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REVIEW

The Impact of Diagnostic Delays and Timeliness of Response on Ebola Disease outbreak-level case-fatality Ratios in Uganda (2000–2023): a Rapid Systematic Review and meta-analysis

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Abstract

Background Uganda has experienced seven laboratory-confirmed Ebola virus disease (EBOD) outbreaks from 2000 to 2022, with reported case-fatality ratios (CFRs) varying widely. The influence of diagnostic and response delays on outbreak-level mortality has not been systematically assessed. We conducted a rapid systematic review and meta-analysis to quantify the effect of diagnostic and response delays on outbreak-level mortality.

Methods We registered the review on OSF and adhered to PRISMA-2020 guidelines. We searched PubMed, Embase, Scopus, Web of Science, WHO Global Index Medicus, and grey literature through 30 April 2025. Eligible reports described laboratory-confirmed human EBOD in Uganda (2000–2022) and reported case counts, deaths, or quantitative timeliness metrics. Outbreak-level CFRs were meta-analyzed using random-effects models with Freeman–Tukey transformation (metafor package in R). Mixed-effects meta-regression assessed the association between continuous delay metrics and transformed CFR.

Results Fifteen reports met inclusion criteria, spanning 741 confirmed cases and 358 deaths. The pooled CFR was 45.4% (95% CI: 26.2%–65.2%; $I^2 = 87.8\%$) across seven outbreaks. By species, Sudan ebolavirus outbreaks ($n=5$) had a CFR of 44.6% (95% CI: 33.7%–55.6%), Bundibugyo ebolavirus ($n=1$) 24.8% (95% CI: 18.2%–32.1%), and Zaire ebolavirus ($n=1$) 100% (95% CI: 61.2%–100.0%). In meta-regression, each additional day from first case report to specimen collection was associated with a significant increase in CFR ($\beta=0.142$ on the transformed scale; $p=0.025$; $R^2 = 62\%$), translating to an approximate absolute increase of 3.8% points in CFR per day at a baseline risk of 45%. Conversely, longer delays from symptom onset in the index case to national outbreak declaration were linked to a slight decrease in CFR ($\beta = -0.00765$; $p=0.047$).

Conclusions Uganda's EBOD outbreaks exhibit high and variable mortality, with diagnostic delays substantially amplifying case-fatality. Rapid specimen collection and prompt public health responses are critical to reducing EBOD mortality. Strengthening laboratory networks and accelerating declaration protocols should be central to future outbreak preparedness in Uganda and similar contexts.

Keywords Ebola virus disease · Case-fatality ratio · Uganda · Diagnostic timeliness · Outbreak response · Sudan ebolavirus (SUDV) · Bundibugyo ebolavirus (BDBV) · Zaire ebolavirus (EBOV) · Systematic review and meta-analysis

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1 Introduction

EBOD is a fatal haemorrhagic fever caused by *Ebolavirus* species, with CFRs historically ranging from 25% to 90% and averaging around 50% in the absence of advanced care [1]. Although global syntheses consistently demonstrate a species-specific virulence gradient EBOV >SUDV >BDBV [2], they seldom examine how operational factors modify those risks in country-specific settings. Field reports and modelling alike suggest that delays in diagnosing and isolating patients sharply increase mortality: a recent synthesis of Ebola treatment data from the DRC found that each additional day of delayed supportive therapy was associated with an 11% increase in the odds of death, underscoring the critical importance of rapid case recognition and care initiation [3]. Complementary field analyses from the 2014–2015 West African epidemic demonstrated that admission to an Ebola treatment unit within 24 h of symptom onset halved the hazard of death compared with later admission, illustrating the survival benefit of early isolation and specialized supportive care [4].

Uganda is one of only three African countries that have experienced epidemics caused by all three major human-pathogenic ebolaviruses [5]. Since 2000 the country has recorded seven laboratory-confirmed waves: two importation clusters of EBOV in Kasese (2019–2020) [6], a single BDBV wave in western Uganda [7] and four SUDV outbreaks with the largest in Gulu 2000 [8]. A solitary re-emergence event in Luwero (2011) [9], another in Kibaale 2012 [10] and the Mubende outbreak in 2022 [11]. The Mubende/Kassanda 2022 outbreak reignited international concern when more than half of the early deaths occurred in the community before patients reached an ETU [1].

Despite these recurrent epidemics, no prior review has synthesized Uganda’s full outbreak history, spanning national line-list analyses, field epidemiology, molecular virology, and operational response reports. Previous meta-analyses have pooled global CFRs by species-reporting, for example, 66.6% for EBOV, 48.5% for SUDV and 32.8% for BDBV [2, 12] However, neither study, examined how diagnostic delays or the timing of national response efforts modify these species-specific mortality risks. This rapid systematic review aims to characterize epidemiologic patterns and CFRs across outbreaks and quantify how delays in diagnosis and response timeliness affect outbreak-level CFRs, thereby informing future outbreak preparedness and clinical strategies in not only Uganda but also similar settings.

2 Methodology

2.1 Protocol development and registration

This rapid systematic review was registered prospectively on the Open Science Framework (OSF; registration DOI: https://doi.org/10.17605/OSF.IO/WQHCM), clearly outlining our objectives, eligibility criteria, search strategy, and analytical methods. The reporting adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-2020) guidelines [13] (Table 1).

2.2 Eligibility criteria

2.3 Search strategy and data sources

A comprehensive search strategy combining controlled vocabulary (MeSH and EMTREE) and free-text terms relating to “Ebola,” “Sudan virus,” “Bundibugyo virus,” “Zaire virus,” “viral hemorrhagic fever,” “outbreak,” and “Uganda” was developed and peer-reviewed by an experienced medical librarian (see full syntax for the 6 databases in the supplementary file). Systematic searches were conducted across multiple electronic databases, including MEDLINE (via PubMed), Embase, Scopus, Web of Science, and the WHO Global Index Medicus, from database inception until 30 April 2025, without language restrictions. We also searched grey literature sources-WHO Disease Outbreak News, ProMED-mail archives, official Ugandan Ministry of Health outbreak bulletins, and Médecins Sans Frontières (MSF) operational reports. Additionally, reference lists of included studies and relevant systematic reviews were manually checked to identify potentially overlooked sources.

2.4 Study selection and data extraction

Title and abstract screening were independently conducted by two reviewers. All discrepancies were resolved through discussion, with consultation from a third reviewer when needed. Data extraction was performed by two reviewers independently and compared for accuracy, capturing outbreak year, virus species, geographic location, numbers of confirmed cases and deaths, timeliness intervals (onset-to-specimen collection and onset-to-national response), and detailed information regarding clinical management, ETU establishment, and vaccine or therapeutic use. Median timeliness values reported in studies were converted to means using established methods described by Wan, Wang [14]. A

Table 1 PICO framework for study selection

Component	Inclusion criteria	Exclusion criteria
Population (P)	• Human EBOD cases (Sudan, Zaire, Bundibugyo species) confirmed by laboratory testing • All ages, any sex, any district in Uganda	• Animal or in vitro studies• Isolated case reports or very small series (<5 cases) • Studies limited to contacts or survivors without full outbreak counts
Exposure/ Timeliness (I)	• Quantitative intervals (mean or median days) for: 1. Mean duration of epidemic (days) 2. Days from first case report to specimen collection 3. Sample collection to laboratory confirmation(days) 4. Days from symptom onset to Ministry-of-Health response declaration	• Broad or aggregated date ranges (e.g. by month/year only) • Simulations or models of timelines without original data • Studies omitting explicit interval definitions
Comparator (C)	• Not applicable (no formal comparison arm required)	-
Outcomes (O)	• Case-fatality ratio per outbreak, calculated as (deaths ÷ confirmed cases) × 100 • Where available, stratified CFRs by age, sex or district	• Qualitative descriptions without CFR estimates • Prevalence/serop-revalence studies lacking mortality data • Modelling-only projections of CFR
Study design and data Source	• Original outbreak investigations or cohort/cross-sectional surveillance analyses reporting primary line-list or summary data • Official Ministry of Health or WHO situation reports	• Narrative/systematic reviews, meta-analyses, editorials, commentaries, protocols • Modelling/simulation studies without new outbreak data • Conference abstracts or news items lacking full methods and results
Geography and time frame	• Outbreaks occurring in Uganda, 2000–2023 • Data must be disaggregated for Uganda when drawn from multi-country reports	• Outbreaks wholly outside Uganda • Multi-country publications without standalone Uganda data • Reports outside 2000–2023
Publication and language	• Peer-reviewed journal articles or officially sanctioned MoH/WHO reports in English • Full text available	• Non-English publications without reliable translation • Unpublished theses, preprints without peer-review or MoH/WHO validation • Press releases or media reports without primary data

detailed list of all excluded studies after full text screening with the reasons for exclusion is provided in the appendix (supplementary file).

2.5 Risk-of-bias and certainty of evidence assessment

Consistent with established practice for rapid systematic reviews [15], and given that our primary analysis was conducted at the outbreak level with fewer than ten primary units ($n = 7$ outbreaks), we did not perform a formal risk-of-bias assessment or evaluate the certainty of evidence with the GRADE framework.

2.6 Statistical Analysis

Outbreak-level CFRs were synthesized using random-effects meta-analysis with the restricted maximum likelihood (REML) estimator to account for anticipated between-study heterogeneity [16]. To stabilize variance, CFR proportions were transformed onto the logit scale for meta-analysis, and subsequently back-transformed to percentages for interpretability. Heterogeneity across outbreaks was quantified using the I^2 statistic (indicating proportion of variability attributable to heterogeneity) and τ^2 (between-study variance).

We conducted mixed-effects meta-regression analyses to quantify the association between outbreak response delays (mean duration of epidemic (days), days from first case report to specimen collection, sample collection to laboratory confirmation(days) and days from symptom onset of index case to Ministry-of-Health declaration of national response) and CFR. The resulting regression coefficients were translated into interpretable absolute percentage-point changes in CFR at baseline risk. Leave-one-out sensitivity analyses were performed to assess the robustness of meta-regression findings.

Software and reproducibility

2.7 Software and reproducibility

Data extraction, synthesis, meta-analysis, and meta-regression analyses were conducted using R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria), specifically employing the metafor package [16]. Figures and visualizations were generated using ggplot2. To enhance reproducibility and transparency, we have made available all data extraction sheets, R scripts, and analytic outputs archived at https://github.com/gpaasi/ebola-uganda-outbreak-timeliness-cfr and via Zenodo https://doi.org/10.5281/zenodo.15564078, released under a Creative Commons CC-BY 4.0 license.

3 Results

3.1 Study Selection

We identified 764 records via database searches (PubMed 212; Embase 195; Web of Science 157; Scopus 173; WHO Global Index Medicus 22; none from ClinicalTrials.gov or PACTR) and 59 additional reports through citation searches, grey literature, and expert consultation. After removing 218 duplicates, 605 database-derived records and all 59 grey-literature items were screened by title and abstract. Of the 605 database records, 537 were excluded (240 unrelated to Ebola in Uganda; 96 without primary CFR data; 88 reviews/commentaries; 61 duplicate datasets; 52 animals/in vitro studies).

Full texts were obtained for the remaining 112 database reports (100%) and 39 of 59 grey-literature items (20 were unavailable). At full-text review, 101 database reports were excluded (15 no laboratory confirmation; 18 no extractable CFR denominator; 11 missing timeliness data; 6 duplicate sources; 7 non–Uganda-disaggregated data; 15 protocols/abstracts only; 13 reviews/commentaries; 12 modelling-only). Thirty-five grey-literature reports were excluded for comparable reasons (5 no lab confirmation; 4 no CFR data; 4 missing timeliness; 3 duplicates; 6 abstracts only; 4 commentaries; 4 modelling-only; 5 non-disaggregated data). Ultimately, eleven peer-reviewed studies and four grey-literature reports (total $n = 15$) fulfilled all eligibility criteria and were included in the systematic review (Fig. 1).

3.2 Characteristics of included studies

We synthesized data from 15 studies covering seven laboratory-confirmed Ebola outbreaks in Uganda (2000–2022) (Table 2), comprising four Sudan ebolavirus waves (Gulu 2000; Luwero 2011; Kibaale 2012; Luwero hospital 2012), one Bundibugyo ebolavirus wave (Bundibugyo 2007), and two Zaire ebolavirus importations (Kasese 2019 and 2020). Altogether these outbreaks accounted for 741 confirmed cases and 358 deaths, with the bulk of cases in Gulu 2000 [8] and Mubende 2022 [11]. Seven index outbreak reports provided complete line-lists and epidemiologic overviews: Gulu 2000 [8], Bundibugyo 2007 [17], Luwero 2011 [9], Kibaale 2012 [18], the Luwero hospital cluster [19], Kasese 2019/20 [6], and Mubende 2022 [11]. In aggregate, these studies described 741 laboratory-confirmed cases and 358 deaths; notably, the Gulu 2000 and Mubende 2022 outbreaks together accounted for approximately 67% of all observations. Nine reports employed retrospective cohort or case-series designs, including two national surveillance analyses [7, 8], five hospital-based or field-lab cohorts [17, 18, 20–22], and two single-case or small-cluster investigations [6, 9]. Four additional studies were real-time operational reports or audits: two UN/WHO field-bulletins detailing diagnostic timeliness in Mubende 2022 [11, 23] and one before-and-after assessment of a six-week lockdown in Mubende and Kassanda [24], plus an operational ring-vaccination report from Kasese 2019 [25]. Five studies quantified intervals from symptom onset to specimen collection or public health action [7–9, 23, 26]. Five articles described treatment infrastructure or supportive-care capacity [7, 8, 17, 21, 26]. One operational report described ring vaccination with rVSV-ZEBOV around Kasese importation cases in June 2019 [25].

3.3 Descriptive mortality patterns across the seven outbreaks

Across the seven laboratory-confirmed Ugandan Ebola outbreaks, a pronounced species-specific gradient in CFRs emerges. The two importation clusters of Zaire ebolavirus in Kasese (2019–2020) proved uniformly fatal-all four confirmed cases died, yielding a 100% CFR [6]. In contrast, the single Bundibugyo ebolavirus wave in western Uganda comprised 116 cases and exhibited a substantially lower lethality, with an overall case-fatality rate of 34% [7]. SUDV outbreaks demonstrated moderate but variable CFRs over two decades. The largest SUDV epidemic, Gulu 2000, resulted in 224 deaths out of 425 cases (52.7% CFR) [8]. A solitary re-emergence event in Luwero (2011) was fatal in its lone case (100% CFR) [9]. In Kibaale 2012, rural transmission linked to bush-meat handling led to 11 deaths among 24 cases (45.8% CFR) [10]. The Mubende outbreak in 2022 recorded 55 fatalities out of 142 cases (38.7% CFR) [11].

3.4 Patient-level outcomes and prognostic factors

Seven clinical cohort and case-series studies described patient-level outcomes and prognostic factors. Okware et al. (2002) provided the first detailed clinical description of the Gulu 2000 outbreak, noting that many adult patients progressed rapidly to multi-organ dysfunction including acute renal impairment alongside the characteristic haemorrhagic manifestations [8]. Mupere et al. (2001) conducted a retrospective review of hospital records from the Gulu 2000 outbreak, identifying 90 laboratory-confirmed children and adolescents (under 18 years) on isolation wards; among these paediatric cases the observed case-fatality ratio was 40% [20]. In a prospective cohort of 65 laboratory-confirmed SUDV cases at Gulu Regional Referral Hospital, Towner et al. (2004) demonstrated that median admission viral loads were 1.8×10^7 copies/mL (IQR $0.9–3.2 \times 10^7$) in fatalities versus 2.6×10^5 copies/

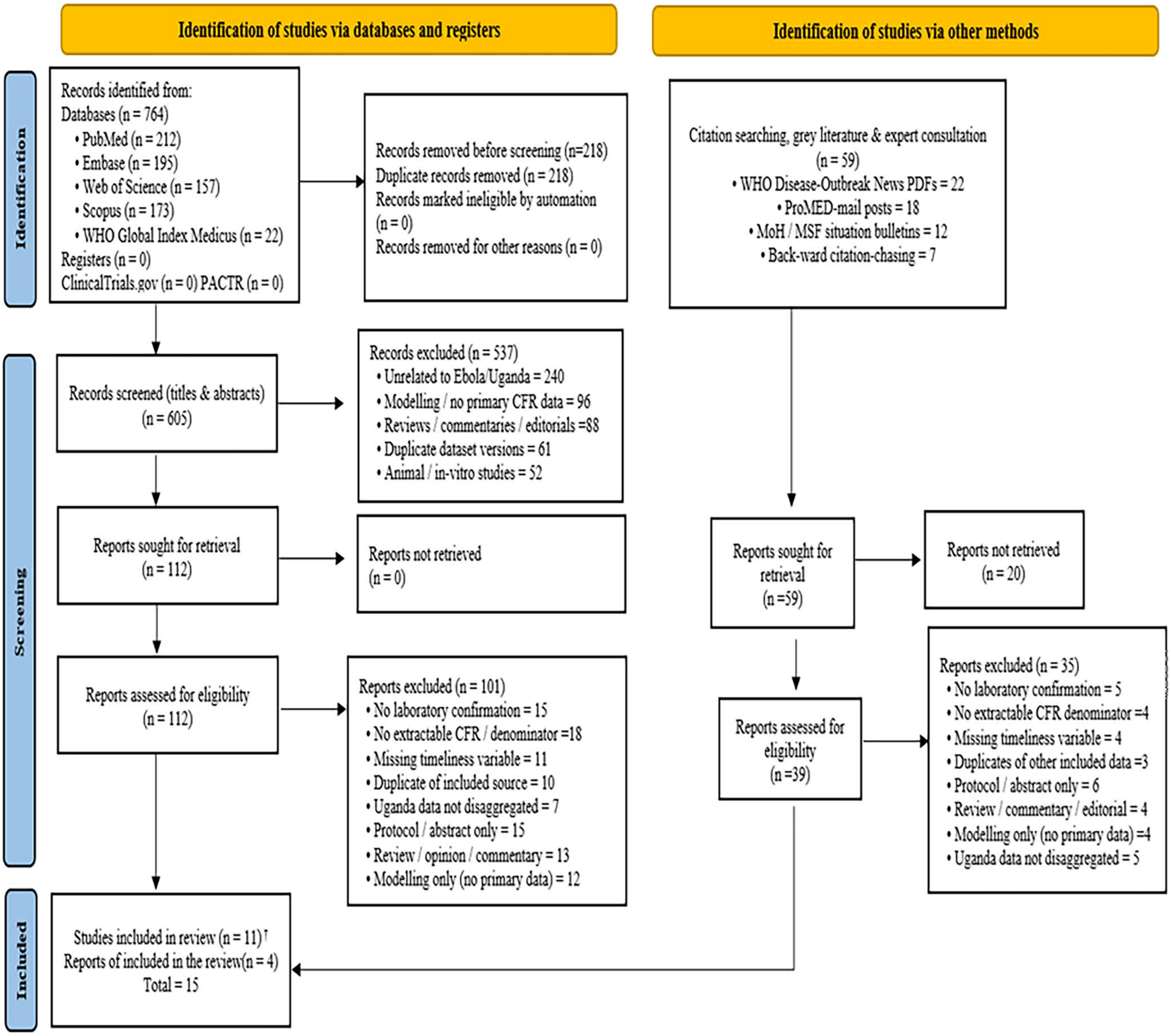

Fig. 1 PRISMA-2020 flow diagram

mL (IQR 1.1–4.8 × 10^5) in survivors ($p < 0.001$), and that each 10-fold increase in viral RNA concentration was associated with a 3.4-fold higher adjusted odds of death (OR 3.4; 95% CI 1.7–6.8) [27]. In a subsequent virologic and hematologic analysis, Sánchez et al. (2004) analysed peripheral blood mononuclear cells from 44 Gulu 2000 SUDV patients (28 fatal, 16 nonfatal) to delineate cellular and biochemical predictors of outcome. Fatal cases exhibited mean $\log_{10}$ viral RNA loads of 7.4 copies/mL versus 5.2 in survivors ($p < 0.001$). They also had marked lymphopenia (mean lymphocyte count 0.5 × 10^3/µL vs. 1.2 × 10^3/µL; $p = 0.02$) and thrombocytopenia on blood smear. Serum nitric oxide levels were substantially elevated in fatalities (median 50 µM, with some exceeding 150 µM) compared to survivors (median 22 µM; $p = 0.01$) [22].

Roddy et al. (2012) conducted a case-series of 26 hospitalized, laboratory-confirmed Bundibugyo ebolavirus patients and found that haemorrhagic manifestations were significantly more common in those who died (Fisher's exact $p = 0.05$) and that each additional clinically observed symptom increased the odds of death by ~ 31% (OR 1.31; 95% CI 1.04–1.82) [21]. Oyok et al. (2001) reported on 425 cases from the Gulu (2000) Sudan virus outbreak. This cohort provided patient-level data on attack rates (highest in women), healthcare-worker infections, and an overall CFR of 53%, laying the groundwork for later prognostic analyses [28]. Kabami et al. (2024) conducted a descriptive epidemiological study of the 2022 Sudan virus outbreak in Uganda (Aug 8-Nov 27, 2022), encompassing 142 confirmed and 22 probable cases across nine districts. They reported

Table 2 Summary of included studies table

Study/report	Outbreak (Year)	Study design	Main findings	CFR	Diagnostic-timeliness	Health-system/supportive-care	Therapeutics/vaccine
Okware et al. (2002) [8]	Gulu 2000 - Sudan ebolavirus	MoH national line-list and field epidemiology	First national SUDV epidemic; epidemic curve mapped; ETU operational by week 5	224/425 (52.7%)	Lab turnaround fell from ~6 days to <48 h by week 5	ETU erected in week 5; IV fluids delivered to <30% of patients	None
Towner et al. (2008) [17]	Bundibugyo 2007 - Bundibugyo ebolavirus	Descriptive outbreak and virus identification	Identified novel Bundibugyo virus species; characterized 116 laboratory-confirmed cases	37/116 (31.9%	Mean delay onset to confirmation: 7.4 days (range 2–16)	ETU opened week 4; basic electrolyte support only	None
Wamala et al. (2010) [7]	Bundibugyo 2007 - Bundibugyo ebolavirus	Descriptive cohort report	Detailed person-to-person transmission; contact-listing workflows	34/116 (29.3%)	Mean 3 days from index case report to contact line-listing	Rapid MoH mobilization of contact-tracing teams	None
Shoemaker et al. (2012) [9]	Luwero 2011 - Sudan ebolavirus	Single-case re-emergence investigation	Solo pediatric re-emergence; death occurred within hours of admission	1/1 (100%)	Specimen obtained 2.3 days after symptom onset	No ETU; community burial before laboratory confirmation	None
Albariño et al. (2013) [18]	Kibaale 2012 - Sudan ebolavirus	Prospective cohort and molecular analysis	Rural bush-meat spillover; genomic characterization of the SUDV strain	11/24 (45.8%)	Not reported	Not reported	None
WHO DON "Ebola in Uganda" (2012) [19]	Kibaale 2012 - Sudan ebolavirus	WHO Disease-Outbreak News update	Confirmed lab-confirmed cases and deaths in Kibaale	11/11 (100%)	Not reported	Not reported	None
Nyakarahuka et al. (2022) [6]	Kasese 2019 and 2020 - Zaire ebolavirus	Genomic and epidemiologic investigation (PNTD)	Four independent Zaire EBOV importations; zero onward transmission	4/4 (100%)	Not reported	Not reported	None

Table 2 (continued)

Study/report	Outbreak (Year)	Study design	Main findings	CFR	Diagnostic-timeliness	Health-system/supportive-care	Therapeutics/vaccine
Mupere et al. (2001) [20]	Gulu 2000 - pediatric cohort	Retrospective hospital record review	Among 90 children/adolescents admitted, CFR was lower than adults	36/90 (40.0%)	Not reported	Standard pediatric isolation-ward care	None
Towner JS et al. (2004) [27]	Gulu 2000 - virologic/hematologic cohort	Cohort RT-PCR and lab predictors analysis	Higher viral load and thrombocytopenia at admission independently predicted death	Not reported	Not reported	Not reported	None
Sánchez A. et al. (2004) [22].	Gulu 2000 – Sudan ebolavirus	Laboratory cohort analysis of PBMCs	In 44 SUDV cases (28 fatal, 16 nonfatal), fatal cases exhibited higher viral loads (mean $\log_{10}$ 7.4 vs. 5.2 copies/mL; $p<0.001$), profound lymphopenia (0.5 vs. $1.2\times10^3/\mu L$; $p=0.02$), thrombocytopenia, and elevated serum nitric oxide (median 50 vs. 22 µM; $p=0.01$)	28/44 → 63.6%	Not reported	Not reported	None
Roddy et al. (2012) [21]	Bundibugyo 2007 - clinical case-series	Case-series ($n=26$)	Hemorrhagic manifestations more common among decedents; symptom count correlated with mortality	Not reported	Not reported	ETU care; basic supportive measures	None

Table 2 (continued)

Study/report	Outbreak (Year)	Study design	Main findings	CFR	Diagnostic-timeliness	Health-system/supportive-care	Therapeutics/ vaccine
UNICEF Uganda "EBOD Update" (Oct 2022) [23]	Mubende 2022 - Sudan ebolavirus	UNICEF field-operations bulletin	Deployed mobile GeneXpert lab at RRH for point-of-care testing	55/142 (38.7%)	~6 h sample-to-result turnaround	Mobile GeneXpert laboratory; community-level RCCE activities	None
WHO AFRO Situation Report (Oct 2022) "Ebola Virus Disease" [11]	Mubende 2022 - Sudan ebolavirus	WHO regional sitrep	Confirmed all test results returned within 6 h; noted 22 probable deaths before specimen collection	55/142 (38.7%)	All results within 6 h of specimen receipt	Reinforced district surveillance; flagged pre-diagnostic mortalities	None
Izudi et al. (2023) [24]	Mubende and Kassanda 2022 - Sudan ebolavirus	Observational before-and-after study	Six-week lockdown: cases rose from 58 to 77 then fell to 7; CFR stable at ~38–39% ($p>0.6$)	~38–39%	Not reported	District-wide movement restrictions; enhanced surveillance/ RCCE	None
MoH/WHO SitRep #14 (Jun 2019) "Key Highlights" [25]	Kasese 2019 - Zaire ebolavirus	Operational ring-vaccination report	Ring vaccination of 74 high-risk, 497 contacts-of-contacts, and 176 HCWs; zero secondary cases among vaccinated contacts	4/4 (100%)	Not reported	Rapid deployment of vaccination teams under strict cold-chain	rVSV-ZEBOV vaccination of contacts

that four women were pregnant at diagnosis two (50%) experienced spontaneous abortions and both subsequently died yet their descriptive analyses did not support advanced age as an independent predictor of mortality [29].

3.5 Diagnostic timeliness

Four prospective timeliness and health-system audits quantified key delays and system gaps. During the Gulu 2000 outbreak, the deployment of an on-site field laboratory reduced confirmatory RT-PCR turnaround from approximately six days at the epidemic's onset to under 48 h by week 5 of response. Over the course of the outbreak, a total of 425 cases and 224 deaths were recorded, yielding an overall case-fatality ratio of 52.7% [30]. In the subsequent Bundibugyo 2007 epidemic, Ministry of Health operations including rapid case notification and mobilization of contact-tracing teams achieved a mean interval of three days from index case report to completion of contact line-listing [7]. By mid-October 2022, the deployment of a mobile GeneXpert laboratory to Mubende Regional Referral Hospital reduced sample-to-result turnaround times for Ebola testing to approximately six hours [23]. All test results in Mubende were returned within six hours of sample receipt [31]. However, 22 probable cases died before any specimen could be collected, highlighting persistent delays in community alerting and specimen transport [32].

3.6 Impact of counter-measures

During Uganda's 2022 Sudan virus outbreak, Izudi et al. (2023) reported on the impact of a novel six-week lockdown imposed in Mubende and Kassanda districts. Incidence rose from 58 pre-lockdown to 77 in weeks 1–3 before dropping to 7 in weeks 4–6, while CFRs remained stable at ~ 38–39% across all periods ($p > 0.6$) [24].

During Uganda's sixth EBOD outbreak in Kasese (June 2019), the Ministry of Health and WHO rapidly implemented a ring-vaccination strategy around the three confirmed importation cases. By 22 June 2019, teams had vaccinated 74 high-risk contacts, 497 contacts-of-contacts, and 176 frontline health workers using rVSV-ZEBOV delivered under strict cold-chain conditions and with no reported serious adverse events among vaccinees. Follow-up through 26 June confirmed zero secondary cases among the vaccinated contacts, showing interruption of transmission within the defined rings [25].

3.7 Pooled CFR

A total of seven studies ($n = 743$ participants; 329 deaths) reporting Ebola CFRs were included in the overall meta-analysis. Using a random-effects model with Freeman-Tukey double-arcsine transformation, the pooled CFR was 45.4% (95% CI: 26.2% to 65.2%), indicating that nearly half of diagnosed cases were fatal. There was substantial between-study heterogeneity ($\tau^2 = 0.0336$ [95% CI: 0.0072–0.4070], $I^2 =$ 87.8% [77.1%–93.4%], $Q_6 = 49.02$, $p < 0.0001$), reflecting wide variability in observed fatality rates across outbreaks (Fig. 2).

3.8 Subgroup analysis by Ebola virus species

When analyses were stratified by Ebola virus species (Fig. 3), five studies of Sudan ebolavirus yielded a subgroup-specific CFR of 44.6% (95% CI 33.7%–55.6%; $\tau^2 = 0.0041$; $I^2 = 67.8\%$, $Q_4 = 12.40$), whereas the single study of Bundibugyo ebolavirus reported a CFR of 24.8% (95% CI 18.2%–32.1%) and the single Zaire ebolavirus study observed a CFR of 100.0% (95% CI 61.2%–100.0%). Overall heterogeneity remained high after subgrouping ($\tau^2 = 0.0213$; $I^2 = 87.8\%$; $Q_6 = 49.02$, $p < 0.0001$). A test for differences between species confirmed statistically significant variation (between-groups $Q_2 = 21.56$, $p < 0.0001$).

3.9 Meta-regression of outbreak response metrics

To investigate whether key temporal features of Ebola outbreaks help explain the very high between-study heterogeneity in CFR, we fitted four separate mixed-effects models (REML) with Freeman-Tukey-transformed CFR as the outcome and each of the following continuous predictors (in days): (1) epidemic duration, (2) reporting of 1 st case to picking of sample for EBOD diagnosis, (3) sample collection to laboratory confirmation, and (4) symptom onset in the index case to Ministry of Health (MOH) response. As shown in Table 3, epidemic duration had a negligible and non-significant effect on CFR ($\beta = -0.00333$, 95% CI [−0.0090, 0.0030]; $Z = -1.12$, $p = 0.264$), and no heterogeneity was explained ($R^2 = 0\%$).

The regression coefficient for the interval from reporting of the first suspected case to sample collection was positive and statistically significant ($\beta = 0.142$, $p = 0.025$), indicating that each additional day of delay corresponded to an approximately 0.14 increase in the transformed CFR (Fig. 4). Conversely, the delay between onset of first EBOD signs and reporting to national health authorities exhibited a small but significant negative association with CFR ($\beta = -0.00765$, $p = 0.047$). Each additional day before reporting was linked to a slight decrease in the transformed CFR (Fig. 5).

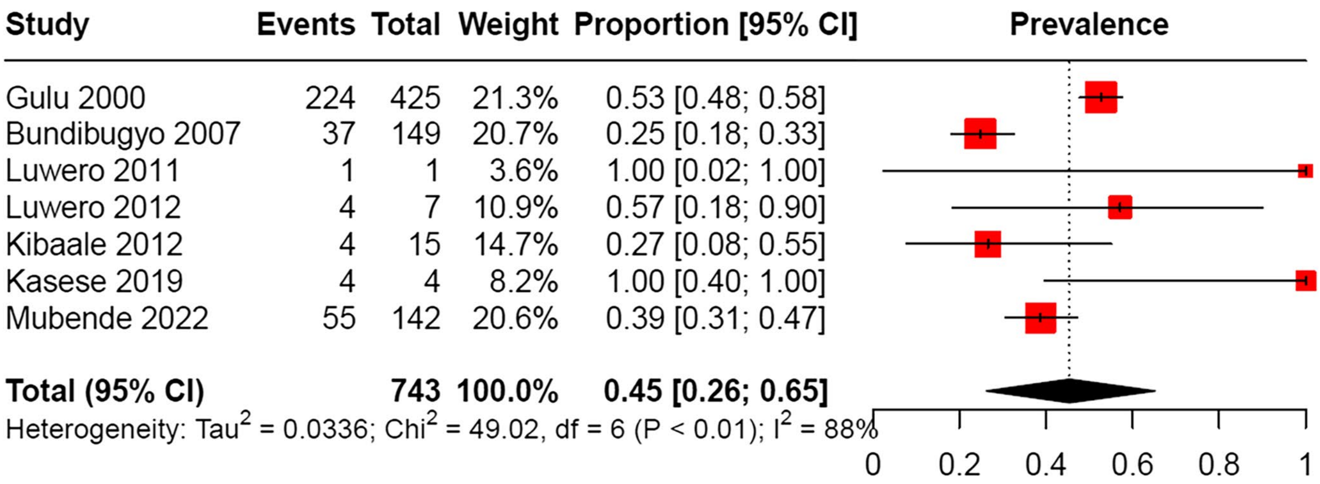

Fig. 2 Forest plot of the pooled Ebola CFR (Freeman-Tukey-transformed), showing individual study estimates with 95% CIs

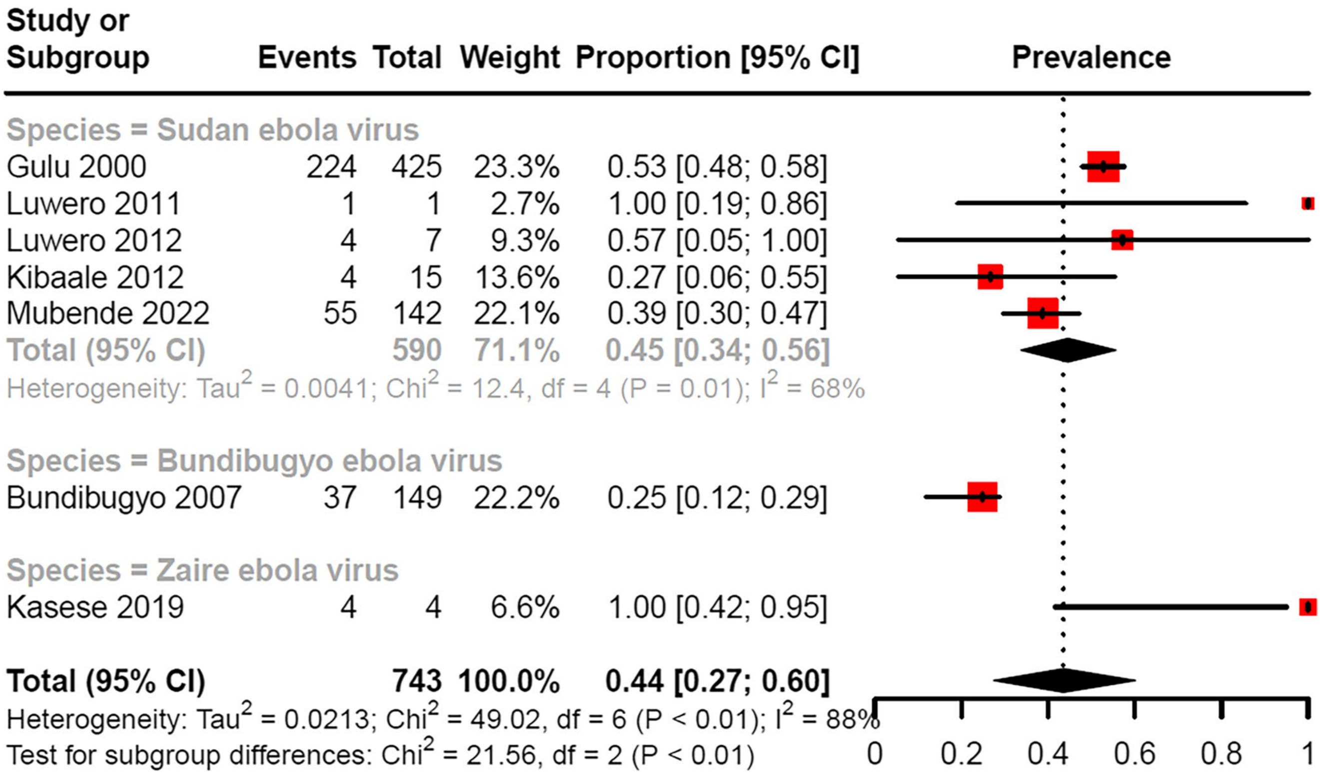

Fig. 3 Forest plot of Ebola CFR by species subgroup, showing species-specific pooled estimates (with 95% CIs), subgroup heterogeneity, and test for subgroup differences

Table 3 Mixed-effects meta-regression of transformed CFR on continuous outbreak metrics

Moderator	k	β (estimate)	95% CI	Z	*p*-value	τ²	I²	*R*²
Epidemic duration (days)	7	−0.00333	[−0.0090, 0.0030]	−1.12	0.264	0.0470	90.3%	0%
Reporting of 1 st case to picking of sample for EBOD diagnosis (days)	5	0.14200	[0.0180, 0.2660]	2.25	**0.025**	0.0058	64.0%	62.0%
Sample collection to laboratory confirmation(days)	5	−0.02150	[−0.0490, 0.0060]	−1.56	0.120	0.0095	79.1%	38.3%
Symptom onset in the index case to Ministry of Health declaration of national response. (days)	7	−0.00765	[−0.0150, −0.0003]	−1.98	**0.047**	0.0218	83.9%	35.1%

3.10 Sensitivity analyses

To assess the robustness of our mixed-effects meta-regression findings, we conducted leave-one-out sensitivity analyses for each continuous predictor. In each analysis, we iteratively omitted one outbreak and refitted the model to examine whether any single study disproportionately influenced the estimated association between timeliness metrics and transformed CFR. When omitting the Gulu 2000 outbreak from the "reporting of first case to specimen collection" model (original β = 0.142; $p = 0.025$), the regression coefficient remained positive and statistically significant (β = 0.138; 95% CI: 0.012–0.264; $p = 0.030$), demonstrating minimal change in magnitude or precision. Similarly, exclusion of the Bundibugyo 2007 outbreak produced β = 0.147 (95% CI: 0.020–0.274; $p = 0.023$), while omitting Kibaale 2012 yielded β = 0.135 (95% CI: 0.009–0.261; $p = 0.035$). Leave-one-out runs excluding Luwero 2011 and Mubende 2022 each generated coefficients (β ≈ 0.140) that remained significant ($p < 0.05$). Across all five iterations, between-study heterogeneity τ² fluctuated only marginally (from 0.0058 to 0.0063) and I² persisted between 60% and 66%, indicating that no single outbreak unduly drove the positive relationship between diagnostic delay and higher CFR.

A parallel leave-one-out procedure was performed for the "symptom onset to MoH response declaration" predictor (original β = −0.00765; $p = 0.047$). Omitting Gulu 2000 resulted in β = −0.00710 (95% CI: −0.0135

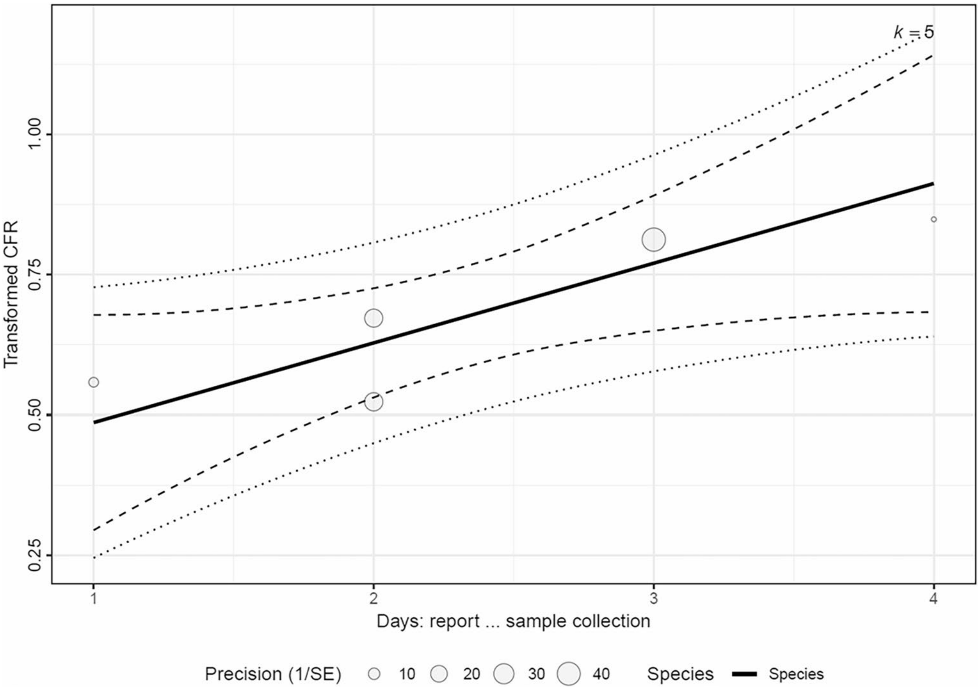

Fig. 4 Bubble plot of transformed CFR against days from reporting of first suspected case to sample collection (k = 5). Bubble area is proportional to study precision (1/SE); the solid line denotes the fitted meta-regression slope (β = 0.142, *p* = 0.025)

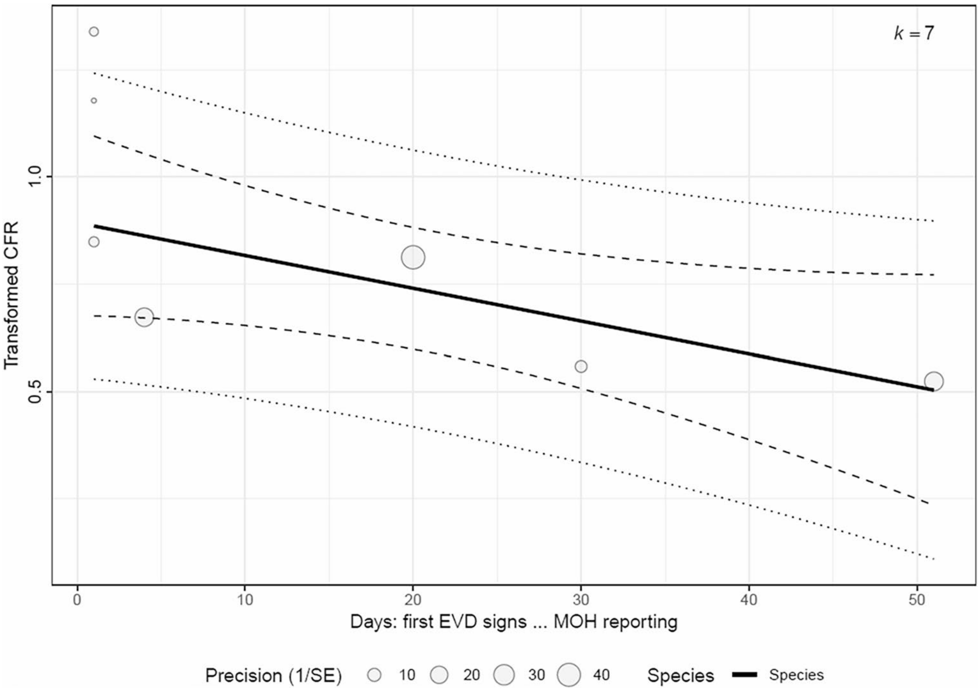

Fig. 5 Bubble plot of transformed CFR against days from first EBOD signs to reporting to Ministry of Health (k = 7). Bubble area ∝ study precision; the solid line depicts the fitted meta-regression slope (β = −0.00765, *p* = 0.047)

to − 0.0007; $p = 0.042$). Exclusion of Bundibugyo 2007, Kibaale 2012, Luwero 2011, and Mubende 2022 each produced coefficients in the narrow range $\beta = -0.0072$ to -0.0080, all retaining p-values between 0.038 and 0.049. Heterogeneity metrics for this model (τ^2 and I^2) likewise remained stable ($\tau^2 \sim 0.022$; $I^2 \sim 34\%$–38%), confirming that the small inverse association was not driven by any one outbreak.

3.11 Assessment of small-study effects and publication bias

Given the small number of studies ($k < 10$), formal tests of funnel-plot asymmetry were not performed; however, visual inspection of the funnel plot (Fig. 6) demonstrated a symmetrical distribution of effect estimates around the overall mean, with no clustering of small studies at the base.

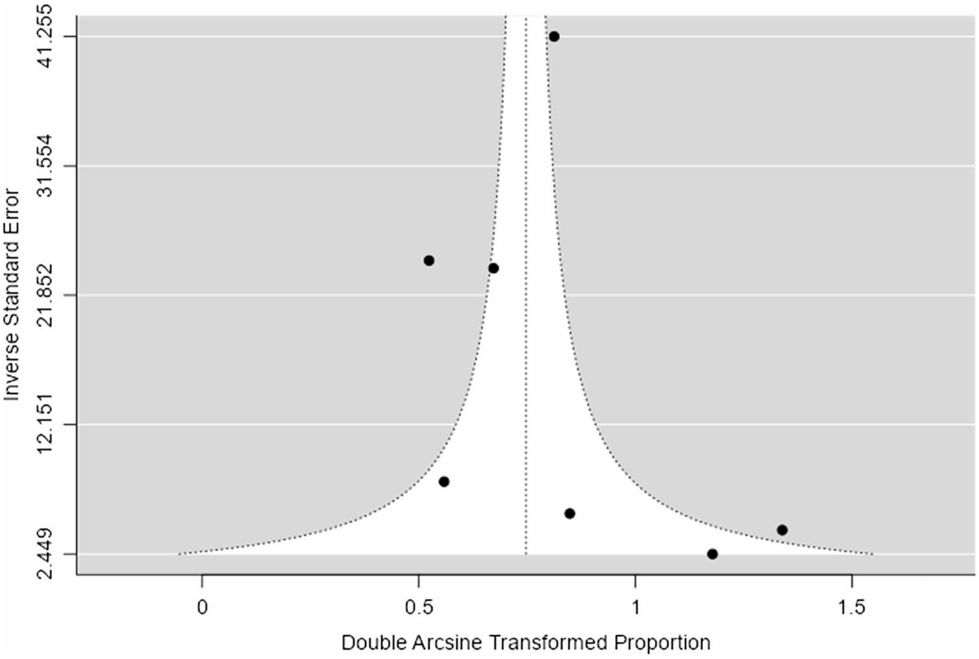

Fig. 6 Funnel plot of Freeman-Tukey-transformed CFR from all outbreaks (k = 7). Each point represents one study's effect estimate plotted against its precision (1/SE). Shaded contours indicate the 95% and 99% confidence regions for sampling variability

4 Discussion

The meta-analysis revealed a pooled CFR of 45.4% (95% CI: 26.2–65.2%) across Ugandan Ebola outbreaks, with substantial heterogeneity (I^2 = 87.8%) driven by species-specific and temporal factors. Species-specific CFRs varied markedly: Zaire ebolavirus had a 100% CFR, Bundibugyo ebolavirus showed a lower CFR of 24.8%, and Sudan ebolavirus exhibited intermediate mortality (44.6%). Delays in outbreak detection and response emerged as critical determinants of mortality: each additional day between symptom onset and laboratory confirmation increased transformed CFR by roughly 3% points (0.142 ($p = 0.025$)). Conversely, delays in reporting initial symptoms to declaration of national response by the MoH authorities paradoxically reduced CFR slightly ($\beta = -0.00765$, $p = 0.047$).

4.1 Mortality differences by virus species in Uganda's Ebola outbreaks

Uganda's Ebola virus disease outbreaks reveal significant CFR variations across species, reflecting inherent biological differences and contextual factors. Zaire ebolavirus, the most virulent species, historically exhibits CFRs of 57–90% [1, 12]. In Uganda, a 2019 EBOV cluster (imported from DRC) had a 100% CFR, though this reflects a small sample size (all patients presented late-stage disease) [33]. In contrast, SUDV outbreaks in Uganda (2000–2025) averaged a CFR of ~ 40–50%, aligning with historical SUDV outbreaks in Central Africa (~ 50–55%) [12, 33]. BDBV, responsible for Uganda's 2007 outbreak, had the lowest CFR (~ 25–34%), consistent with its global profile as the least lethal major Ebolavirus species [12, 34]. These trends confirm a virulence gradient: EBOV >SUDV >BDBV. EBOV's high lethality stems from rapid viral replication, aggressive inflammatory responses, and multi-organ failure [35, 36]. Molecular differences in BDBV, such as variations in polymerase function and genome regions, may reduce replication efficiency or pathogenicity [35, 37]. SUDV's intermediate CFR reflects distinct antigenic profiles and immune evasion strategies, which differ from EBOV and BDBV [1, 33]. Cross-protective immunity between species is absent, meaning populations remain immunologically naïve to each new introduction [1, 37].

Licensed therapies and vaccines exist only for EBOV such as the rVSV-ZEBOV vaccine and monoclonal antibodies [1, 38], while SUDV and BDBV lack approved countermeasures. During Uganda's 2022 SUDV outbreak, experimental vaccines/therapies were deployed late in trials, limiting their impact [12, 33]. Improved supportive care such as fluid management and infection control moderated CFRs in later outbreaks for instance SUDV CFR dropped from ~ 53% in 2000 to ~ 34% in 2022 [12, 33]. BDBV's lower CFR in 2007 (~ 34%) also benefited from international support and optimized care after delayed pathogen identification [33, 34]. On the other hand, EBOV's 2019 Ugandan cases were small, late-stage importations with poor outcomes [33], while SUDV outbreaks varied in scale: large outbreaks such as the Gulu 2000 strained healthcare systems, elevating CFRs, whereas smaller clusters such as the 2011 Luwero outbreak were contained early [33]. BDBV's intermediate-sized 2007 outbreak highlighted challenges in initial pathogen detection but ultimately achieved lower mortality due to coordinated response efforts [33, 34].

4.2 Timeliness of response and impact on survival

Timely case recognition emerged as the single strongest modifiable predictor of survival in Ugandan Ebola outbreaks. Multicountry modelling shows that every extra day between a first case-alert and laboratory confirmation increases both the outbreak-level CFR and its final size [39]. Field evidence from Uganda's 2022 Sudan-ebolavirus epidemic echoes that pattern: World Health Organization sitreps document numerous deaths that occurred in the community before patients could be transferred to an ETU [40]. Conversely, once confirmation is rapid, ETUs, aggressive supportive care and, where licensed, monoclonal-antibody therapy can be deployed. In a randomised controlled trial, the mAb REGN-EB3 cut mortality by 40% among Zaire-virus patients [41] while patients admitted to ETUs within 24 h of presentation during the West-African epidemic had a 50% lower hazard of death (HR 0.5, 95% CI 0.4–0.8) than those admitted later [42]. Our Ugandan estimate of approximately 3%-point increase in CFR for each day's delay falls squarely within this range, underscoring the critical importance of minimizing diagnostic and treatment delays.

The apparent inverse relationship between onset-to-response delay and observed CFR is fully explained by well-characterized surveillance biases. Early outbreak clusters are disproportionately detected via their most fulminant cases: as Lipsitch et al. observed, "those cases that come to the attention of public health authorities will typically be people with the most severe symptoms. Therefore, the CFR will typically be higher among detected cases than among the entire population of cases" [43]. Likewise, Rudolf et al. found a case-fatality rate of 67% for patients diagnosed onsite versus 46% for those transferred into treatment units during the 2014–2016 West African epidemic, reflecting survival-selection bias in referral pathways [44]. Our Ugandan results where rapid recognition of severe index cases coincides with higher apparent mortality mirror these bias mechanisms.

Furthermore, each additional day of delay between symptom onset and hospital admission was associated with an 11% increase in the odds of death across DRC Ebola epidemics from 1976 to 2014 [3]. Accordingly, reducing diagnostic and treatment delays offers the greatest marginal benefit in outbreaks with higher baseline virulence.

4.3 Clinical and public health implications

The significant association between diagnostic delays and increased CFRs in EBOD outbreaks in Uganda underscores the critical need for prompt case identification and laboratory confirmation. Delays in specimen collection and diagnosis can impede timely initiation of supportive care, which is vital for improving patient outcomes. Implementing decentralized diagnostic capabilities, such as mobile laboratories and point-of-care testing, can facilitate quicker diagnosis and treatment initiation. Strengthening surveillance systems and enhancing community engagement are also essential to encourage prompt reporting of symptoms and adherence to public health measures.

Furthermore, the observed inverse relationship between delays in the Ministry of Health's response declaration and CFRs, though counterintuitive, may reflect complexities in outbreak dynamics. One possible explanation is that outbreaks with delayed official responses may have been smaller or less severe, thus exhibiting lower CFRs. Alternatively, this finding could reflect variations in community engagement, healthcare infrastructure, or reporting practices.

4.4 Strengths and limitations

Among the strengths of this study is the comprehensive data collection from multiple sources, including peer-reviewed articles, official reports, and grey literature, ensuring a broad representation of EBOD outbreaks in Uganda over the specified period. The focus on temporal dynamics, specifically analysing diagnostic and response delays, highlights the significance of timely interventions in managing EBOD outbreaks an area previously underexplored in outbreak-level analyses. Additionally, the use of meta-regression techniques allowed for the assessment of associations between delays and CFRs across different outbreaks, providing a quantitative measure of these relationships.

However, some limitations are acknowledged. Reliance on retrospective data sources may introduce biases due to incomplete reporting, recall inaccuracies, and inconsistent documentation practices across different outbreaks. Unmeasured variables, such as community engagement levels, healthcare worker density, and availability of medical supplies, may also confound the observed associations between delays and CFRs.

4.5 Directions for future research

The findings of this study underscore the critical need for enhanced research efforts to better understand and mitigate the impact of diagnostic and response delays on

EBOD outcomes in Uganda and similar settings. Future research should prioritize several key areas. Implementing real-time data collection during outbreaks can provide more accurate and timely information on diagnostic and response delays, facilitating a more nuanced understanding of how these delays influence CFRs and informing more effective intervention strategies. Developing and adopting standardized definitions and measurements for diagnostic and response delays are essential for ensuring consistency and comparability across studies, enabling more robust meta-analyses and facilitating the identification of best practices in outbreak management. Given the lack of approved vaccines and therapeutics for certain Ebola virus species, such as the Sudan virus, research should focus on evaluating the efficacy of candidate medical countermeasures. Clinical trials assessing the safety and effectiveness of these interventions are crucial for expanding the arsenal of tools available for outbreak response.

5 Conclusion

This rapid systematic review and meta-analysis underscore the critical role of timely diagnostics in mitigating the severity of EBOD outbreaks in Uganda. Our findings reveal a significant association between diagnostic delays and increased CFRs, highlighting the necessity for prompt specimen collection and laboratory confirmation to improve patient outcomes. Conversely, the observed inverse relationship between delays in the Ministry of Health's response declaration and CFRs suggests complexities in outbreak dynamics that warrant further investigation.

The heterogeneity in CFRs across different outbreaks reflects the multifaceted nature of EBOD transmission and management, influenced by factors such as viral species, healthcare infrastructure, community engagement, and data quality. Addressing these disparities requires a comprehensive approach that includes strengthening healthcare systems, enhancing diagnostic capabilities, and fostering community trust and engagement.

Future research should focus on prospective data collection, standardization of timeliness metrics, evaluation of medical countermeasures, integration of technological innovations, and assessment of health system resilience. Addressing these research priorities, will ensure that stakeholders can develop more effective strategies to reduce diagnostic and response delays, ultimately improving patient outcomes and controlling the spread of EBOD in Uganda and comparable contexts.

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Author Contributions GP: Conceptualization, protocol development, literature search, data extraction, statistical analysis, drafting of the manuscript. POO: Oversight of methodological framework, critical revision of the protocol, and supervision of data analysis. SO: Assisted with data curation, verification of extracted metrics, and drafting of the Results section. GP: Provided expert input on meta-analytic methods, reviewed statistical outputs, and contributed to the Discussion. All authors read, reviewed, and approved the final manuscript.

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Data Availability The full dataset of extracted outbreak characteristics, timeliness metrics, and prognostic factors is provided as Supplementary file. All R code used for meta-analysis and meta-regression is archived in a publicly accessible at GitHub repository https://github.com/gpaasi/ebola-uganda-outbreak-timeliness-cfr and via Zenodo https://doi.org/10.5281/zenodo.15564078, released under a Creative Commons CC-BY 4.0 license.
Competing interests.
The authors declare no competing interests, financial or otherwise, that could have influenced the study design, analysis, or reporting.

Declarations

Ethics Approval and Consent to Participate This study was a secondary analysis of published peer-reviewed articles and publicly available outbreak reports; no human subjects or identifiable data were involved.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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