: the ChAdOx1 nCoV-19 Vaxzevria vaccine (Oxford/AstraZeneca) and the JNJ-7836735 Johnson & Johnson vaccine (Janssen). It is unknown if TTS is a class-mediated effect of adenovirus-based vaccines or if it could worsen known hypercoagulable states. Since most cases of TTS happen in women of childbearing age, pregnancy is a crucial risk factor to assess. Understanding these risks is important for advising vaccine recipients and future adenovirus vector vaccine development.

Methods. To explore the potential associations of adenovirus-based vaccine components with symptoms of TTS in the general clinical trial population and in pregnant women in clinical trials, we conducted a systematic review and meta-analysis of adenovirus-based vector vaccines to document cases of thrombocytopenia, coagulopathy, and or pregnancy from 1 January 1966 to 9 August 2021.

Results. We found 167 articles from 159 studies of adenovirus vector–based vaccines, 123 of which targeted infectious diseases. In the general population, 20 studies reported an event of thrombocytopenia and 20 studies indicated some coagulopathy. Among pregnant women, of the 28 studies that reported a total of 1731 pregnant women, thrombocytopenia or coagulopathy were not reported.

Conclusions. In this systematic review and meta-analysis, there was no class-wide effect of adenovirus vector vaccines toward thrombocytopenia or coagulopathy events in the general population or in pregnant women.

Keywords. COVID-19; adenovirus; platform-based vaccines; thrombosis; pregnancy.

As vaccination against coronavirus disease 2019 (COVID-19) has begun across the globe, in rare cases the administration of adenovirus-based COVID-19 vaccines has been linked with unusual cases of thrombosis such as cerebral venous sinus thrombosis and portal vein thrombosis [1]. ChAdOx1 nCoV-19 Vaxzevria (Oxford/AstraZeneca), a chimpanzee adenovirus vaccine, encodes the nonstabilized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein whereas the JNJ-7836735 Johnson & Johnson vaccine (Janssen) uses an adenovirus (Ad) 26 viral vector to encode the SARS-CoV-2 spike protein.

The syndrome, called thrombosis with thrombocytopenia syndrome (TTS), or vaccine-induced thrombotic thrombocytopenia (VITT), is broadly defined as any venous or arterial thrombosis associated with thrombocytopenia (platelet count $<150 \times 10^9$/L), elevated D-dimer (>4 times the upper limit of normal), and positive PF4 heparin-induced thrombocytopenia enzyme-linked immunosorbent assay within 42 days of COVID-19 vaccination [2, 3]. There has been some variability in the definition of this new syndrome, including slight variations in laboratory parameters and timing of presentation [4–7]. The term TTS will be used for this article in line with the Centers for Disease Control and Prevention (CDC), US Food and Drug Administration (FDA), and World Health Organization. Unusual sites of thrombosis after vaccination have been noted such as cerebral venous sinus and splanchnic vein thrombosis, which occur in the general population at 0.22–1.57 cases per 100 000 person-years [1, 8]. More common sites of thrombosis in the general population, such as lower-extremity deep venous thrombosis and pulmonary embolism, as well as arterial thrombosis, have also been reported [3, 9, 10].

TTS is triggered by complexes of PF4 and anti-PF4 antibodies that activate platelets via FcγIIa receptors. This mirrors the mechanism of heparin-induced thrombocytopenia, though the trigger for antibody formation is not known [11, 12]. Platelet activation with endothelial cell injury results in thrombocytopenia and thrombosis.

Most cases of TTS are described in women of childbearing age [1]. Pregnancy and the postpartum period are

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Correspondence: L. Pischel, Section of Infectious Diseases, Yale School of Medicine, 135 College St, Suite 323, New Haven, CT 06510-2483 (lauren.pischel@yale.edu).

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themselves prothrombotic states due to the Virchow triad of (1) increased venous stasis of the lower extremities, (2) intrinsic hypercoagulability of pregnancy, and (3) endothelial injury of delivery [13, 14].

In first-generation Ad5 viral vectors, used mostly for gene therapy experiments in rhesus macaques, thrombocytopenia was one of many side effects, along with increased fibrinogen and von Willebrand factor, and clotting time prolongation [15]. Thrombocytopenia was thought to be related to increased platelet clearance after vaccine administration [16, 17].

The COVID-19 pandemic marks the first time the adenovirus vector vaccines are being administered globally. With large numbers of people receiving these vaccines, rare side effects are more likely to surface. If TTS is a class-wide effect, examining the adverse effects reported from prior adenovirus vector vaccine trials could speak to the risk of thrombosis with adenovirus vector COVID-19 vaccines, both in the general population and in the hypercoagulable state of pregnancy. We conducted a systematic review and meta-analysis of pregnancy and thrombotic outcomes in adenovirus vector vaccine trials.

METHODS

Search Strategy, Information Sources, and Eligibility Criteria

PubMed was searched for clinical trials of adenovirus vector vaccines using the terms "(Adenovirus vaccine) AND (Clinical trial)" and separately "Adenovirus vaccine" and the clinical trials filter. Articles were included from 1 January 1966 to 9 August 2021. The last search was on 24 August 2021. All relevant citations were explored. Gray literature was searched from FDA documents for COVID-19 vaccine trials with adenovirus vector vaccines, and the company web pages of Johnson & Johnson and AstraZeneca were queried for further publications. Titles and abstracts were reviewed and included if they reported human phase 1–4 clinical trials or postmarketing studies. Studies were excluded if they did not report primary clinical trial results, were not reported in English, or involved autologous dendritic cell trails transduced with adenovirus, inactivated or oral vaccine trials against adenovirus from the 1960s to 1970s (this vaccine was thought to be sufficiently distinct from the adenovirus viral vector vaccines). Preclinical vaccine trials in animals were excluded, as were vaccine targeting infectious diseases of nonhuman animals. Studies were grouped based on outcomes of thrombocytopenia, coagulopathy (defined as bleeding, prolonged prothrombin time [PT], or activated partial thromboplastin time [aPTT], or report of thrombosis including transient ischemic attacks), pregnancy, and pregnancy outcomes. This systematic review and meta-analysis were completed prior to registration and otherwise was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1).

Search and Selection Process

One author (L. P.) reviewed studies for eligibility criteria. Two authors (L. P. and K. M. P.) reviewed full articles and supplements for cases of thrombocytopenia, thrombosis, coagulopathy, pregnancy, and pregnancy outcomes, as well as number of participants in each study arm. If agreement could not be met between the 2 authors, a third author (S. B. O.) was available to resolve the discrepancy. No automated tools were used in the search or selection process.

Data Collection Process

Grade of laboratory abnormality was noted. Coagulopathy and thrombocytopenia events were used as a proxy for TTS. Pregnancy outcomes were grouped into (1) healthy term births and elective abortions and (2) all other events: spontaneous abortions, therapeutic abortions, preterm birth, congenital abnormality, fetal distress in labor, and/or hemorrhage in labor. As a pregnant woman may be pregnant with multiple gestations (eg, twins), the number of pregnancies does not equal the number of pregnancy outcomes. If no outcomes were reported, the outcomes of interest were marked as zero. If the exact number of outcomes was unclear, this was noted, and the nearest estimate was included in meta-analysis if possible. If specified that the adverse event occurred before adenovirus vector administration and in response to another vaccine, this event was counted toward a non–adenovirus vector event even if the person was in the adenovirus-based vaccine arm.

Synthesis Methods and Risks of Bias

Clinical trials were divided into studies that targeted infectious diseases and those that targeted cancers. For those studies that targeted infectious diseases, 3 meta-analyses were conducted for thrombocytopenia, coagulopathy, and pregnancy outcomes. Studies included in systematic review and meta-analyses that contributed to the relative risk were assessed for reporting bias. Meta-analyses was planned for the cancer targeted clinical trials, but as nearly all participants received an adenovirus vector vaccine, these results were simply described. For the meta-analysis, the Paule and Mandel method was used for binary outcomes and forest plots were generated. Relative risk (RR) with 95% confidence interval (CI) was used as an effect measure. A fixed-effects model was used if $I^2 < 25$ and a random-effects model if $I^2 > 50$. If I^2 was between 25 and 50, both models were reported. Funnel plots and linear regression test of funnel plot asymmetry were generated to assess reporting bias, and asymmetry of funnel plots was evaluated by linear regression via Harbord method with a P value of $< .05$ noted as significant. Sensitivity analysis was performed with removal of trials where the comparison arm was another viral vector. Data extracted from included studies, data for analysis, and code are available upon request. All analysis was performed in R (version 4.0.2) software with the meta package [18].

RESULTS

Search Results

The PubMed search returned 648 articles. After duplicates were removed, 401 articles were screened for outcomes (Figure 1). Of these, 49 were animal trials and excluded. The remaining 352 articles were assessed for eligibility, and 218 met inclusion criteria. Thirty-seven additional articles were identified from the gray literature: 27 from company websites, 5 from the FDA, 3 from back-tracing citations from already included articles, and 2 from ClinicalTrials.gov. Of these, 4 were excluded as they were not adenovirus vector–based vaccine clinical trials [19–22]. A total of 167 articles spanning 159 trials were included in the final analysis.

Adenovirus Vaccines Targeting Infectious Diseases

For adenovirus vector–based vaccines targeting infectious diseases, there were 123 trials for 17 infectious diseases using 17 adenovirus vector types and 157 907 total participants. Of those with known arm allocation (n = 92 056), 65.3% (n = 60 154) received an adenovirus vector vaccine and the remainder received placebo or another vaccine. The most common vectors used were Ad5 (30.1% of studies) and chimpanzee adenovirus 63 (ChAd63) (16.2% of studies). Studies targeting human immunodeficiency virus (HIV) and Ebola virus disease were the most common, making up 29.3% and 16.2% of studies, respectively.

Adenovirus Vaccines Targeting Noninfectious Diseases

For adenovirus-based vaccines for malignancies or noninfectious disease targets, 36 trials were found covering 13 diseases. Nine hundred five participants were enrolled, of whom 96.9% (n = 877) received an adenovirus-based vaccine. The most common vector used was Ad5 (55.6% of studies), following by chimeric Ad2/Ad5 vector (25% of studies). The most common target was metastatic or advanced malignancy (5 studies).

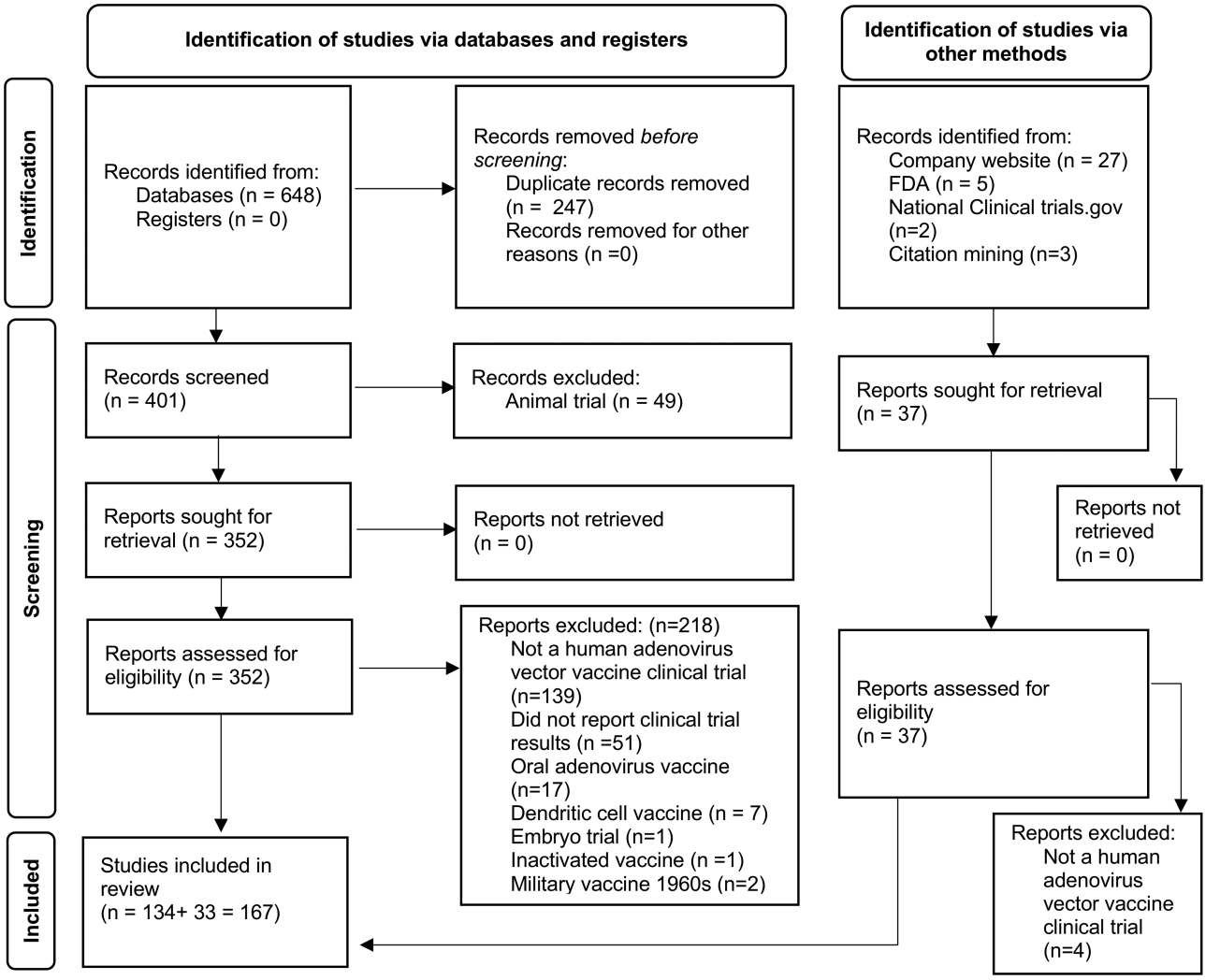

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram: identification, screening, and inclusion of manuscripts reviewed for adenovirus vector–based vaccines. Adapted from: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. doi:10.1136/bmj.n71. For more information, visit http://www.prisma-statement.org/. Abbreviation: FDA, US Food and Drug Administration.

THROMBOCYTOPENIA OUTCOMES

Twenty studies reported thrombocytopenia events (Supplementary Table 2). One study did not report exact numbers of thrombocytopenia events [23]. Six studies were testing vaccination dosage, and all participants received at least 1 dose of adenovirus vector vaccine [24–29]. ChAd3 and Ad5 were the most common viral vectors, used in 32% and 26% of studies, respectively. The most frequent diseases targeted were Ebola virus (7 studies) and *Plasmodium falciparum* (5 studies). Of 33 events in the adenovirus vector vaccine group, 22 (67%) had grades associated with them: 9 grade 1, 7 grade 2, and 6 grade 3. Of the 20 episodes of thrombocytopenia in the non–adenovirus vector vaccine group, 6 (30%) had associated grades: 1 grade 1, 4 grade 2, 1 grade 3. Across all studies, the incidence of thrombocytopenia was 0% (interquartile range [IQR], 0%–0%) in the adenovirus and nonadenovirus arms.

After removing studies where all participants received an adenovirus vector vaccine or exact numbers of thrombocytopenia were not reported, 13 studies were included in the meta-analysis (Figure 2). Using a fixed-effects model, the risk ratio for thrombocytopenia events in adenovirus vector arms compared with non–adenovirus vector arms was 0.460 (95% CI, .255–.830; $I^2 = 0\%$). The funnel plot was symmetric (Supplementary Figure 1).

Sensitivity Analysis

For sensitivity analysis, thrombocytopenia events that occurred after receipt of other viral vectors or vaccines were removed. In the study by Tamminga et al, the episode of thrombocytopenia in the trial arm occurred after the DNA prime dose but before the adenovirus boost [30]. In the study by Ogwang et al, participants in the active arm received ChAd63 encoding multiple epitopes-Thrombospondin-Related Adhesion Protein (ME-TRAP) followed by Modified Vaccinia Virus Ankara (MVA) ME-TRAP vaccine whereas placebo recipients received 2 doses of rabies vaccine. There was 1 episode of thrombocytopenia after ChAd63, 4 episodes after the MVA ME-TRAP, and 6 after the rabies vaccine [31]. After the removal of these 2 articles, the RR was 0.568 via fixed-effects model, though this was not a significant difference (95% CI, .293–1.102; $I^2 = 0\%$) (Supplementary Figure 2).

COAGULOPATHY OUTCOMES

Twenty studies also reported at least 1 prolongation of PT, aPTT, thrombotic event, or coagulopathic event (Supplementary Table 3). One study did not report exact numbers of prolongations but rather that the aPTT was increased in the ChAd3 group and decreased in the recombinant vesicular stomatitis virus group [29]. ChAd3, Ad35, and Ad5 were the most common viral vectors (20% each). The most frequent diseases targeted were Ebola (40%) and HIV (25%). Four of the studies were testing dosage of vaccination and all participants were allocated to receive at least 1 dose of adenovirus vector vaccine [26, 32–34]. Seventy episodes of coagulopathy were reported in the adenovirus arms and 16 in the nonadenovirus arms. Overall, there was 0% (IQR, 0%–0%) incidence of thrombocytopenia in the adenovirus and nonadenovirus arms.

Of 48 events of PT or aPTT prolongation in the adenovirus vector vaccine group, 27 reported grades: 18 grade 1, 6 grade

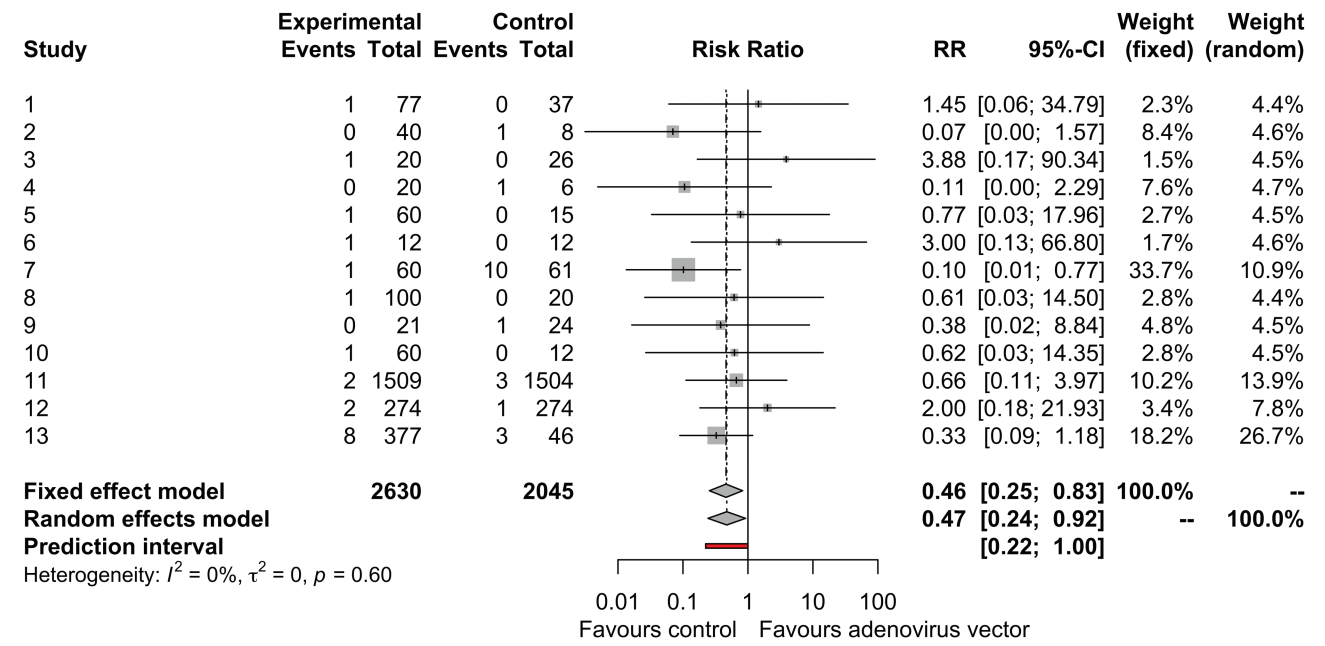

Figure 2. Forest plot of thrombocytopenia events in the adenovirus vector vaccine arm or placebo arm. Abbreviations: CI, confidence interval; RR, relative risk.

2, 1 grade 3, and 2 grade 4. Of the 8 episodes of PT or aPTT prolongation in the non–adenovirus vector vaccine group, 3 reported grades: 2 grade 1 and 1 grade 3. Of the participants in the adenovirus arm, 0.08% had a prolongation of PT/aPTT compared to 0.03% in the nonadenovirus arm. Overall, this was a rare event, with 0% (IQR, 0%–0%) occurring in both adenovirus vector and non–adenovirus vector recipients. The prolongation of aPTT was frequently attributed to a positive antiphospholipid antibody/positive lupus anticoagulant [34, 35].

There were 20 thrombotic events in the adenovirus vector vaccine arm (8 deep vein thrombosis [DVT], 8 pulmonary emboli [PE], 2 cerebral venous sinus thrombosis, 1 thrombosis not otherwise specified, and 1 ischemic stroke) and 5 in the non–adenovirus vector vaccine arm (4 deep vein thrombosis, 1 pulmonary embolism). Six of the DVTs were reported in JNJ-78436735/Ad26.COV2.S along with 4 PEs [36, 37]. One DVT, PE, and ischemic stroke occurred in the adenovirus arm for ChAdOx1 nCoV-19 compared with 1 DVT and 1 hemolytic anemia in the placebo group [38]. Two cerebral sinus thromboses were reported, 1 in JNJ-78436735 and 1 in Ad26.ZEBOV, although these were not attributed to vaccination [36, 37]. One hemorrhagic stroke was reported in the placebo arm of Gam-COVID-Vac [39]. There was no overlap of thrombocytopenic events in these cases with thrombotic events.

In the meta-analysis of coagulopathy outcomes, 16 publications were included. The risk ratio for coagulopathy via a fixed-effects model was 1.013 (95% CI, .659–1.557; I^2 = 4.6%) comparing adenovirus-based vectors to non-adenovirus-based vectors or controls (Figure 3). Visually there was heterogeneity of publications via funnel plot with an absence of small studies with an RR <1, although test for heterogenicity failed to reject the null hypothesis of publication bias (P = .076) (Supplementary Figure 3).

PREGNANCY OUTCOMES

Twenty-eight studies reported at least 1 pregnancy for a total of 1731 pregnancies (Supplementary Table 4). Of these, the majority of 1199 pregnancies did not have full information fully reported [40, 41]. In trials where arm allocation was described and full results were reported, 285 received an adenovirus vector–based vaccines (54.5%) and 238 received a placebo or another vaccine. Ad5 and Ad26 were the most common viral vectors used (27.6% and 24.1%, respectively). HIV and Ebola trials were again the most frequent diseases target and comprised 48.3% and 20.7% of the studies, respectively. These were larger trials, did not have pregnancy as an exclusion criterion, or were specifically studying pregnant individuals. Of the 80 pregnancies in the adenovirus vector vaccine group where the pregnancy outcomes were reported, 57.5% resulted in healthy full-term births. Of the 76 pregnancies in placebo or non–adenovirus vector arms, 61.8% resulted in healthy full-term births. This is overall consistent with the established background risk of major birth defects of 2%–4% and miscarriage of 15%–20% in the general population of the United States [40]. No cases of DVT, cerebral sinus thrombosis, or other coagulopathy was reported with these pregnancies, although 1 placebo recipient had postpartum hemorrhage [42].

Thirteen studies reported adverse pregnancy events. In 1 of these studies, all participants received study vaccine [43]. Using a fixed-effects model, the RR of adverse event in pregnancy

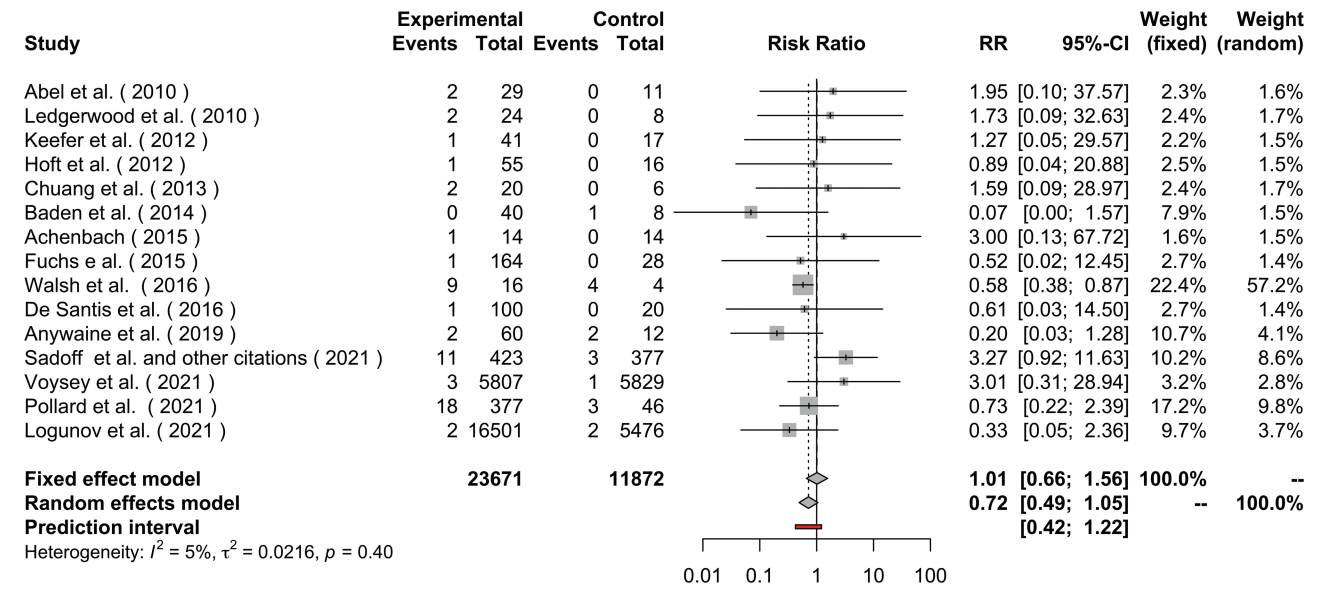

Figure 3. Forest plot of coagulopathy events in the adenovirus vector vaccine arm or placebo arm. Coagulopathy events described as elevated prothrombin, partial thromboplastin time, bleeding event, or thrombosis event. Abbreviations: CI, confidence interval; RR, relative risk.

was 0.675 (95% CI, .448–1.017; I^2 = 0%) (Figure 4). The funnel plot of publications was grossly symmetric (test for heterogeneity $P > .05$). (Supplementary Figure 4). Across all pregnancy events, the RR for pregnancy was not different between adenovirus and nonadenovirus arms (Supplementary Figure 5).

Of the 36 clinical trials of adenovirus vector therapy for malignancy or gene therapy, 5 reported thrombocytopenia [44–48] and 5 studies reported a coagulopathy [45, 49–52] (Supplementary Table 5). There were no pregnant individuals in these trials. In majority of these trials (34 of 36), all participants received an adenovirus vector–based vaccine. In the 2 trials where all participants did not receive an adenovirus vector–based vaccine [53, 54], there were no outcomes of interest.

DISCUSSION

To our knowledge, this is the largest systematic review and meta-analysis examining the adverse effects of thrombocytopenia, coagulopathy, or adverse birth outcomes of adenovirus vector vaccines. We found (1) no increased risk for thrombocytopenia, coagulopathy, or adverse pregnancy outcome and (2) no evidence of coagulopathy in pregnant individuals. By aggregating clinical trials of adenovirus vector vaccines in a systematic review and meta-analysis, we were able to analyze for class-adverse effects of thrombocytopenia, coagulopathy, and adverse pregnancy outcome.

Events of thrombocytopenia and coagulopathy were quite rare, with a median of 0 participants having these outcomes in both the adenovirus and nonadenovirus arms [55]. For thrombocytopenia, it initially appeared that adenovirus-based vector vaccines had a lower risk for thrombocytopenic events compared with control (RR, 0.460 [95% CI, .255–.830]; I^2 = 0%). This effect was no longer significant after removal of studies that had other viral vectors or rabies vaccines in the control arm (RR, 0.569 [95% CI, .293–1.102]; I^2 = 0%). In addition to the coagulopathy associated with the Vaxzevria and Johnson & Johnson COVID-19 vaccines, it should be noted that the Ad26.ZeBOV phase 2 trial was paused briefly due to 2 neurologic events, 1 of which was a cerebral venous sinus thrombosis.

Understanding potential risks of vaccination in pregnancy remains paramount for best advising pregnant women in the decision of vaccination during pregnancy. From this meta-analysis there was no increased risk of thrombocytopenia, coagulopathy, or adverse birth outcome associated with receipt of adenovirus vaccination. Furthermore, the hypercoagulability of pregnancy does not seem to predispose toward the more phenotypically severe spectrum of thrombotic disease seen in TTS. Altogether, these findings are in line with the CDC's recommendations for all pregnant persons to receive a COVID-19 vaccine [56].

This systematic review and meta-analysis has several limitations. Primarily, though this study examined all available clinical trials, with an estimated 10.6 cases of TTS per million doses in women aged 30–39 years (and 3.8 cases per million doses in the general population), it may be underpowered to detect a different in TTS rates given the low baseline population incidence [57]. Second, we did not include in our case definition a D-dimer >4 times the upper limit of normal, which is a part of the American Society for Hematology TTS definition [2]. This was to cast as wide a net as possible and not exclude potential cases, as TTS was not defined when most of these studies were conducted. Furthermore, several studies used nonexact statements about the number or grade of adverse effects. For pregnancy, outcomes had not yet been fully reported

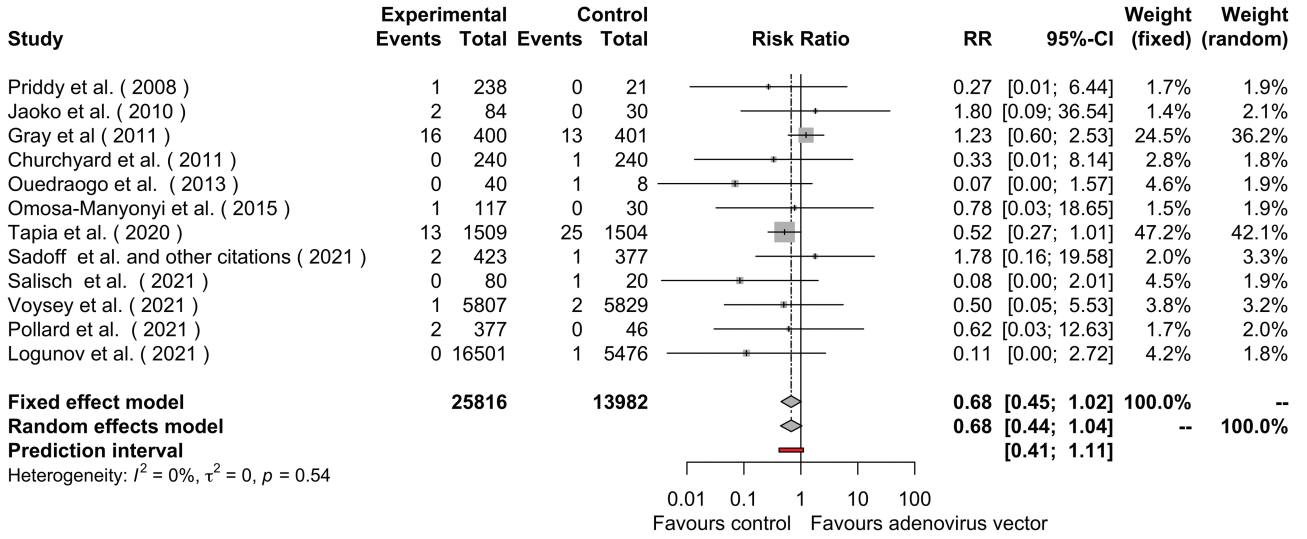

Figure 4. Forest plot of adverse pregnancy events in the adenovirus vector vaccine arm or placebo arm. Abbreviations: CI, confidence interval; RR, relative risk.

for several studies. Some data were not publicly available; for example, in FDA documents, 1522 pregnancies were reported as related to the AD26.ZEBOV vaccine [40], whereas our search yielded only 1087 pregnancies. Finally, the review was limited to English-language literature.

CONCLUSIONS

Though rare cases of TTS have been associated with COVID-19 adenovirus vector vaccines, in this systematic review and meta-analysis of clinical trial data there was no increased risk of thrombocytopenia or coagulopathy when comparing adenovirus vector vaccines to placebo arms. Additionally, there was no increase of adverse fetal outcome across these studies and no report of thrombosis or coagulopathy in pregnant women.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. L. P., K. M. P., G. G., and S. B. O. report being supported on a T32 training grant as part of a Yale University Infectious Disease Fellowship, which has paid for conference attendance and educational materials.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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