INFECTIOUS DISEASE

A meta-analysis of clinical studies conducted during the West Africa Ebola virus disease outbreak confirms the need for randomized control groups

Lori E. Dodd[1,2]*, Dean Follmann[1], Michael Proschan[1], Jing Wang[3], Denis Malvy[4,5], Johan van Griensven[6], Iza Ciglenecki[7], Peter W. Horby[8], Rashid Ansumana[9,10], Jia-Fu Jiang[11], Richard T. Davey[12], H. Clifford Lane[13], Aurelie Gouel-Cheron[1,14]

Recent Ebola virus disease outbreaks affirm the dire need for treatments with proven efficacy. Randomized controlled clinical trials remain the gold standard but, during disease outbreaks, may be difficult to conduct due to ethical concerns and challenging field conditions. In the absence of a randomized control group, statistical modeling to create a control group could be a possibility. Such a model-based reference control would only be credible if it had the same mortality risk as that of the experimental group in the absence of treatment. One way to test this counterfactual assumption is to evaluate whether reasonable similarity exists across nonrandomized control groups from different clinical studies, which might suggest that a future control group would be similarly homogeneous. We evaluated similarity across six clinical studies conducted during the 2013–2016 West Africa outbreak of Ebola virus disease. These studies evaluated favipiravir, the biologic ZMapp, the antimalarial drug amodiaquine, or administration of convalescent plasma or convalescent whole blood. We compared the nonrandomized control groups of these six studies comprising 1147 individuals infected with Ebola virus. We found considerable heterogeneity, which did not disappear after statistical modeling to adjust for prognostic variables. Mortality risk varied widely (31 to 66%) across the nonrandomized control arms of these six studies. Models adjusting for baseline covariates (age, sex, and cycle threshold, a proxy for viral load) failed to sufficiently recalibrate these studies and showed that heterogeneity remained. Our findings highlight concerns about making invalid conclusions when comparing nonrandomized control groups to cohorts receiving experimental treatments.

INTRODUCTION

The 10th Ebola virus disease outbreak in the Democratic Republic of the Congo began in August 2018 and continues to spread as of November 2019, demonstrating the urgent need for effective Ebola virus disease treatments. Multiple drug treatments such as the biologic ZMapp were studied during the West Africa Ebola virus disease outbreak of 2013–2016, but none provided definitive evidence about therapeutic efficacy. All but one of these clinical studies relied on data from nonrandomized control groups consisting of individuals infected with Ebola virus who were not given experimental treatments. The only randomized, controlled clinical trial, the Prevail II–ZMapp trial, closed before full accrual when the outbreak ended. Nonetheless, multiple experimental agents were administered during this outbreak without randomized controlled trials under the World Health Organization's Monitored Experimental Use of Unregistered and Investigational Interventions (1).

Conclusive evidence about experimental treatment efficacy requires an appropriate control group. Ideally, the only factor differing between the treatment and control groups is the intervention, with all other factors balanced. By balancing such factors across patients and study arms, randomization strengthens the evidence collected in support of treatment efficacy. Randomization may not always be feasible, and the ethics of randomization in clinical studies during a disease outbreak have been the subject of debate (2, 3). In the absence of randomized control groups, statistical models can attempt to equalize risk factors between the control and experimental groups. During the Ebola virus disease outbreak in West Africa, relevant factors identified to date include baseline viral load (4–6), age (7, 8), sex (9, 10), and supportive care measures. However, a model-based approach produces a valid reference control group only if the model reliably represents the risk of death in the population receiving the experimental therapy under the counterfactual assumption that the experimental therapy was not given.

Meta-analysis statistical techniques provide a framework for evaluating the validity of this assumption through a comparison of control group mortality proportions across studies, after adjustments for covariates. Analysis of patient-level data (as compared to the study-level summary data typically used for meta-analysis) from multiple studies offers a more powerful and comprehensive analysis of risk factors. For example, a comparison of the strength of the relationship between viral load and mortality risk across studies can characterize the heterogeneity among studies. Homogeneity of regression coefficients across studies may provide confidence that a

[1]Biostatistics Research Branch, Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. [2]School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa. [3]Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research Sponsored by the National Cancer Institute, Frederick, MD, USA. [4]Inserm, UMR 1219, Université de Bordeaux, Bordeaux, France. [5]Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France. [6]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium. [7]Operational Centre Geneva, Médecins Sans Frontières, 1211 Geneva, Switzerland. [8]Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK. [9]Mercy Hospital Research Laboratory, Kulanda Town, Bo, Sierra Leone. [10]School of Community Health Sciences, Njala University, Bo, Sierra Leone. [11]Beijing Institute of Microbiology and Epidemiology, Beijing, China. [12]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. [13]Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. [14]Anesthesiology and Intensive Care Department, Hopital Bichat—Claude Bernard, Assistance Publique—Hopitaux de Paris, Paris, France.
*Corresponding author. Email: doddl@mail.nih.gov

representative control group can be generated as a comparator for experimental groups. Here, we compare regression models across six studies from the West Africa Ebola virus disease outbreak and evaluate their potential contribution to studies of experimental treatment efficacy. Our approach makes many assumptions, including that all relevant prognostic variables were measured and appropriately modeled in the analysis, a goal unlikely to be met in any clinical research setting.

RESULTS

Summary of eight clinical studies conducted during the West Africa outbreak

Eight therapeutic intervention studies during the West Africa outbreak of Ebola virus disease were identified from our literature search (fig. S1). Individual patient data from all eight studies were obtained. Covariates of baseline cycle threshold (a proxy measure of viral load), age, and sex were only available for six of the eight studies. Information about the use of intravenous fluids was not available in sufficient numbers for analysis. In total, complete data were provided for 1582 individuals infected with Ebola virus. However, to make studies more comparable and because of the U-shaped relationship between age and mortality (11–14), children under 6 years old were not included, resulting in data from a total of 1493 subjects. Notably, whereas studies did not always use the same endpoint definition (e.g., mortality at 14 days versus mortality at 28 days), most deaths occurred within the first 14 days, making the impact of this difference negligible. Table 1 describes the data included, along with comparisons to reported results.

Of the eight clinical studies identified, the Prevail II–ZMapp trial was the only randomized, controlled clinical trial. This trial was conducted in Liberia, Sierra Leone, Guinea, and the United States and tested the ZMapp triple monoclonal antibody therapy. There were 36 individuals infected with Ebola virus who received this biologic compared to 35 individuals infected with Ebola virus who did not with both arms of the trial receiving optimized standard of care. Per-protocol, optimized standard of care was defined as the most optimal standard of care possible for the setting. This included "the application of aggressive fluid resuscitation, hemodynamic and respiratory support, metabolic corrections, diagnostic evaluation, and other modalities of advanced critical care that are generally available in most academic centers capable of caring for critically ill patients," although this was not widely achieved given conditions in the field (15). The study enrolled from March 2015 to November 2015, at which point new cases of Ebola virus disease had ceased (16).

The other seven studies used nonrandomized control groups defined as Ebola virus–infected individuals who did not receive one of the experimental therapies and who were not enrolled in a randomized controlled trial. These clinical studies had one of two types of nonrandomized control group. The first type consisted of individuals infected with Ebola virus who did not receive experimental treatments but who provided data from the same treatment center over a similar time period, e.g., the clinical study conducted in Liberia using the antimalarial drug amodiaquine (17). During a 12-day period in August 2014, the supply of the first-line antimalarial drug combination (artemether-lumefantrine) ran out, and 71 individuals with Ebola virus disease were prescribed artesunate-amodiaquine. The amodiaquine treatment was considered experimental, and this group was compared to 194 Ebola virus–infected individuals prescribed the standard regimen of artemether-lumefantrine from June to October 2014.

In the clinical study conducted in Sierra Leone testing the efficacy of convalescent whole-blood administration, individuals with a blood type that matched stored whole blood from Ebola virus disease survivors were enrolled from December 2014 until April 2015 (18). Patients who had a matching blood type and agreed to a transfusion (n = 43) were included in the experimental group; 25 patients who did not receive a transfusion were considered controls. Cycle threshold data were only available for 11 patients in the experimental arm and 20 patients in the control arm.

The remaining five clinical studies used the second type of control group, historical controls, which included individuals hospitalized in a different center from that used in the clinical trial or those hospitalized during an initial preparation period in the same treatment center. The convalescent-plasma study enrolled individuals with Ebola virus disease in Guinea from mid-February through early August 2015 (19). Control patients consisted of individuals enrolled during a preparatory period from September 2014 to January 2015. After exclusion of deceased patients within the first 3 days (for both experimental and control groups), a total of 84 participants received a transfusion of convalescent plasma. Data from the remaining 418 patients who did not receive a transfusion were available as historical controls.

There were two clinical studies testing the experimental antiviral drug favipiravir, and these studies also used historical controls. The Favi-Bai study enrolled 85 individuals with Ebola virus disease for the control group in Sierra Leone from 10 to 30 October 2014, and 39 individuals for the experimental group from 1 to 10 November 2014 (20). The Favi-JIKI trial enrolled participants for the experimental arm (n = 99) from late December 2014 to mid-April 2015 at three sites in Guinea (21). For this trial, historical controls (n = 540) comprised patients hospitalized at Ebola treatment centers in Guinea run by Medecins Sans Frontieres from mid-September 2014 to mid-December 2014.

In Guinea, a small study of interferon-β1a (IFN-β1a) treatment was conducted in nine patients with Ebola virus disease enrolled at an Ebola treatment unit from late March through mid-June 2016 (22). Data from the 28 historical control subjects were not available for this meta-analysis. A study testing the small interfering RNA (siRNA) molecule TKM-130803 enrolled 14 participants from 1 March until 15 June 2015 in a single Ebola treatment unit in Sierra Leone (23). The futility boundary for this study was based on historical control data from 1820 Ebola virus disease cases obtained from Medecins Sans Frontieres. The study closed due to crossing a futility boundary due to the high number of deaths. Cycle threshold data from historical controls were not available for this study.

Mortality and cycle threshold associations with time

Figure 1 shows a plot of the date range of enrollment relative to mortality rate and mean baseline cycle threshold for six reference control groups. Analysis of the subjects' date of enrollment was not possible. The figure suggests a decline in mortality over time, although this effect was driven by the Prevail II–ZMapp trial data and the relationship was not statistically significant (P = 0.23). Likewise, the mean baseline cycle threshold values did not change significantly over time (P = 0.48). Next, we evaluated the relationship between cycle threshold and mortality, using patient-level data.

Analytical challenges with pooling control arm data

Standard of care and symptomatic patient management measures were not always extensively described in the eight studies we identified

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Table 1. Demographic summary of the six clinical studies included in the meta-analysis by treatment group. Trt, treatment; IVF, intravenous fluids; NA, not applicable.

Study	Arm (N)	Enrollment dates	Meta-analysis dataset*				Published study results		
			Age Mean (SD)	Females	C_T Mean (SD)	Mortality	N	Mortality	IVF use
Prevail II–ZMapp (16)	Control (29)	3/1/2015–11/1/2015	33 (13.1)	41.4%	22.9 (3.7)	31.0%	35	37%	63%
	Trt (31)	3/1/2015–11/1/2015	27.6 (17.5)	58.1%	24.1 (5.2)	19.4%	36	22%	61%
Amodiaquine (17)	Control (169)	6/5/2014–10/24/2014	31.1 (14.8)	48.5%	20.2 (4.1)	62.1%	194	64.4%	32%
	Trt (58)	8/18/2014–8/30/2014	29.5 (18.3)	46.6%	19.9 (4.2)	51.7%	71	50.7%	35.2%
ConvBlood (18)	Control (11)	12/1/2014–4/30/2015	35.8 (13.0)	36.4%	27.7 (7.2)	54.5%	25	44%	NA
	Trt (20)	12/1/2014–4/30/2015	26.2 (11.5)	60%	25.4 (5.0)	20%	43	28%	100%
ConvPlasma (19)	Control (382)	9/1/2014–1/1/2015	33.2 (15.8)	49.5%	26.4[†] (4.1)	36.9%	418	38%	NA
	Trt (78)	1/1/2015–7/7/2015	31.6 (14.8)	56.4%	27.9[†] (4.1)	32.1%	84	31%	NA
Favi-Bai[‡] (20)	Control (78)	10/10/2014–10/30/2014	29.6 (15.0)	53.8%	26.0 (4.6)	65.4%[‡]	85	64.7%	0%
	Trt (38)	11/1/2014–11/10/2014	31.7 (17.8)	47.4%	27.3 (5.4)	42.1%[‡]	39	43.6%	0%
Favi-JIKI (21)	Control (478)	9/15/2014–12/15/2014	36.0 (17.2)	50.6%[†]	20.8 (4.2)	56.9%	540	58%	NA
	Trt (99)	12/17/2014–4/8/2015	37.6 (16.7)	63.6%[†]	21.0 (4.3)	51.5%	99	51.5%	92%
IFN-β1a (22)	Control (NA)	3/26/2015–6/12/2015	NA	NA	NA	NA	21	81.0%	NA
	Trt (9)	3/26/2015–6/12/2015	33.9 (14.6)	55.6%	23.5 (4.4)	33.3%	9	33.3%	100%
TKM-130803[§] (23)	Control (NA)	NA	NA	NA	NA	NA	1820	55%	NA
	Trt (13)	3/11/2015–6/15/2015	41.7 (18.1)	38.5%	22.8 (3.9)	76.9%	12	75%	100%

*Patients below 6 years of age were excluded from this meta-analysis. Three studies had subjects with missing cycle threshold (C_T) values: amodiaquine ($n = 9$), Favi-Bai ($n = 1$), and TKM-130803 ($n = 1$). †In the Favi-JIKI study, the difference in the proportion of females was statistically significant at $P < 0.05$. In the ConvPlasma study, the mean cycle thresholds were different at $P < 0.05$. ‡In the published manuscript for the Favi-Bai study, primary analyses were reported excluding patients who were transferred out of the Ebola treatment unit, leading to 18 controls and 17 cases, with a 72 and 35% mortality rate ($P = 0.044$), respectively. The data provided for the meta-analysis included all patients, including those transferred out of the Ebola treatment unit. §In the published paper for the TKM-130803 trial, the primary analyses reported mortality eliminated deaths within the first 48 hours. However, in the meta-analysis, all deaths were included to parallel the other studies.

in our literature search, making comparisons difficult. Among the eight studies, all standard-of-care measures were reported to include oral hydration, prophylactic antibiotics, antipyretics/analgesics, electrolyte supplementation (guided by a point-of-care device for some of the studies), and antimalarial drug therapy. Reporting of the use of intravenous fluids varied widely among studies, ranging from 0% (Favi-Bai trial) to 85% or more (Favi-JIKI, Prevail II–ZMapp, TKM-130803, and IFN-β1a trials). Because intravenous fluid use is thought to be an important means of fluid resuscitation in patients with Ebola virus disease, this is a critical missing variable to consider when evaluating the analyses. The Prevail II–ZMapp trial allowed favipiravir treatment as a standard of care in Guinea. The Favi-Bai

study reported use of either artesunate or amodiaquine (17). Some studies reported use of antihelminthic drugs, antiemetic drugs, antidiarrheals, anticonvulsants, anxiolytics, mechanical ventilation, or corticosteroids. None of these variables were available for analysis.

Figure 2A shows a plot of the unadjusted mortality proportions from the six study control groups, ranging from 31% [Prevail II–ZMapp trial: 95% confidence interval (CI), 15 to 51%] to 66% (Favi-Bai trial: 95% CI, 55 to 76%). The control arm for the Favi-Bai trial had the highest mortality rate, despite the more favorable distribution of baseline characteristics relative to the other studies.

We next adjusted mortality for age, sex, and log cycle threshold using logistic regression. Even with adjustment, the mortality risk
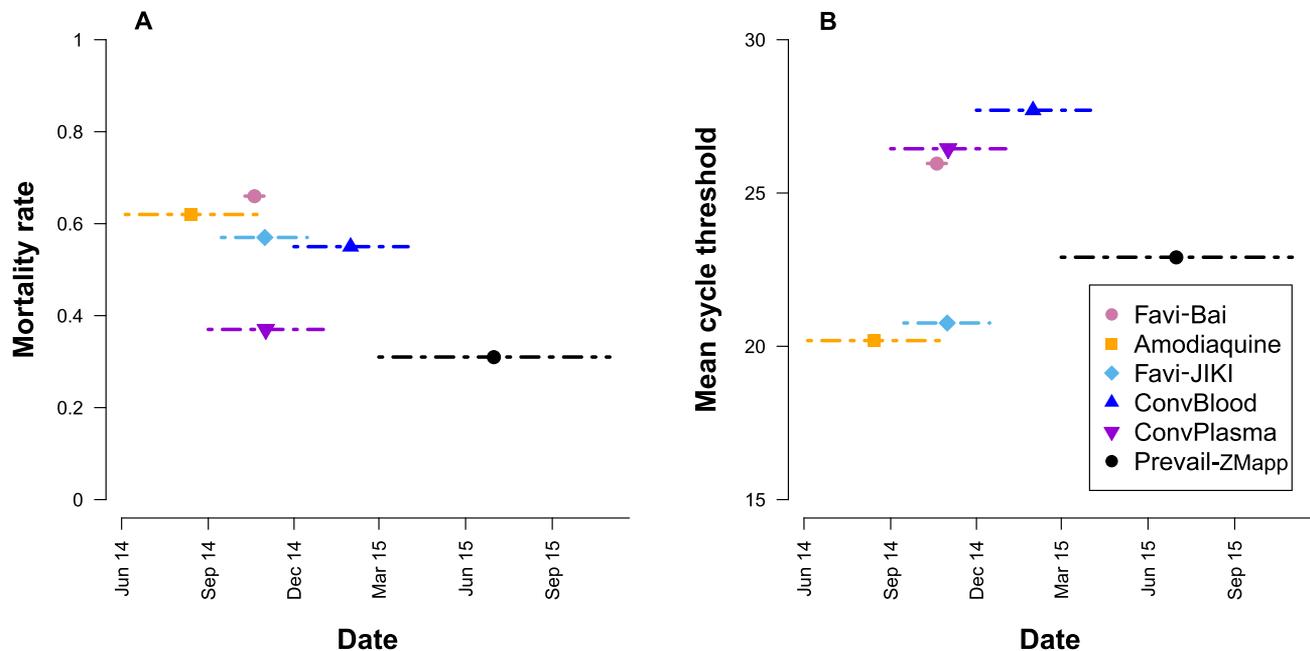
Fig. 1. Evaluation of mortality rates and cycle thresholds by enrollment date for control groups from the six clinical studies. These six control groups were included as comparator arms for the following six clinical studies: treatment with the antiviral drug favipiravir (Favi-Bai, Favi-JIKI), treatment with the antimalarial drug amodiaquine, administration of convalescent whole blood from Ebola virus disease survivors (ConvBlood), administration of convalescent plasma from Ebola virus disease survivors (ConvPlasma), and treatment with the triple monoclonal antibody therapy ZMapp (Prevail-ZMapp). (**A**) Mortality rates by dates during which enrollment was open for each study. (**B**) Mean cycle thresholds (a proxy for viral load) for each study according to enrollment dates.

varied significantly across studies ($P < 0.0001$). Furthermore, the relationship between log cycle threshold and mortality differed markedly across studies ($P < 0.001$), resulting in the logistic regression model $\text{logit}(p) = \beta_0 + \beta_1\text{sex} + \beta_2\text{age} + \beta_3\text{logCT} + \beta_{4j}\text{study}_j + \beta_{5j}(\text{study}_j \times \text{logCT})$ for $j = 1, \ldots, 5$. Figure 2B shows expected mortality as a function of log cycle threshold for women aged 34 across the six studies. The lack of reduction in mortality with high cycle thresholds (i.e., lower viral load) for the Favi-Bai study control group compared to the other studies is notable. Other control groups appeared to be more similar but remained significantly different ($P < 0.001$). Interaction tests of the study with age and sex were not significant ($P = 0.22$ and $P = 0.38$, respectively). Figure 2C is a Galbraith plot used to confirm heterogeneity. The slope of the black line is the weighted average across studies, relating mortality to log cycle threshold. If the relationship between log cycle threshold and mortality did not differ by study, then one would expect only 1 in 20 points to lie outside the dashed lines; instead, 3 of 6 points were outside those boundaries. Figure 2D shows predicted mortality for average covariate values (corresponding to 53% females, an age of 30.1 years, and a cycle threshold of 25.6) under the logistic regression model above (table S2 provides model estimates). Table 2 tabulates the estimated mortality risk in the control groups for a 34-year-old female for various cycle threshold values. For a cycle threshold value of 30, mortality ranged from 1 to 59%, whereas for a cycle threshold value of 20, mortality ranged from 47 to 74%.

Evaluation of the experimental treatments
The large between-study variability made combining data for a common control model problematic. However, it was possible to evaluate each therapeutic intervention in the eight clinical studies relative to each of six control groups, in turn adjusting for avail-

able baseline covariates (i.e., log cycle threshold, age, and sex) (Figs. 3 and 4). If the six control groups represented the range of controls, then a consistent pattern of efficacy across the heterogeneous control groups might contribute to the evidence base. Notably, however, this assumption was not testable, and the analysis assumed that model fit was adequate. Hence, we caution against overinterpretation.

All but two CIs for the antimalarial drug amodiaquine compared to the control groups were below one, suggesting an association of reduced mortality with amodiaquine treatment (Fig. 3A). Confidence intervals comparing TKM-130803 included odds ratios above 1 for comparisons with two control groups (Favi-JIKI and Prevail II–ZMapp), suggesting an association of increased mortality with TKM-130803 treatment (Fig. 3B). The CI for the odds ratios for the Prevail II–ZMapp treatment group relative to other control groups indicated improved survival for individuals administered ZMapp compared to all control groups, except its own (internal) randomized control group (Fig. 3C). One of six CIs for the IFN-β1a treatment compared to control groups suggested improvement in survival (Fig. 3D).

Three of six CIs for the Favi-JIKI treatment group compared to control groups suggested improvement in survival (Fig. 4A). Results for IFN-β1a treatment (Fig. 3D), convalescent plasma administration (Fig. 4B), Favi-Bai treatment (Fig. 4C), and convalescent whole-blood administration (Fig. 4D) were mixed. Figures S2 and S3 display treatment-effect odds ratios, adjusting for log cycle threshold, age, and sex within the subgroup with a cycle threshold of ≥20, a reported subgroup of the Favi-JIKI study. Figure S4 compared the per-protocol and intent-to-treat samples for the TKM-130803 study, the only study for which this comparison could be evaluated. Tables S3 and S4 provide model estimates for Figs. 3 and 4.
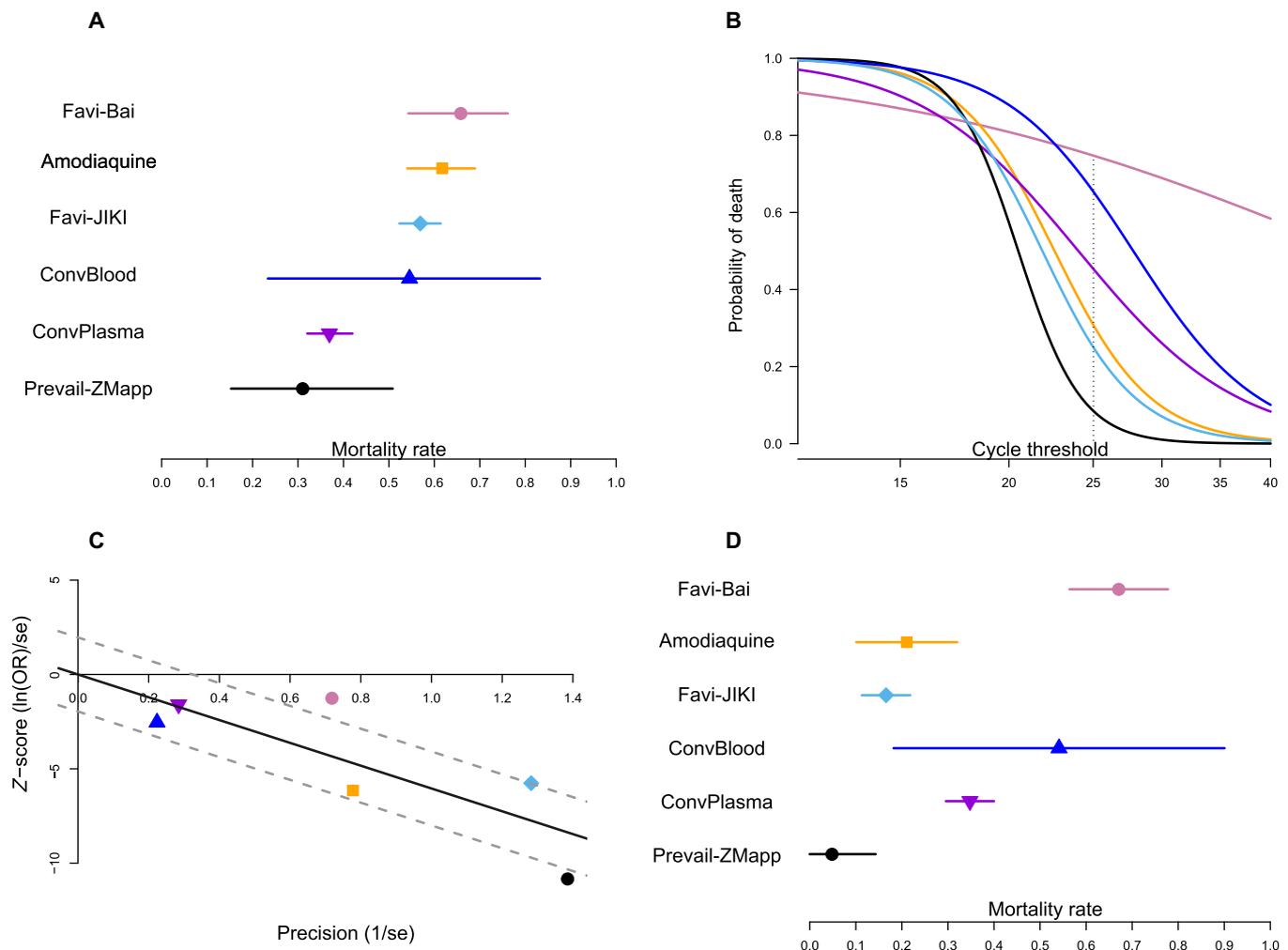
Fig. 2. Comparison of the control groups from the six clinical studies. (**A**) Raw mortality rates from the control groups of the six clinical studies. These studies included treatment with the antiviral drug favipiravir (Favi-Bai, Favi-JIKI), treatment with the antimalarial drug amodiaquine, administration of convalescent whole blood from Ebola virus disease survivors (ConvBlood), administration of convalescent plasma from Ebola virus disease survivors (ConvPlasma), and treatment with the triple monoclonal antibody therapy ZMapp (Prevail-ZMapp). (**B**) Expected mortality as a function of cycle threshold (a measure of viral load) for a woman aged 34 across the six studies. (**C**) A Galbraith plot confirmed heterogeneity between studies. (**D**) Predicted mortality rates for covariate values corresponding to 53% females, with an average age of 30.1 years, and an average cycle threshold of 25.6.

Table 2. Expected study-specific mortality risk for control patients according to cycle threshold (C_T) values, adjusting for sex and age based on a logistic regression model for a 34-year-old female.

	Prevail II–ZMapp (16)	Amodiaquine (17)	ConvWBlood (18)	ConvPlasma (19)	Favi-Bai (20)	Favi-JIKI (21)
C_T 20	0.47 (0.23, 0.72)	0.55 (0.37, 0.71)	0.83 (0.31, 0.98)	0.61 (0.49, 0.71)	0.74 (0.54, 0.87)	0.57 (0.5, 0.64)
C_T 25	0.06 (0.01, 0.28)	0.15 (0.04, 0.45)	0.55 (0.22, 0.84)	0.35 (0.29, 0.42)	0.66 (0.54, 0.76)	0.18 (0.13, 0.24)
C_T 30	0.01 (0, 0.17)	0.04 (0, 0.29)	0.29 (0.06, 0.7)	0.19 (0.14, 0.25)	0.59 (0.43, 0.73)	0.05 (0.03, 0.08)

DISCUSSION

Nonrandomized control data are only credible reference comparators if they represent the risk of death in the population who received experimental treatment under the counterfactual condition that the experimental treatment was not given. We sought to test this assumption by evaluating the homogeneity among control groups

derived from clinical study data from 2013 to 2016 obtained during the West Africa outbreak of Ebola virus disease. This analysis revealed considerable heterogeneity, which was not removed after statistical modeling. Therefore, we conclude that we cannot rely on nonrandomized control data as a valid benchmark for efficacy evidence in clinical studies lacking a randomized control group.
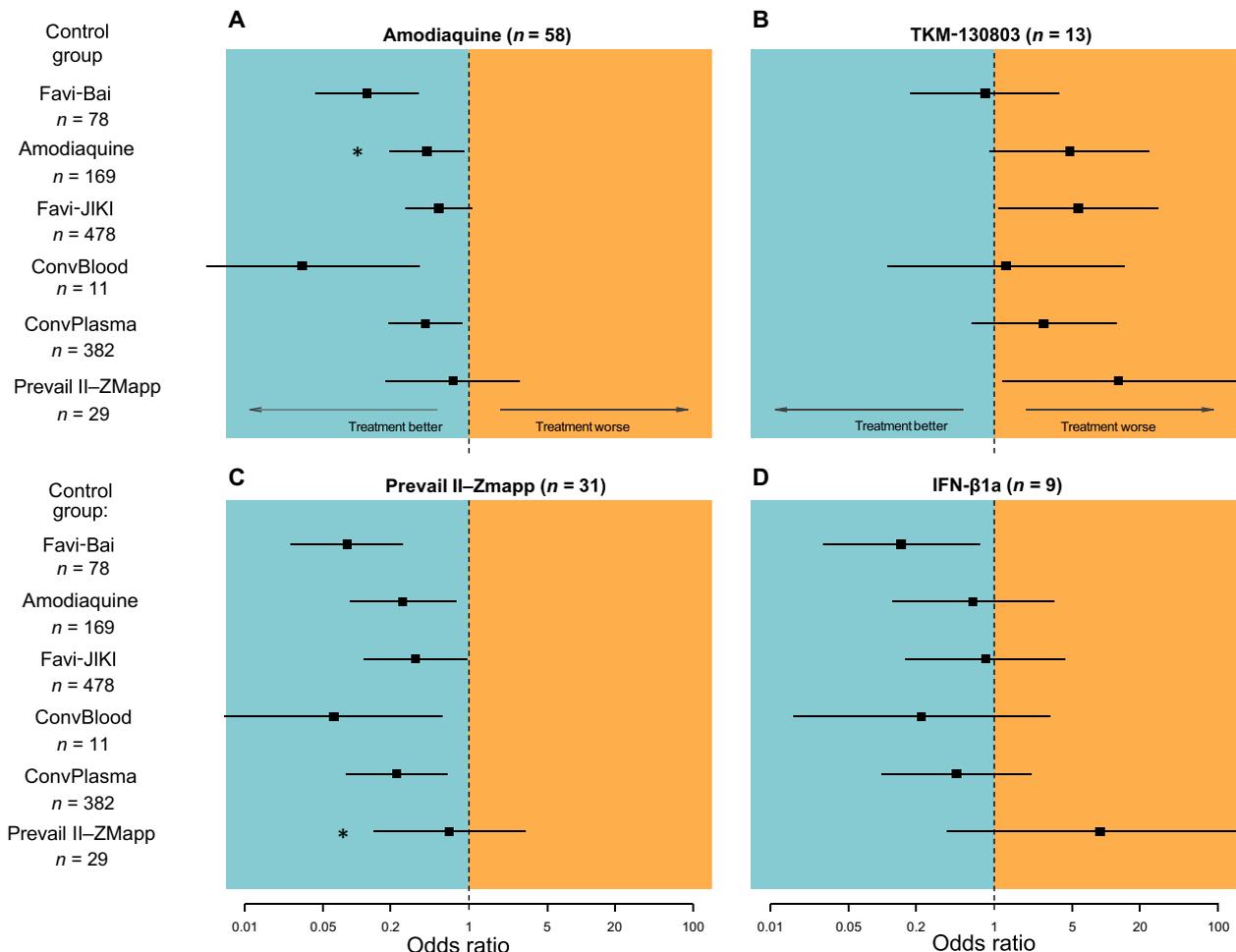
Fig. 3. Standardized odds ratios for treatment effects for four investigational drugs. Standardized odds ratios for treatment effects are shown for the experimental arms relative to each control group of the clinical studies investigating (**A**) the antimalarial drug amodiaquine, (**B**) the siRNA drug TKM-130803, (**C**) the triple monoclonal antibody therapy ZMapp, and (**D**) IFN-β1a. For each standardized odds ratio, a logistic regression model was fit using data from the control group listed in the left column and the experimental arm indicated above the plot. The odds ratios for the models are reported in table S3.

The results of our meta-analysis underscore the difficulties of conducting Ebola virus disease clinical research. The rapid course of the disease and challenging field conditions present enormous challenges (*24*). Factors that change over time and across sites (e.g., pathogen virulence, access to diagnostics, and stage of disease at presentation) are potential confounders of efficacy analyses. Additional confounders include supportive care, which may vary across sites or time due to case load, resource constraints, interruptions in the supply or cold chain, and different clinician preferences related to evolving medical practices gleaned from clinical observations (*25*, *26*). Survivor bias, which happens when the sickest patients do not live long enough to be seen in the Ebola treatment unit, may occur differentially across sites (*27*). This panoply of factors creates a high degree of between-study variability, making it difficult to validate any particular nonrandomized control group as a comparator for a given investigational drug.

In our meta-analysis, study-specific effects were needed after adjusting for age, sex, and baseline cycle threshold. The Favi-Bai study had the highest mortality rate, even after adjustments, whereas the Prevail II–ZMapp study had the lowest mortality rate. Although not confirmed in our study, timing in the epidemic may partially explain

this finding. The relationship between cycle threshold and mortality differed by study, pointing to unmeasured covariates that contributed to sizeable differences between studies. The finding that study and study-by-log cycle threshold effects were different from zero implied that estimation of a common control model [as done in (*28*)] was not feasible.

Because the regression modeling approach failed to provide a common control group, we evaluated another approach. Under a different assumption that control groups broadly represented the range of controls, we hypothesized that consistency of results for a specific experimental treatment across the (heterogeneous) collection of control groups would add to the body of evidence for or against that investigational agent. We compared eight experimental treatments to each available control group with adjustments for available baseline covariates. This analysis suggested that amodiaquine improved survival when using three of six control groups. Notably, the potential efficacy of the antimalarial drug amodiaquine against Ebola virus is under debate. In vitro studies have reported anti–Ebola virus activity of this drug (*29*–*31*), but such activity was not confirmed in a mouse model of Ebola virus infection (*32*). Similar positive results about improved survival were noted for the Prevail II–ZMapp
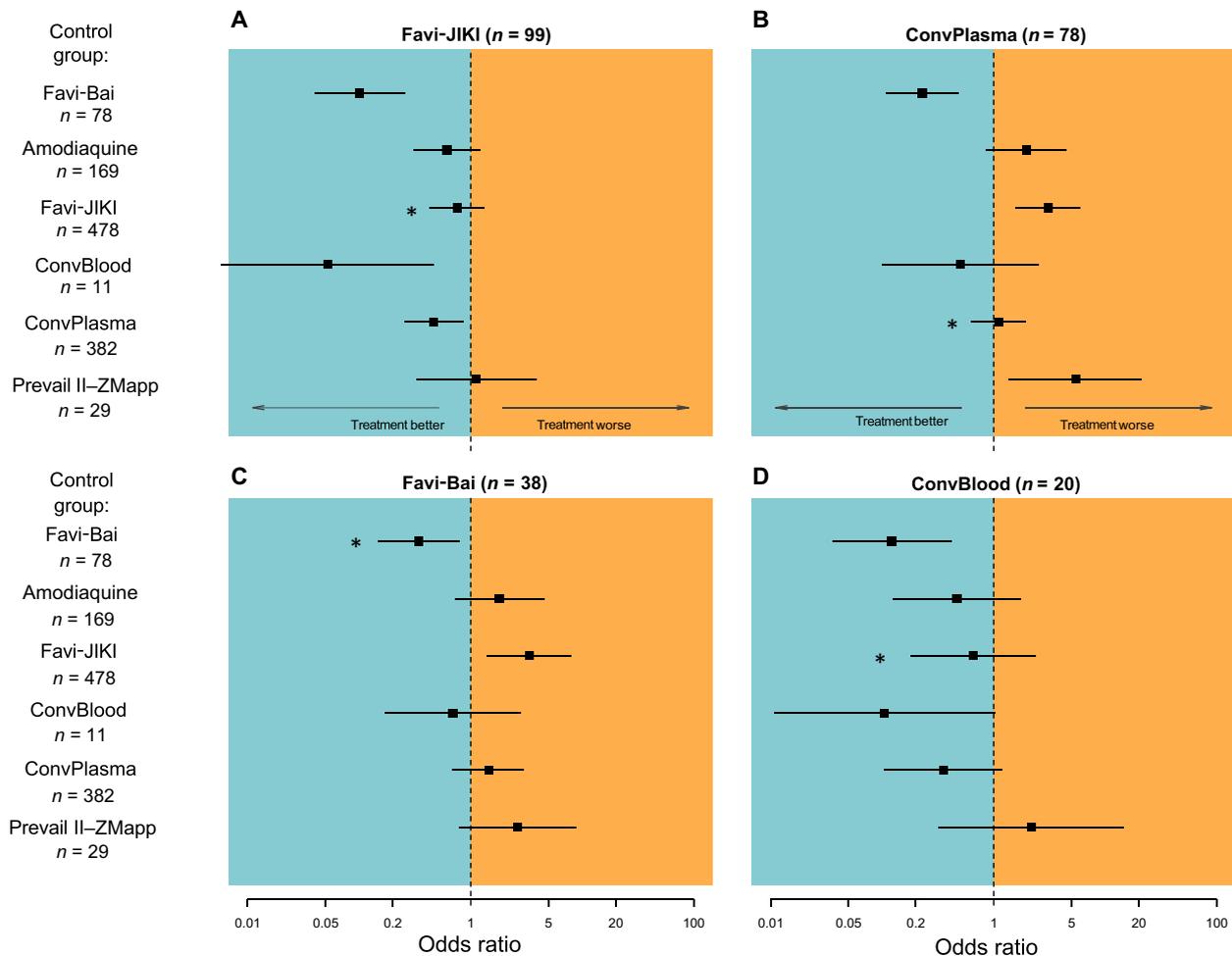
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Fig. 4. Standardized odds ratios for treatment effects for four investigational therapies. Standardized odds ratios for treatment effects are shown for the experimental arms relative to each control group of the studies investigating: (**A**) the antiviral drug favipiravir (Favi-JIKI), (**B**) administration of convalescent plasma from Ebola virus disease survivors (ConvPlasma), (**C**) the antiviral drug favipiravir (Favi-Bai), and (**D**) administration of convalescent whole blood from Ebola virus disease survivors (ConvBlood). For each standardized odds ratio, a logistic regression model was fit using data from the control group listed in the left column and the experimental arm indicated above the plot. The odds ratios for the models are reported in table S4.

clinical trial. The Prevail II–ZMapp trial had a randomized control group; thus, the comparison of the experimental arm of this study with its own control group deserves attention. However, because the Prevail II-ZMapp trial stopped before complete accrual due to the end of the Ebola virus disease outbreak, the study was underpowered for the study-specified targeted treatment effect. Whereas results comparing the Prevail II–ZMapp experimental group to historical control data rank considerably lower in terms of scientific evidence relative to the randomized control trial, it is reassuring that the comparisons indicated drug efficacy. Notably, the assumption that the control groups included in our meta-analysis represent the spectrum of variability expected in future studies is an untestable assumption, highlighting concerns about overinterpretation of our results.

Our meta-analysis raises several important questions. First, do consistent results across studies with large variability add to the evidence base for a given treatment? Could a consistent pattern of benefit (or harm) in the context of this heterogeneity be reassuring? This heterogeneity highlights the potential risks to the validity of nonconcurrent, nonrandomized control groups. Another important question is whether a given study's chosen control group is, in some

way, more valid than control groups constructed from different studies. Greater similarities in patient population and management would provide a better comparator control group. Furthermore, differences in the type of nonrandomized control group are important. Some control groups were based on retrospective collection of data from patients outside of a clinical trial context, whereas other control groups were based on data collected from prospectively enrolled patients at the same center. Data collection and other factors are more likely to be standardized in the latter setting. In any event, none of these considerations outweigh the value of a concurrently randomized control group.

There were many limitations to our meta-analysis. A key limitation was lack of sufficient covariates. Differences between cycle threshold assays may have contributed to between-study variability (33), and data about specific cycle threshold assays were not always available. Future studies should aim to standardize cycle threshold assay platforms or, at a minimum, record those used. In addition, more consistent administration of standard-of-care measures across control arms would have strengthened this analysis, as would documentation of the supportive care given. For example, data on

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administration of intravenous fluids, had they been available, could have helped explain between-study variability. Additional variables that would have been informative include date of diagnosis or enrollment and measures of patient case load, which vary by site and over time. The limited study sample size is another weakness. The analysis of control groups was based on only six studies, which is a relatively small sample size for a meta-analysis. Further, we note that the strength of conclusions from statistical models also depends on adequacy of model fit. Missing covariates and an incorrectly specified functional form may lead to biased estimation and inference. Last, conclusions based on the comparison of experimental treatments to the various control groups assumed that the six control groups represented the range of heterogeneity across future control groups, which is an untestable assumption. These potential weaknesses further limit the conclusions that can be drawn from the analyses of studies investigating experimental therapeutics. Our meta-analysis revealed considerable heterogeneity across control group data, which was not removed after statistical modeling. Thus, nonrandomized control data are not reliable as a valid benchmark for efficacy evidence in clinical studies of investigational treatments lacking a randomized control group. Although our meta-analysis applies to clinical trials of experimental treatments for Ebola virus disease, similar results potentially could be obtained in other emerging infectious disease outbreak settings.

MATERIALS AND METHODS
Study design
We conducted a meta-analysis to include all published studies evaluating experimental interventions during the West Africa outbreak of Ebola virus disease from 2013 to 2016. Eligible studies included those with control groups in the following three categories: randomized controls, historical controls, and concurrent but nonrandomized controls (e.g., individuals who refused or were ineligible for experimental treatments). Studies reporting case-fatality rates over time were not eligible for inclusion. To identify studies, we conducted a literature review following Preferred Reporting for Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (table S5) (34). A comprehensive search of the Medline/PubMed, EMBASE, Scopus, and Web of Science databases was performed for papers published from December 2013 until February 2017 (see Supplementary Materials and Methods). In addition, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov were searched. Results were further restricted to those evaluating curative treatments, either in the context of a randomized controlled clinical trial or with external control data. Independent literature searches were performed by L.E.D. and A.G.-C. Clinical study data were obtained through multiple data-sharing agreements. De-identified data included information about mortality, age, sex, baseline polymerase chain reaction (PCR) cycle threshold (a proxy for viral load), and administration of intravenous fluids.

Statistical analysis
Logistic regression models were fitted using the covariates of age, sex, log cycle threshold, and study (e.g., the six studies with data from control subjects). Likelihood ratio tests were applied to evaluate significance of additional covariates to models. A Galbraith plot was used to illustrate between-study heterogeneity (35). All tests were two-sided with statistical significance set to $\alpha = 0.05$; 95% CIs were two-sided. Weighted least squares logistic regression methods were applied to summary-level (as opposed to patient-level) regression models to evaluate the relationship between mortality rate, mean cycle threshold, and study timing (evaluated as midpoint of study enrollment). Mixed-effects logistic regression models were estimated but failed due to convergence problems arising from the small number of studies relative to the amount of between-study variability.

SUPPLEMENTARY MATERIALS
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Materials and Methods
Fig. S1. PRISMA 2009 flow diagram.
Fig. S2. Adjusted odds ratios for amodiaquine, TKM-130803, Prevail II–ZMapp, and IFN-β1a study treatment arms for patients with a cycle threshold of ≥20 relative to each control group.
Fig. S3. Adjusted odds ratios for Favi-JIKI, convalescent plasma, Favi-Bai, and convalescent whole-blood study treatment arms for patients with a cycle threshold of ≥20 relative to each control group.
Fig. S4. Adjusted odds ratios for treatment relative to each of six control groups for patients of the TKM-130803 study, from the per-protocol and intent-to-treat samples.
Table S1. Weighted least squares regression for models in Fig. 1, evaluating association of midpoint of study enrollment dates and mortality rate/cycle threshold.
Table S2. Model estimates from logistic regression models for Fig. 2D.
Table S3. Model estimates from logistic regression models for Fig. 3 (A to D).
Table S4. Model estimates from logistic regression models for Fig. 4 (A to D).
Table S5. PRISMA 2009 checklist.

View/request a protocol for this paper from *Bio-protocol*.

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Citation: L. E. Dodd, D. Follmann, M. Proschan, J. Wang, D. Malvy, J. van Griensven, I. Ciglenecki, P. W. Horby, R. Ansumana, J.-F. Jiang, R. T. Davey, H. C. Lane, A. Gouel-Cheron, A meta-analysis of clinical studies conducted during the West Africa Ebola virus disease outbreak confirms the need for randomized control groups. *Sci. Transl. Med.* **11**, eaaw1049 (2019).

Science Translational Medicine

A meta-analysis of clinical studies conducted during the West Africa Ebola virus disease outbreak confirms the need for randomized control groups

Lori E. Dodd, Dean Follmann, Michael Proschan, Jing Wang, Denis Malvy, Johan van Griensven, Iza Ciglenecki, Peter W. Horby, Rashid Ansumana, Jia-Fu Jiang, Richard T. Davey, H. Clifford Lane and Aurelie Gouel-Cheron

The importance of randomization

Conclusive evidence from clinical studies about treatment efficacy requires an appropriate control group, usually requiring randomization to balance out factors. During fatal disease outbreaks, randomization may be difficult to conduct due to ethical concerns and challenging field conditions. Dodd *et al.* have now performed a meta-analysis of six clinical studies conducted during the West Africa Ebola virus disease outbreak. These authors examined whether statistical modeling of multiple cohorts from these studies would facilitate a reasonable comparator for experimental treatments in future clinical studies lacking a randomized control group. The meta-analysis revealed considerable heterogeneity in the different control groups, which was not removed after statistical modeling. This suggests that nonrandomized control group data cannot be used as a comparator.

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