Differential symptomology of possible and confirmed Ebola virus disease infection in the Democratic Republic of the Congo: a retrospective cohort study

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Summary

Background In its earliest phases, Ebola virus disease's rapid-onset, high fever, and gastrointestinal symptoms are largely indistinguishable from other infectious illnesses. We aimed to characterise the clinical indicators associated with Ebola virus disease to improve outbreak response.

Methods In this retrospective analysis, we assessed routinely collected data from individuals with possible Ebola virus disease attending 30 Ebola health facilities in two provinces of the Democratic Republic of the Congo between Aug 1, 2018, and Aug 28, 2019. We used logistic regression analysis to model the probability of Ebola infection across 34 clinical variables and four types of possible Ebola virus disease exposures: contact with an individual known to have Ebola virus disease, attendance at any funeral, health facility consultation, or consultation with an informal health practitioner.

Findings Data for 24 666 individuals were included. If a patient presented to care in the early symptomatic phase (ie, days 0–2), Ebola virus disease positivity was most associated with previous exposure to an individual with Ebola virus disease (odds ratio [OR] 11·9, 95% CI 9·1–15·8), funeral attendance (2·1, 1·6–2·7), or health facility consultations (2·1, 1·6–2·8), rather than clinical parameters. If presentation occurred on day 3 or later (after symptom onset), bleeding at an injection site (OR 33·9, 95% CI 12·7–101·3), bleeding gums (7·5, 3·7–15·4), conjunctivitis (2·4, 1·7–3·4), asthenia (1·9, 1·5–2·3), sore throat (1·8, 1·3–2·4), dysphagia (1·8, 1·4–2·3), and diarrhoea (1·6, 1·3–1·9) were additional strong predictors of Ebola virus disease. Some Ebola virus disease-specific signs were less prevalent among vaccinated individuals who were positive for Ebola virus disease when compared with the unvaccinated, such as dysphagia (–47%, p=0·0024), haematemesis (–90%, p=0·0131), and bleeding gums (–100%, p=0·0035).

Interpretation Establishing the exact time an individual first had symptoms is essential to assessing their infection risk. An individual's exposure history remains of paramount importance, especially in the early phase. Ebola virus disease vaccination reduces symptom severity and should also be considered when assessing the likelihood of infection. These findings about symptomatology should be translated into practice during triage and should inform testing and quarantine procedures.

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Introduction

In its earliest phases, Ebola virus disease's rapid-onset, high fever, and gastrointestinal symptoms are largely indistinguishable from other infectious illnesses, especially in tropical environments in which Ebola virus disease typically occurs.[1,2] This ambiguity leaves clinicians and relatives caring for patients with Ebola virus infection at substantial risk of contracting it before diagnosis. More severe Ebola virus disease symptoms emerge as the disease progresses, especially diarrhoea, abdominal pain, vomiting, sore throat, dysphagia, and bleeding (driven by vascular disorders), although patients are usually infectious for some time before they appear.[3–11] Despite improved Ebola knowledge, conclusive evidence on when and which symptoms are most likely to emerge is lacking.

Ebola virus disease's intense transmissibility, social affect, and severity normally necessitate a broad clinical definition for suspected disease.[12] This definition results in large numbers of people with possible infections being quarantined and tested, often resulting in delays confirming disease. Thus, proper management of patients who are positive for Ebola virus is also often delayed, as is care for other infectious illnesses while waiting for it to be excluded as a diagnosis.[13,14] A more reliable and predictive risk categorisation for possible infections could improve overall quality of care, and better understanding of symptomatology could strengthen surveillance and make disease control efforts more efficient once an outbreak is declared. Additionally, although immunisation with anti-Ebola recombinant vesicular stomatitis virus vaccines is

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Research in context

Evidence before this study

We searched PubMed for articles reporting associations of signs and symptoms with Ebola infection using the terms "Ebola infection/s," OR "Ebola disease," "EVD" AND "clinical indicator/s," "predictor/s," "symptom/s," "symptomatology," OR "case definition/s" in the title or abstract fields from 1976 to May 31, 2022, without language restrictions and screened for related citations. We excluded outcome studies to focus on those that investigated factors predictive of Ebola virus disease infection. We found that Ebola virus disease symptomatology has only ever been documented in clinical reports and 16 cohort studies (comparing those with and without Ebola virus disease), almost all from the 2014–16 outbreak in west Africa, and two meta-analyses. Yet, these cohorts were relatively small (ie, 300–1000 patients), and data collection was not always harmonised across cohorts, leading to variable or conflicting conclusions. One of the two meta-analyses concluded that the current WHO case definition had insufficient sensitivity and specificity and both of these analyses advocated for the improvement of the case definition. Practically, the absence of consensus about the strongest predictors of Ebola means that assessing an individual's actual risk of Ebola virus disease positivity often still relies on health workers' clinical intuition rather than firm evidence. This prospect is daunting considering the quarantine procedures associated with the suspicion of many Ebola virus disease infections. The situation is further complicated by the often high burden of illnesses with similar symptomatology found in Ebola-affected areas.

Added value of this study

Because both clinical recovery and outbreak control require the earliest possible identification of Ebola virus disease, a more accurate description of the clinical course of disease could help clinicians recognise individuals with possible Ebola virus disease infection and triage them on the basis of their likelihood of infection. Using data from every Ebola isolation centre across two provinces of the Democratic Republic of the Congo during the tenth Ebola virus disease outbreak, we retrospectively investigated the interaction between the onset, an individual's type of symptoms, and the likelihood of an eventual positive diagnosis. Logistic regression analysis revealed a natural threshold before or after which various symptoms were associated with infection. This analysis exposed an early phase (ie, days 0–2 after disease onset) and a late phase (ie, day 3 or later after symptom appearance) of Ebola virus disease symptomatology, providing clinicians with a practical framework with which to infer whether an individual's symptoms are more likely to be Ebola virus disease or another pathology. This study is the largest analysis of Ebola virus disease symptomatology ever conducted (ie, of more than 24 000 patients). It is also the first analysis to occur in the recombinant vesicular stomatitis vaccine era, allowing investigation into how the course of disease is affected in populations with some access to immunisation.

Implications of all the available evidence

These results show the crucial importance of establishing both timing (ie, when exactly an individual's Ebola virus disease symptoms began) and exposure history when assessing the risk of infection, since possible exposures to Ebola virus disease (through health care, funeral attendance, or personal contacts) were still the most important predictors of disease regardless of a patient's symptomatology, especially in the first 2 days after symptoms appeared. In this early symptomatic stage, clinical indicators (with some exceptions) ultimately proved to be less effective than exposure histories at predicting Ebola virus disease infection, although their usefulness improved with time. Moving forward, these results can inform and improve established Ebola virus disease case definitions and evidence-base, bedside clinical algorithms for clinicians. Finally, this study is the first to show how immunised patients who nevertheless acquired Ebola virus disease were less likely to develop many Ebola virus disease symptoms, especially in the late phase of disease.

an increasingly important outbreak response tool, it does not prevent all infections, and the effect of vaccination on symptomatology in vaccinated individuals who nevertheless become infected merits research to expand and enrich understanding of the vaccine and Ebola virus disease clinical course.[15]

We assessed symptomatology among individuals with possible Ebola virus disease during the 2018–20 Ebola epidemic in the Democratic Republic of the Congo to investigate the relationship between individuals' symptoms when presenting to care, differences in the timing of symptom appearance between individuals positive for Ebola virus disease and those negative for the disease, and different patients' overall likelihood of positivity. We describe clinical indicators of Ebola virus disease infection and identify predictive approaches to case identification in the recombinant vesicular stomatitis vaccine era, in which immunisation could attenuate disease severity.

Methods

Study population

We conducted a retrospective analysis of individuals with possible Ebola virus disease, registered by response authorities according to the WHO case definition, and admitted to 30 Ebola facilities (ie, treatment or transit centres, or isolation units in health centres) in North-Kivu and Ituri provinces of the Democratic Republic of the Congo between Aug 1, 2018, and Aug 28, 2019. Facilities were managed jointly by the Democratic Republic of the Congo Ministry of Health and one of several medical humanitarian partners (ie, Médecins

Sans Frontières, Alima, International Medical Corps, Medair, or Samaritan's Purse). Clinical and epidemiological data were collected at admission by clinicians. Patient data were entered into standardised electronic spreadsheets at each facility before export, aggregation, and quality control, conducted by data managers at a centralised site.

Collected for epidemiological purposes during the epidemic, outside the context of research the Coordination of the Ebola Response and the Democratic Republic of the Congo Ministry of Health authorised the analyses and publication of these data.

Variables and Ebola status

Venous blood samples were collected and sent to regional laboratories (Institut National de Recherche Biomédicale, Butembo and Beni, Democratic Republuc of the Congo) for diagnosis, which occurred by detecting Ebola glycoprotein or nucleoprotein RNA by PCR. Results are henceforth defined as Ebola virus disease positive or negative. The viral load of each patient positive for Ebola virus disease was quantified by their cycle threshold value (ie, the minimum number of PCR cycles needed to detect Ebola glycoprotein RNA in blood samples). Other variables included dates of symptom onset, dates of presentation to care, demographic and clinical variables (including subjective fever), vaccination status (provided by patient or caregiver recall and outbreak response teams), and exposure history in the 21 days before symptom appearance. Exposure history was categorised into four types of possible transmission events: first, contact with an individual known to be Ebola virus disease positive; second, attendance at any funeral (regardless of the deceased's cause of death); third, health facility consultation for any reason; and fourth, consultation with an informal health practitioner for any reason. Individuals could have had multiple potential exposures. Time-to-registration or time-to-presentation (in days) was defined as the date of symptom onset until the date of the patient's registration as potentially having Ebola virus disease, although registration usually coincided with the individual's admission to an Ebola facility for testing. An individual who was vaccinated was defined as such by being vaccinated before suspicion of Ebola. Considering time to protection, a long time since vaccination was defined as occurring 10 days or more before symptom onset and a short time since vaccination was defined as occurring less than 10 days before onset. Unless specified (eg, stratified by time-since-vaccination), analyses were performed on all individuals who were vaccinated. Missing data seen in this operational dataset were assessed using the MICE R package.[16]

Statistical analysis

Univariate analysis compared symptom prevalence using χ^2 or Fisher's exact tests. Average cycle threshold values were compared using non-parametric Wilcoxon tests when assessing viral loads between strata.

Logistic regression modelled the probability of Ebola infection across 34 clinical variables and four types of possible Ebola virus disease exposure. When appropriate, time-to-presentation, age, or vaccination status were used as stratification variables. In a stepwise manner, variables least associated with infection were progressively removed from the model (ie, when the p value was >0·3), retaining only significant variables at the last step (p<0·05). Outcomes are presented unadjusted for age, although adjusted analyses produced similar results. Similarly, we present associations excluding observations with missing values, but diagnostics obtained by substitution with explicit unknown values were very close (appendix pp 4–9). The introduction of interaction terms in tested models did not modify associations of variables with infection.

See Online for appendix

To identify two distinct phases of disease, the cohort was stratified into early and late groups by individuals' time-to-registration as an individual with possible Ebola virus disease using different time thresholds (range 1–4 days after symptom onset). For each threshold tested, regression diagnostics were analysed in both strata. The longer than day 2 threshold resulted in the most striking differences in predictors of infection between early and late groups and was kept for further analyses. Consequently, a shorter time-to-presentation group was defined as individuals registered as possibly having Ebola virus disease on days 0–2 after symptom onset. Those registered on day 3 or later comprised a longer time-to-registration group.

Patients' age influenced the presence (or reporting) of some signs or symptoms (appendix p 3), and therefore was also considered as a stratification variable when looking at risk factors for infection.

Role of the funding source

The study sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the Article.

Results

The study included 24 666 individuals with possible Ebola virus disease, among whom 1950 (7·9%) were positive for Ebola virus disease. The sex ratio in the study population was 1·02, but more adult women than men had a confirmed Ebola virus disease diagnosis (table 1). The highest confirmation rate was in adults 26 years and older (11·3%), and more Ebola virus disease was confirmed in children younger than 5 years (5·4%) than in children aged 6–12 years (3·6%). 11 138 (48·0%) of 23 192 patients with data of patients presented within 0–2 days, whereas 5692 (24·5%) presented on days 3 and 4, after symptom appearance (table 1). The confirmation rate of Ebola virus disease (7·9% overall) increased with time-to-registration as an individual with possible Ebola virus disease.

	All individuals with possible Ebola virus disease infection	Ebola virus disease negative	Ebola virus disease positive	p value
Overall	24 666	22 716	1950	..
Sex				
Female	12 180/24 641 (49·4%)	11 072/22 695 (90·9%)	1108/1946 (9·1%)	ref
Male	12 461/24 641 (50·5%)	11 623/22 695 (93·3%)	838/1946 (6·7%)	<0·0001
Age				
≤5 years	4133/24 646 (16·8%)	3910/4133 (94·6%)	223/4133 (5·4%)	ref
6–12 years	3487/24 646 (14·1%)	3361/3487 (96·4%)	126/3487 (3·6%)	<0·0003
13–25 years	7316/24 646 (29·7%)	6813/7316 (93·1%)	503/7316 (6·9%)	0·0021
≥26 years	9710/24 646 (39·4%)	8614/9710 (88·7%)	1096/9710 (11·3%)	<0·0001
Time of symptom onset-to-presentation				
0–2 days	11 138/23 192 (48·0%)	10 595 (95·1%)	543 (4·9%)	<0·0001
3–4 days	5692/23 192 (24·5%)	5224 (91·8%)	468 (8·2%)	<0·0001
5–6 days	2599/23 192 (11·2%)	2252 (86·6%)	347 (13·4%)	0·68
7–8 days	1868/23 192 (8·1%)	1634 (87·5%)	234 (12·5%)	0·26
≥9 days	1895/23 192 (8·2%)	1633 (86·2%)	262 (13·8%)	ref
Contact with an individual positive for Ebola virus disease				
No	17 386/21 690 (80·2%)	16 813 (96·7%)	573 (3·3%)	ref
Yes	4304/21 690 (19·8%)	3221 (74·8%)	1083 (25·2%)	<0·0001
Recombinant vesicular stomatitis vaccine status				
Negative	13 435/16 467 (81·6%)	12 546 (93·4%)	889 (6·6%)	ref
Positive	3032/16 467 (18·4%)	2723 (89·8%)	309 (10·2%)	<0·0001
Time since vaccination				
≥10 days (long)	856/1450 (59·0%)	803 (93·8%)	53 (6·2%)	ref
<10 days (short)	594/1450 (41·0%)	428 (72·1%)	166 (27·9%)	<0·0001

Data are n (%) or n/n assessed (%). Percentages in the Ebola virus disease negative and positive columns are shown as the proportion of all individuals in that category.

Table 1: **Characteristics of patients with possible Ebola virus disease admitted to Ebola health facilities from Aug 1, 2018, to Aug 28, 2019 (during the outbreak in North Kivu, DR Congo)**

Ebola virus disease status and sex were specified in all observations. Among variables necessary for analysis there were 1326 (68·0%) of 1950 complete cases for patients who were positive for Ebola virus disease and 13 720 (60·4%) of 22 716 complete cases for those who were negative. Exposure histories were less frequently documented for patients positive for Ebola virus disease than for patients who were negative for all exposure types. Collinearity was assessed by computing variance inflation factors using the car package: there was no major collinearity between variables as all variance inflation factor values were comprised between 1·03 and 1·67 (variance inflation factor threshold criteria for collinearity=5).

3032 (18·4%) of 16 467 patients with data had received a recombinant vesicular stomatitis vaccine (ie, a Merck single dose), most frequently through a reactive ring vaccination campaign. Among 1950 individuals positive for Ebola virus disease, 309 (15·8%) were individuals who had been vaccinated before disease onset and 889 (45·6%) had never been vaccinated (752 [38·6%] of patients positive for Ebola virus disease had missing vaccination status). Considering individuals with complete data on their time of vaccination, 856 (59·0%) of 1450 had been so for 10 days or more before symptom onset, but this proportion was lower, 53 (24·2%) of 219, in those positive for Ebola virus disease compared with those who were negative (803 [65·2%] of 1231; table 1). Confirmed Ebola virus disease diagnosis was much lower in those who had been vaccinated for 10 days or more (6·2%) than in those who had only recently received a vaccine (ie, within <10 days of illness onset; 27·9%, p<0·0001; table 1). Dates of vaccination were missing for approximately half of the vaccinated. The distribution of patients by time-to-registration and vaccination group showed that individuals who were Ebola virus disease positive and unvaccinated were registered later than those who were Ebola virus disease positive and vaccinated (and all those who were Ebola virus disease negative; appendix p 1).

Associations between Ebola infection and various signs, symptoms, and Ebola virus disease exposure types are detailed in table 2. The symptomatology most associated with Ebola virus disease positivity included asthenia, dysphagia, sore throat, conjunctivitis, bleeding gums, bleeding at an injection site, and each of the four possible exposure types. Although around half of patients positive for Ebola virus disease reported a history of fever before presenting to care, this clinical indicator was not associated with Ebola virus disease infection in univariate analyses. Contact with a person known to be positive for Ebola virus disease emerged as the most important risk factor for infection, with 1083 (65·4%) of 1656 individuals positive for Ebola virus disease reporting such contact before symptom onset. Previous contact with an individual known to be positive for Ebola virus disease was also known or declared in 4304 (19·8%) of all Ebola virus disease suspects.

Aside from this broader picture, symptom prevalence often differed by time-to-registration as an individual with possible Ebola virus disease, particularly among those who were positive (figure 1). Among these patients, some clinical signs (eg, conjunctivitis, asthenia, bleeding gums, bleeding at an injection site, dysphagia, and sore throat) became increasingly prevalent as time elapsed between the appearance of symptoms and an individual's registration. Other symptoms (eg, myalgia, dysphagia, arthralgia, chest pain, and hiccups) were more likely to be seen only among individuals positive for Ebola virus disease who were identified and registered on days 3 and 4 after becoming symptomatic, although the magnitude was less important. For initially negative predictors such as diarrhoea and vomiting, prevalence curves crossed days 3 and 4 after symptom onset, after which these signs became positive predictors. Viral load increased with time-to-registration (figure 1). The varied association between indicators and infection was confirmed by using different time thresholds to stratify the population into two groups indicating whether individuals were registered with health authorities

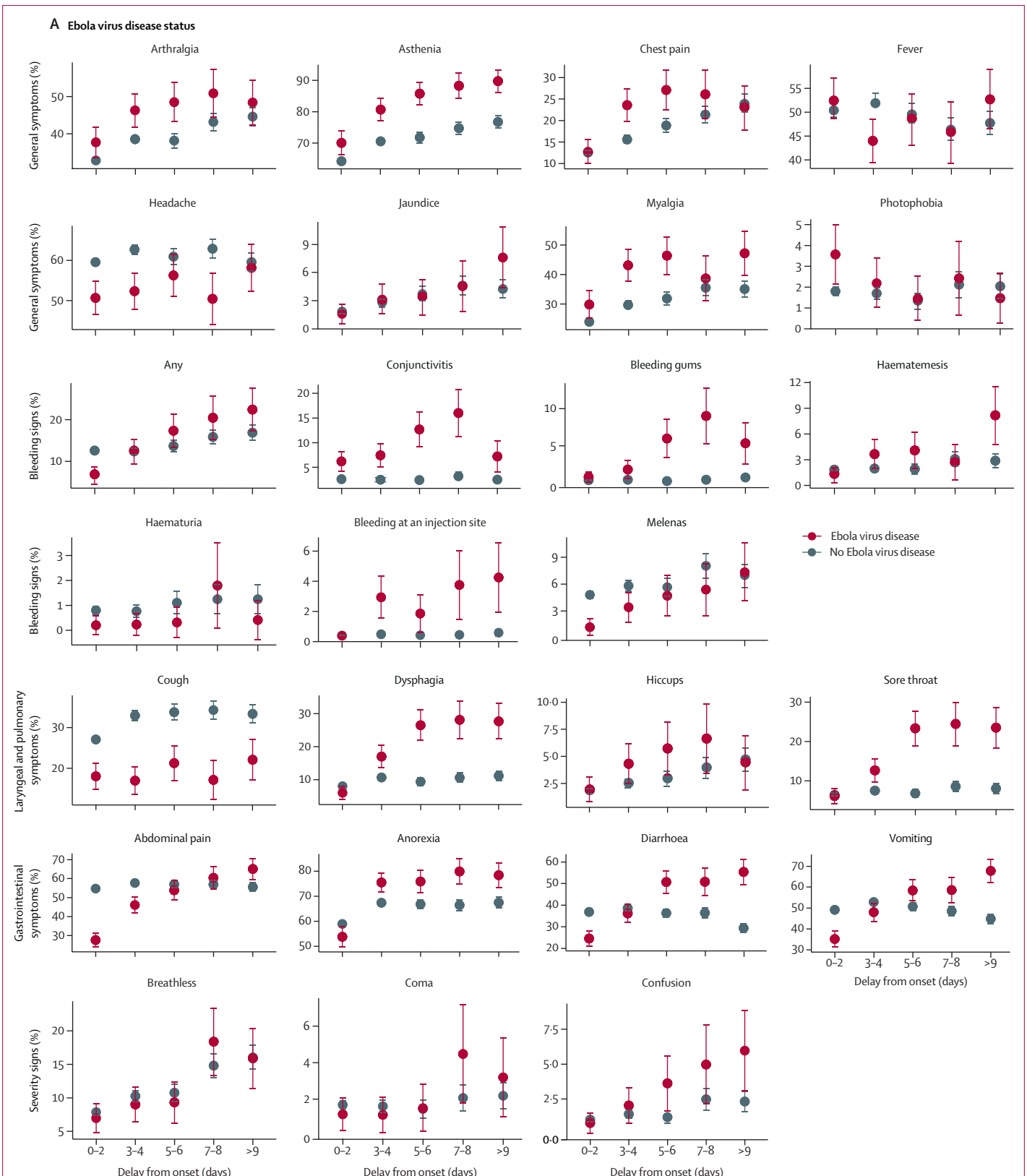
	Prevalence in the study population (n=24 666)	Prevalence, n/n (%)		Unadjusted analysis		Adjusted analysis	
		Positive for Ebola virus disease	Negative for Ebola virus disease	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Symptoms and clinical signs							
Bleeding at injection or collection site	51/20 289 (0·3%)	36/1778 (2·0%)	15/18 511 (0·1%)	25·5 (13·9–46·6)	<0·0001	33·2 (13·8–86·6)	<0·0001
Bleeding gums	158/20 334 (0·8%)	69/1781 (3·9%)	89/18 553 (0·5%)	8·3 (6·1–11·5)	<0·0001	8·8 (5·1–14·9)	<0·0001
Conjunctivitis	682/21 818 (3·1%)	168/1832 (9·2%)	514/19 986 (2·6%)	3·8 (3·2–4·6)	<0·0001	2·0 (1·5–2·6)	<0·0001
Sore throat	1709/21 972 (7·8%)	287/1829 (15·7%)	1422/20 143 (7·1%)	2·5 (2·1–2·8)	<0·0001	1·8 (1·4–2·2)	<0·0001
Dysphagia	2218/21 984 (10·1%)	342/1835 (18·6%)	1876/20 149 (9·3%)	2·2 (2·0–2·5)	<0·0001	1·5 (1·2–1·8)	<0·0001
Confusion or disorientation	340/21 822 (1·6%)	56/1827 (3·1%)	284/19 995 (1·4%)	2·2 (1·6–2·9)	<0·0001	1·5 (0·9–2·4)	0·078
Asthenia	16 340/23 418 (69·8%)	1511/1874 (80·6%)	14 829/21 544 (68·8%)	1·9 (1·7–2·1)	<0·0001	1·9 (1·6–2·2)	<0·0001
Hiccups	608/21 869 (2·8%)	79/1830 (4·3%)	529/20 039 (2·6%)	1·7 (1·3 -2·1)	<0·0001	1·1 (0·8–1·6)	0·52
Haematemesis (black)	108/20 273 (0·5%)	15/1780 (0·8%)	93/18 493 (0·5%)	1·7 (1·0–2·9)	0·087	0·6 (0·2–1·6)	0·36
Bone or muscle pain	6481/22 291 (29·1%)	697/1828 (38·1%)	5784/20 463 (28·3%)	1·6 (1·4–1·7)	<0·0001	1·2 (1·1–1·4)	0·084
Bleeding (other)	262/21 364 (1·2%)	33/1806 (1·8%)	229/19 558 (1·2%)	1·6 (1·1–2·3)	0·0207	1·2 (0·7–1·9)	0·49
Thoracic pain	3557/22 041 (16·1%)	394/1829 (21·5%)	3163/20 212 (15·6%)	1·5 (1·3–1·7)	<0·0001	1·4 (1·2–1·6)	0·0012
Haematemesis (red)	509/20 370 (2·5%)	63/1786 (3·5%)	446/18 584 (2·4%)	1·5 (1·1–1·9)	0·0045	1·7 (1·1–2·5)	0·0141
Arthralgia	8318/22 469 (37·0%)	828/1836 (45·1%)	7490/20 633 (36·3%)	1·4 (1·3–1·6)	<0·0001	1·3 (1·1–1·5)	<0·0001
Anorexia	14 859/23 266 (63·9%)	1313/1871 70·2%	13 546/21 395 (63·3%)	1·4 (1·2–1·5)	<0·0001	1·5 (1·3–1·7)	<0·0001
Photophobia	347/21 800 (1·6%)	40/1823 (2·2%)	307/19 977 (1·5%)	1·4 (1·0–2·0)	0·0404	0·7 (0·5–1·2)	0·21
Jaundice	593/21 820 (2·7%)	64/1828 (3·5%)	529/19 992 (2·6%)	1·4 (1·1–1·7)	0·0378	0·8 (0·5–1·1)	0·15
Skin rash	708/21 837 (3·2%)	74/1829 (4·0%)	634/20 008 (3·2%)	1·3 (1·0 -1·6)	0·050	1·1 (0·8–1·5)	0·66
Coma	384/21 820 (1·8%)	37/1829 (2·0%)	347/19 991 (1·7%)	1·2 (0·8–1·7)	0·42	0·8 (0·5–1·4)	0·46
Diarrhoea	8458/22 626 (37·4%)	749/1853 (40·4%)	7709/20 773 (37·1%)	1·1 (1·0–1·3)	0·0051	1·3 (1·2–1·5)	<0·0001
Difficulty breathing	2205/21 984 (10·0%)	199/1837 (10·8%)	2006/20 147 (10·0%)	1·1 (0·9–1·3)	0·23	0·9 (0·7–1·1)	0·38
Nausea or vomiting	11 613/22 978 (50·5%)	948/1873 (50·6%)	10 665/21 105 (50·5%)	1·0 (0·9–1·1)	0·95	1·0 (0·9–1·2)	0·75
Fever	11 625/22 742 (51·1%)	897/1808 (49·6%)	10 728/20 934 (51·2%)	0·9 (0·9–1·0)	0·43	1·3 (1·1–1·4)	<0·0011
Epistaxis	787/20 461 (3·8%)	54/1784 (3·0%)	733/18 677 (3·9%)	0·8 (0·6–1·0)	0·07	0·9 (0·6–1·3)	0·58
Haemoptysis	214/20 308 (1·1%)	16/1782 (0·9%)	198/18 526 (1·1%)	0·8 (0·5–1·4)	0·58	0·5 (0·2–1·1)	0·12
Abdominal pain	12 823/23 102 (55·5%)	868/1859 (46·7%)	11 955/21 243 (56·3%)	0·7 (0·6–0·8)	<0·0001	0·7 (0·6–0·7)	<0·0001
Headache	14 182/23 229 (61·1%)	988/1859 (53·1%)	13 194/21 370 (61·7%)	0·7 (0·7–0·8)	<0·0001	0·6 (0·5–0·7)	<0·0001
Melena	1224/20 543 (6·0%)	72/1785 (4·0%)	1152/18 758 (6·1%)	0·6 (0·5–0·8)	<0·0004	0·5 (0·3–0·7)	<0·0001
Haematuria	185/20 343 (0·9%)	10/1779 (0·6%)	175/18 564 (0·9%)	0·6 (0·3–1·1)	0·14	0·3 (0·1–0·9)	0·0058
Cough	6718/22 576 (29·7%)	345/1835 (18·8%)	6373/20 741 (30·7%)	0·5 (0·5–0·6)	<0·0001	0·6 (0·5–0·7)	<0·0001
Vaginal bleeding*	731/7170 (10·2%)	39/868 (4·5%)	692/6302 (11·0%)	0·4 (0·3–0·5)	<0·0001	..	..
History of contact (in the past 21 days)							
Contact with an individual positive for Ebola virus disease	4304/21 690 (19·8%)	1083/1656 (65·4%)	3221/20 034 (16·1%)	9·9 (8·9–11·0)	<0·0001	6·9 (6·0–8·0)	<0·0001
Funeral attendance	2135/22 702 (9·5%)	571/1660 (34·4%)	1564/21 042 (7·4%)	6·5 (5·8–7·3)	<0·0001	2·0 (1·7–2·4)	<0·0001
Contact with a health facility	2514/22 558 (11·1%)	449/1647 27·3%	2065/20 911 (9·9%)	3·4 (3·0–3·9)	<0·0001	1·9 (1·6–2·2)	<0·0001
Contact with an informal healer	269/22 559 (1·2%)	52/1632 (3·2%)	217/20 927 (1·0%)	3·1 (2·3–4·3)	<0·0001	1·5 (0·9–2·2)	0·072
Sex							
Female	12 180/24 641 (49·4%)	1108/1946 (56·9%)	11 072/22 695 (48·8%)	1·4 (1·3–1·5)	<0·0001	1·4 (1·3–1·6)	<0·0001
Male	12 461/24 641 (50·6%)	838/1946 (43·1%)	11 623/22 695 (51·2%)	0·7 (0·7–0·8)	<0·0001	Ref	Ref

*Among women older than 12 years.

Table 2: **Prevalence of clinical indicators and types of contact among patients who were positive for and patients who were negative for Ebola virus disease and associations with Ebola infection**

in an early (ie, days 0–2) or late (ie, day 3 or later) stage of symptomatology. Logistic regression diagnostics were similar for time thresholds (>day 1) and (>day 2) both in early and late groups, although they appeared quite different when using the threshold (>day 3; not shown).

Few clinical indicators were significantly associated with Ebola virus disease positivity on days 0–2 after the appearance of symptoms (figure 1; appendix pp 4–6). However, an individual's previous possible Ebola virus disease exposures were strong predictors of infection, for



(Figure 1 continues on next page)

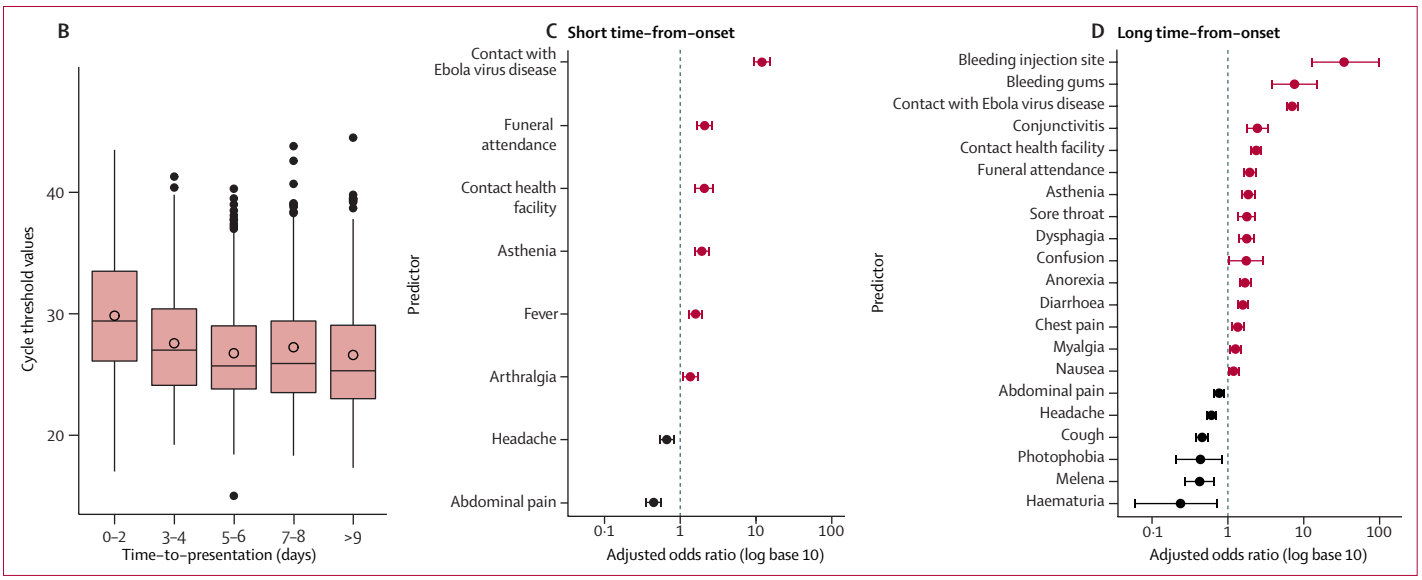


Figure 1: **Prevalence of clinical indicators in individuals with possible Ebola virus disease stratified by time to notification, Ebola virus disease positive viral load, and associations with Ebola virus disease**

(A) Prevalence of Ebola clinical indicators with 95% CI among patients with Ebola virus disease and those without classified by time-to-presentation (note that for readability, the scales of the y-axes were adjusted to the prevalence of each symptom). (B) Viral loads among patients with Ebola virus disease by time-to-presentation, from onset of disease. (C) Adjusted odds ratios between risk factors and Ebola virus disease infection for short time-to-presentation (ie, days 0–2 after symptom onset). (D) Adjusted odds ratios of risk factors and Ebola infection for long time-to-presentation (ie, day 3 or later after symptom onset).

those who registered on days 0–2, including contact with an individual known to be positive for Ebola virus disease (odds ratio [OR] 11·9, 95% CI 9·1–15·8), any consultation at a health facility (2·1, 1·6–2·8), and any funeral attendance (2·1, 1·6–2·7). Three clinical signs and symptoms (ie, asthenia OR 1·9 [95% CI 1·5–2·5], p<0·0001; fever 1·6 [1·3–2·0], p<0·0001; and joint pain 1·4 [1·1–1·7], p=0·0124) were slightly associated with Ebola virus disease illness whereas headache (0·7 [0·5–0·8], p=0·0005) and abdominal pain (0·4 [0·3–0·6], p<0·0001) predicted other illnesses (appendix pp 4–6). Some associations were age-dependent: in the youngest patients (ie, 0–5 years), nausea and vomiting were associated with other illnesses (OR 0·3, p=0·0082), whereas confusion and disorientation in 6–12 year olds (13·1, p=0·0255) and hiccups in those aged 26 years or older (2·7, p=0·0037) were linked with Ebola virus disease.

When individuals presented later to care—that is day 3 or later after symptom onset—an individual's previous exposures were still strongly associated with infection, although bleeding at an injection site (OR 33·9 [95% CI 12·7–101·3], p<0·0001) and bleeding gums (7·6 [3·7–15·4], p<0·0001) were additional strong indicators of positivity (figure 1; appendix pp 7–9). Asthenia (OR 1·9 [95% CI 1·5–2·3], p<0·0001), conjunctivitis (2·4 [1·7–3·4], p<0·0001), sore throat (1·8 [1·3–2·4], p<0·0001), dysphagia (1·8 [1·4–2·3], p<0·0001), confusion and disorientation (1·7 [1·0–2·9], p=0·0416), anorexia (1·7 [1·4–2·0], p<0·0001), and diarrhoea (1·6 [1·3–1·9], p<0·0001) were also indicative of Ebola virus disease. Nausea and vomiting (OR 1·2 [95% CI 1·0–1·4], p=0·0456), chest pain (1·4 [1·1–1·6], p=0·0034), and myalgia (1·3 [1·0–1·5], p=0·0189) were associated with Ebola virus disease, but less so.

By contrast, cough (OR 0·5, p<0·0001), melena (0·4, p<0·0003), haematuria (0·2, p=0·0244), and photophobia (0·4, p=0·0213) were unlikely to be seen in patients who were positive for Ebola virus disease on or after day 3 (figure 1). Abdominal pain (OR 0·8, p=0·0019) and headache (0·6, p<0·0001) also predicted other illnesses. Notably, hiccups might have signalled Ebola virus disease infection in adults (ie, those aged ≥26 years) only (OR 1·9, p=0·0506), whereas fever was negatively associated with disease in 6–12 year olds (0·4, p=0·0033).

In general, most signs and symptoms were less prevalent among patients who were vaccinated versus unvaccinated, although not always significantly. This finding was true both in the Ebola virus disease positive (table 3) and Ebola virus disease negative (appendix pp 10–13) groups. For individuals who were positive for Ebola virus disease registered as potentially positive early on (ie, days 0–2), vaccination status affected few clinical indicators. Among individuals who were positive for Ebola virus disease registered as potentially positive Ebola virus disease later in their disease course (ie, on or after day 3), abdominal pain was 18% less likely to be present (p=0·0315) and notably, dysphagia was 47% (p=0·0024) and sore throat was 38% (p=0·0342) less likely to be present. Bleeding gums was 100% (p=0·0035), haematemesis was 90% (p=0·0131), melena was 77% (p=0·0390), and breathlessness was 55% (p=0·0126) less

	Unvaccinated	Vaccinated any time before onset		Vaccinated ≥10 days before onset		Vaccinated <10 days before onset	
		Patients	Percent change (p value)	Patients	Percent change (p value)	Patients	Percent change (p value)
Short time-to-presentation							
Patients	211	132	..	28	..	70	..
Asthenia	146/207 (70·5%, 64·0–76·3)	94/128 (73·4%, 65·1–80·3)	4% (0·65)	20/28 (71·4%, 52·9–84·7)	1% (1)	49/67 (73·1%, 71·4–82·2)	4% (0·80)
Chest pain	26/199 (13·1%, 9·1–18·5)	17/124 (13·7%, 8·7–20·9)	5% (1)	7/27 (25·9%, 13·2–44·7)	98% (0·0853*)	8/64 (12·5%, 6·5–22·8)	–5% (1)
Fever	117/204 (57·3%, 50·5–63·9)	55/125 (44·0%, 35·6–52·8)	–23% (0·0251)	12/27 (44·4%, 27·6–62·7)	–23% (0·29)	33/67 (49·3%, 37·5–61·1)	–14% (0·26)
Headache	93/203 (45·8%, 39·1–52·7)	74/129 (57·4%, 48·7–65·6)	25% (0·0525)	21/28 (75·0%, 56·6–87·3)	64% (0·0071)	32/65 (49·2%, 37·7–60·9)	8% (0·73)
Joint pain	69/200 (34·5%, 28·3–41·3)	50/126 (39·7%, 31·7–48·4)	15% (0·41)	12/28 (42·9%, 26·5–60·9)	24% (0·51)	23/65 (35·4%, 24·9–47·5)	3% (1)
Myalgia	53/202 (26·2%, 20·7–32·7)	42/124 (33·9%, 26·1–42·6)	29% (0·18)	9/26 (34·6%, 19·4–53·8)	32% (0·50)	24/65 (36·9%, 26·2–49·1)	–36% (0·14)
Abdominal pain	65/202 (32·2%, 26·1–38·9)	27/127 (21·3%, 15·0–29·2)	–33·9% (0·0432)	2/27 (7·4%, 8·1–23·4)	–77% (0·0150)	16/66 (24·2%, 15·5–35·8)	–25% (0·29)
Anorexia	115/206 (55·8%, 49·0–62·4)	62/128 (48·4%, 40·0–57·0)	–13% (0·23)	11/27 (40·7%, 24·5–59·2)	–27% (0·20)	32/67 (47·8%, 36·3–59·5)	–14% (0·31)
Diarrhoea	50/204 (24·5%, 19·1–30·8)	33/125 (26·4%, 19·4–34·7)	8% (0·80)	6/27 (22·2%, 10·6–40·8)	–9% (0·89)	23/65 (35·4%, 24·9–47·5)	44% (0·12)
Vomiting and nausea	68/205 (33·1%, 27·1–40·0)	46/126 (36·5%, 28·6–45·2)	10% (0·62)	11/27 (40·7%, 24·5–59·2)	22% (0·57)	25/65 (38·5%, 27·6–50·6)	16% (0·53)
Dysphagia	11/202 (5·4%, 3·1–9·5)	10/125 (8·0%, 4·4–14·1)	48% (0·49)	0/27 (0·0%, 0–12·5)	–100% (0·37*)	9/65 (13·8%, 7·4–24·3)	156% (0·0324*)
Sore throat	12/200 (6·0%, 3·5–10·2)	8/124 (6·5%, 3·3–12·2)	8·3% (1)	1/27 (3·7%, 0·7–18·3)	–38% (1*)	5/64 (7·8%, 3·4–17·0)	30% (0·57*)
Any bleeding	18/204 (8·8%, 5·7–13·5)	5/126 (4·0%, 1·7–9·0)	–55% (0·14)	2/27 (7·4%, 2·1–23·4)	–16% (1*)	3/65 (4·6%, 1·6–12·7)	–47% (0·40)
Bleeding gums	3/196 (1·5%, 0·5–4·4)	0/122 (0·0%, 0·0–3·1)	–100% (0·29*)	0/26 (0·0%, 0·0–12·9)	–100% (1*)	0/64 (0·0%, 0·0–5·7)	–100% (1*)
Bleeding injection site	0/196 (0·0%, 0·0–1·9)	0/122 (0·0%, 0·0–3·1)	NA	0/26 (0·0%, 0·0–12·9)	NA	0/64 (0·0%, 0·0–5·7)	NA
Melena	2/196 (1·0%, 0·2–3·6)	1/122 (0·8%, 0·1–4·5)	–20% (0·80)	1/26 (3·8%, 0·7–18·9)	280% (0·31)	0/64 (0·0%, 0·0–5·7)	–100% (1*)
Haematemesis	3/196 (1·5%, 0·5–4·4)	0/64 (0·0%, 0·0–3·1)	–100% (0·29*)	0/26 (0·0%, 0·0–12·9)	–100% (1*)	0/64 (0·0%, 0·0–5·7)	–100% (1*)
Conjunctivitis	12/203 (5·9%, 3·4–10·0)	8/126 (6·3%, 3·3–12·0)	7% (1)	3/27 (11·1%, 3·9–28·1)	88% (0·40)	2/66 (3·0%, 0·8–10·4)	–49% (0·53*)
Breathlessness	15/203 (7·4%, 4·5–11·8)	7/125 (5·6%, 2·7–11·1)	–24% (0·6878)	3/27 (11·1%, 3·9–28·1)	50% (0·45*)	4/65 (6·2%, 2·4–14·8)	–16% (1*)

(Table 3 continues on next page)

likely (figure 2). Although power was insufficient to show an effect in the long-time-since-vaccination, univariate analyses showed decreased prevalence of many symptoms if vaccination occurred less than 10 days before onset.

For individuals presenting to care on days 0–2 after symptom onset, adjusted analysis found three predictors of Ebola virus disease positivity regardless of vaccination status, including contact with an individual with Ebola virus disease, asthenia, and abdominal pain (table 3; appendix p 14). Among the vaccinated, attendance at any funeral (OR 2·0, p=0·0003), dysphagia (3·5, p=0·0127), and diarrhoea (2·0, p=0·0146) were also associated. Among those presenting to care on day 3 or later after symptom appearance, bleeding at an injection site, bleeding gums, diarrhoea, sore throat, or dysphagia were notably not associated with infection among the vaccinated (appendix p 14). By contrast, possible previous exposures (eg, contact with an individual positive for Ebola virus disease, funeral attendance, and health facility consultation) and some clinical indicators (eg, anorexia, conjunctivitis, chest pain, and asthenia) were associated with Ebola virus disease infections in vaccinated individuals.

Cycle threshold values in different strata showed no difference by sex, but viral load was higher in younger patients with Ebola virus disease, those who presented to care on day 3 or later after onset, patients without a

	Unvaccinated	Vaccinated any time before onset		Vaccinated ≥10 days before onset		Vaccinated <10 days before onset	
		Patients	Percent change (p value)	Patients	Percent change (p value)	Patients	Percent change (p value)
(Continued from previous page)							
Long time-to-presentation							
Signs and symptoms	n=648 (95% CI)	n=167 (95% CI)	Percent change (p value)	n=25 (95% CI)	Percent change (p value)	n=96 (95% CI)	Percent change (p value)
Asthenia	558/639 (87·3%, 84·5–89·7)	134/162 (82·7%, 76·2–87·8)	−5% (0·16)	18/24 (75·0%, 55·1–88·0)	−14% (0·15)	80/93 (86·0%, 77·5–91·6)	−1·4 (0·85)
Chest pain	149/623 (23·9%, 02·7–27·4)	47/159 (29·6%, 23·0–37·1)	24% (0·17)	8/25 (32·0%, 17·2–51·6)	34% (0·49)	29/89 (32·6%, 23·7–42·9)	36% (0·10)
Fever	285/627 (45·5%, 41·6–49·4)	66/162 (40·7%, 33·5–48·4)	−11% (0·32)	10/25 (40·0%, 23·4–59·3)	−12% (0·74)	40/92 (43·5%, 33·8–53·7)	−4% (0·81)
Headache	360/637 (56·5%, 52·6–60·3)	96/163 (58·9%, 51·2–66·1)	4% (0·65)	16/25 (64·0%, 44·5–79·8)	13% (0·59)	55/93 (59·1%, 49·0–68·6)	4% (0·72)
Joint pain	297/625 (47·5%, 43·6–51·4)	88/161 (54·7%, 46·9–62·1)	15% (0·13)	15/25 (60·0%, 40·7–77·0)	26% (0·31)	54/91 (59·3%, 49·1–68·9)	25% (0·0460)
Myalgia	257/624 (41·2%, 37·4–45·1)	66/156 (42·3%, 34·8–50·2)	−3% (0·87)	8/23 (34·8%, 18·8–55·1)	−16% (0·69)	46/89 (51·7%, 41·5–61·8)	25% (0·08)
Abdominal pain	351/636 (55·2%, 51·3–59·0)	72/159 (45·3%, 37·7–53·0)	−18% (0·0315)	10/24 (41·7%, 24·5–61·2)	−24% (0·27)	45/90 (50·0%, 39·9–60·1)	−9% (0·41)
Anorexia	502/639 (78·6%, 75·2–81·6)	126/161 (78·3%, 71·3–83·9)	0% (1)	16/24 (66·7%, 46·7–82·0)	−15% (0·26)	75/92 (81·5%, 72·4–88·1)	4% (0·61)
Diarrhoea	291/636 (45·8%, 41·9–49·6)	62/159 (39·0%, 31·8–46·7)	−15% (0·15)	7/24 (29·2%, 14·9–49·2)	−36% (0·16)	38/90 (42·2%, 32·5–52·5)	−8% (0·61)
Vomiting and nausea	354/642 (55·1%, 51·1–58·9)	83/161 (51·6%, 43·9–59·1)	−6% (0·47)	11/24 (45·8%, 27·9–64·9)	−17% (0·49)	39/92 (42·4%, 32·7–52·5)	−23% (0·0292)
Dysphagia	160/629 (25·4%, 22·2–29·0)	21/155 (13·5%, 9·0–19·8)	−47% (0·0024)	3/24 (12·5%, 4·3–31·0)	−51% (0·23)	9/87 (10·3%, 5·5–18·5)	−59% (0·0030)
Sore throat	130/629 (20·7%, 17·7–24·0)	20/156 (12·8%, 8·5–19·0)	−38% (0·0342)	2/24 (8·3%, 2·3–25·8)	−59% (0·20)	12/87 (13·8%, 8·1–22·6)	−33% (0·17)
Any bleeding	117/631 (18·5%, 15·7–28·1)	12/160 (7·5%, 4·3–12·6)	−59% (0·0011)	3/24 (12·5%, 4·3–31·0)	−32% (0·60*)	5/91 (5·5%, 2·4–12·2)	−70% (0·0009)
Bleeding gums	37/616 (6·0%, 4·4–8·2)	0/155 (0·0%, 0·0–2·4)	−100% (0·0035)	0/23 (0·0%, 0·0–14·3)	−100% (0·39*)	0/88 (0·0%, 0–4·2)	−100% (0·0096*)
Bleeding injection site	17/613 (2·8%, 1·7–4·4)	2/155 (1·3%, 0·4–4·6)	−54% (0·39)	1/23 (4·3%, 0·8–21·0)	54% (0·49)	0/88 (0·0%, 0·2–6·2)	−100% (0·15)
Melena	35/616 (5·7%, 4·1–7·8)	2/154 (1·3%, 0·4–4·6)	−77% (0·0390)	0/23 (0·0%, 0·0–14·3)	−100% (0·63*)	1/87 (1·1%, 0·2–6·2)	−80% (0·11*)
Haematemesis	36/618 (5·8%, 4·2–8·0)	1/154 (0·6%, 0·1–3·6)	−90% (0·0131)	0/23 (0·0%, 0·0–14·3)	−100% (0·63*)	0/87 (0·0%, 0·0–4·2)	−100% (0·0158)
Conjunctivitis	63/618 (10·2%, 7·9–12·7)	17/159 (10·7%, 6·8–16·5)	6% (0·93)	3/24 (12·5%, 4·3–31·0)	24% (0·73)	9/90 (10·0%, 5·4–17·9)	−1% (1)
Breathlessness	88/625 (14·1%, 11·6–17·0)	10/158 (6·3%, 3·5–11·2)	−55% (0·0126)	2/24 (8·3%, 2·3–25·8)	−41% (0·62)	8/89 (9·0%, 4·6–16·7)	−36% (0·25)

*Comparison using Fisher's exact test.

Table 3: **Comparison of the prevalence of signs and symptoms for patients with Ebola virus disease between patients who are recombinant vesicular stomatitis negative and recombinant vesicular stomatitis positive for short time-to-presentation (ie, days 0–2) and long time-to-presentation (ie, day 3 or later)**

(known) recent exposure to Ebola virus disease, and patients who were unvaccinated (appendix p 15). The lower viral load among the vaccinated, compared with the unvaccinated, was significant in patients who were Ebola virus disease positive registered on day 3 or later after onset (1·7 cycle threshold increase, three-fold reduction, p<0·0001; figure 2, appendix p 16). Among vaccinated individuals, more time since vaccination (ie, ≥10 days before disease onset) resulted in lower viral load (2·6 cycle threshold value increase) compared with the recently vaccinated (ie, <10 days). This effect was very important for patients registered as a potentially positive on days 0–2 (4·7 cycle threshold value increase, a 26-fold decrease in viral load, p=0·0012), but was not significant for those presenting later to care (figure 2; appendix pp 16).

Discussion

Although symptomatology of Ebola virus disease has been partly described in cohorts of patients hospitalised

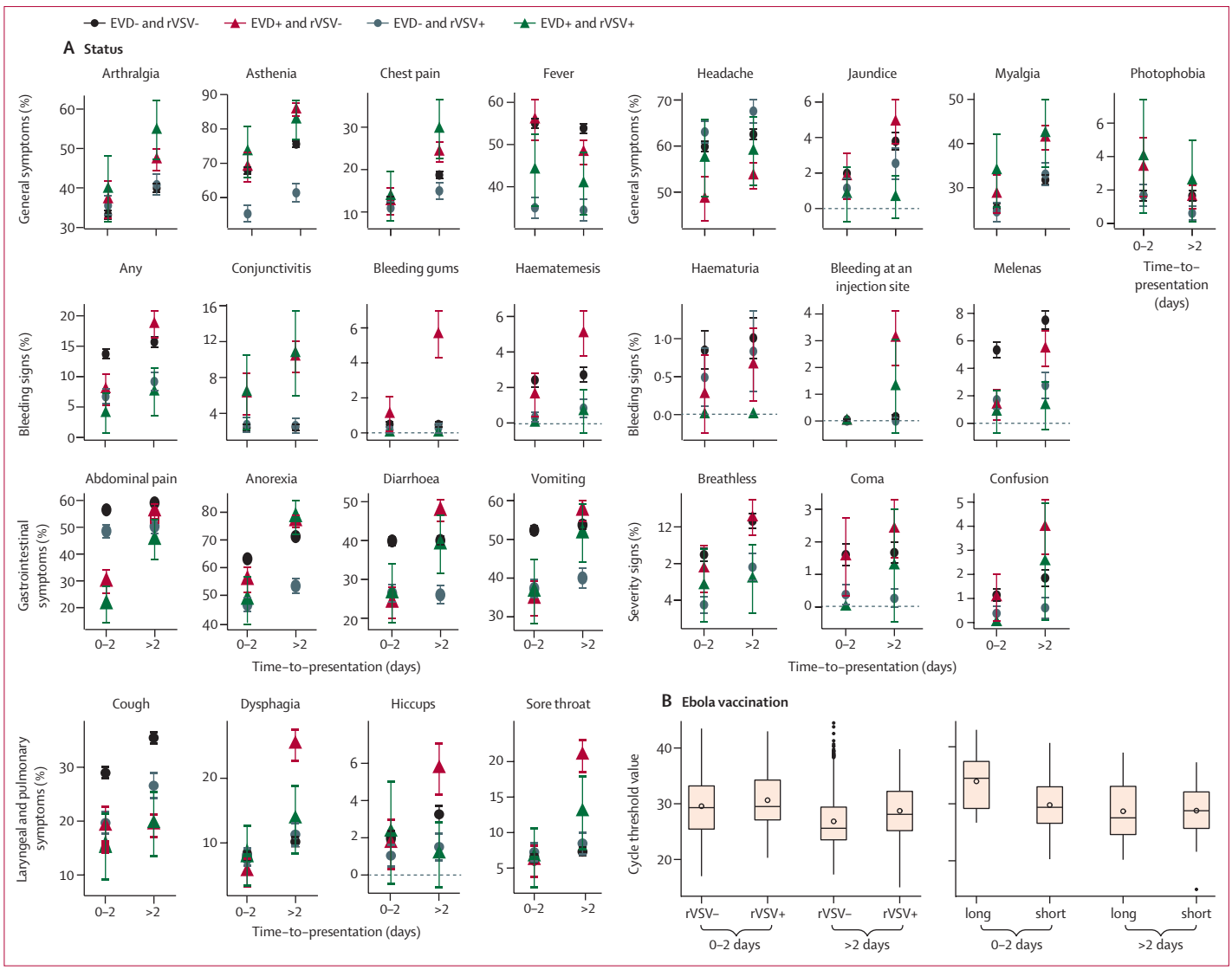


Figure 2: **Prevalence of clinical indicators in patients with possible Ebola virus disease stratified by time to notification among vaccinated and unvaccinated patients, and Ebola virus disease positive viral load**

(A) Prevalence of signs and symptoms among patients who are EVD– and rVSV–, patients who are EVD– and rVSV+, patients who are EVD+ and rVSV–, and patients who are EVD+ and rVSV+ for short time-to-presentation (ie, days 0–2) and long time-to-presentation (ie, day 3 or later; note that for readability, the scales of the y-axes were adjusted to the prevalence of each symptom). (B) Right panel, among patients with Ebola virus disease, viral load by time-to-presentation and vaccination status; left panel, among patients who are EVD+ and rVSV+, viral load by time-to-presentation and time of vaccination, either long (ie, ≥10 days before disease onset) or short (ie, <10 days before disease onset). EVD–=Ebola virus disease negative. rVSV–=recombinant vesicular stomatitis virus vaccine negative. rVSV+=recombinant vesicular stomatitis virus vaccine positive. EVD+=Ebola virus disease positive.

with Ebola virus disease and in comparative analyses (eg, fatal *vs* convalescent patients and patients with Ebola virus disease *vs* matched patients without Ebola virus disease), to our knowledge our study is the first investigation across a large geographical cohort to include all those individuals potentially positive for Ebola virus disease. We also considered the role vaccination might have had in clinical presentation during an outbreak with available, widely used vaccines. By using data from every Ebola facility across two provinces, from more than 24000 individuals who were potentially positive for Ebola virus disease, we are able to robustly describe Ebola virus disease symptomatology at presentation, identify the strongest associations with Ebola infection, and detail the likelihood of infection based on the time between an individual being identified and registered as potentially having Ebola virus disease and illness onset. We found notable the difference in clinical presentation between individuals with Ebola virus disease arriving to a facility nearly immediately (ie, on days 0–2) and those waiting more than 3 days, and that both Ebola virus disease infection and higher viral load were increasingly likely over time, which was consistent across clinical indicators.

Our results provide depth to previous studies' descriptions of how, during the first 2 days of Ebola virus disease illness, symptomatology resembles many diseases endemic to Ebola-affected regions, with no specific clinical pattern to sufficiently differentiate it.[5,17,18] Our cohort confirms that during this period, an individuals exposure history is the most important predictor of infection. Assessing potential exposure to Ebola virus disease requires patients' trust and willingness to share deeply personal information about themselves and their communities. It also demands formidable history-taking and knowledge of Ebola virus disease transmission by health workers. Although most potential transmission events documented in this study were found to be important (including in-person attendance at any funeral, a health facility consultation for any reason, or a consultation with an informal health practitioner for any reason), an individual's contact with another person known to have Ebola virus disease remained the single most important risk factor for disease, as reported elsewhere.[11,19–23]

Among the clinical indicators that did presage an Ebola virus disease diagnosis, asthenia was confirmed to be associated with Ebola virus disease positivity in those who presented from days 0–2, as were fever and arthralgia (in those ≥26 years).[11,20,24] These symptoms could help clinicians identify Ebola virus disease in its earliest stages. Notably, gastrointestinal symptoms were not indicative of Ebola virus disease at this early stage (abdominal pain was even negatively associated). Since other studies have posited that gastrointestinal symptoms are predictors of Ebola virus disease, this finding shows the importance of establishing timing (ie, from the onset of symptoms) when assessing Ebola virus disease risk. Our cohort also confirms previous research suggesting that the presence of headache is not associated with Ebola virus disease.[8,21,24]

More than 3 days after an individual's first symptoms, some clinical indicators became more clearly associated with an eventual Ebola virus disease diagnosis: some gastrointestinal issues (eg, diarrhoea, nausea and vomiting, and anorexia) were predictive of Ebola virus disease (although others such as melena and abdominal pain were not, nor were cough or headache despite being common symptoms in patients with Ebola virus disease) and some bleeding signs (eg, bleeding gums, bleeding at an injection site, and conjunctivitis) were very strong predictors (though haematuria and melena were not). Our data support the idea that dysphagia and sore throat are Ebola virus disease symptoms, concurring with other research but additionally revealing that this symptomatology is especially the case once a patient has been symptomatic for 3 days or longer.[11,19]

Now that Ebola vaccines are approved and widely used, Ebola virus disease infections among the vaccinated will be increasingly seen during outbreaks.[25] In our study, vaccination appeared to have little effect on the clinical presentation of Ebola virus disease in those registered as possibly having an infection within 3 days of having symptoms. In this early period, previous exposure to an individual known to have Ebola virus disease might be the most useful predictor of infection, even among immunised people. Individuals with Ebola virus disease and recombinant vesicular stomatitis virus vaccine were also much less viraemic when vaccinated more than 10 days before becoming symptomatic (26-fold reduction in viral load when compared with those who were recently vaccinated).

In the later period of symptomatology, that is day 3 or later, some of the signs that proved useful indicators of Ebola virus disease infection in unvaccinated people were less present, especially dysphagia, sore throat, breathlessness, and some bleeding signs (eg, bleeding gums, haematemesis, and melena). Their reduced prevalence among the vaccinated validated their specificity in the late phase of Ebola virus disease, and was correlated with a three-fold reduction in viral load in those who were vaccinated. The reduced prevalence and viral load seen in vaccinated individuals supports the theory that Ebola virus disease severity is reduced by immunisation, as observed during experimental challenges,[26,27] and corroborates evidence of vaccine efficacy seen in studies of Ebola transmission[28,29] and fatality.[30] That this reduced prevalence held true for individuals with Ebola virus disease vaccinated late has great value from a public health perspective.

Regardless of when an individual was registered as potentially having Ebola virus disease (ie, early or late), some predictors of Ebola infection differed by vaccination status, suggesting that clinical assessments should consider both a person's vaccination status and the timing of their first symptoms. Yet other associations were consistent across both vaccinated and unvaccinated individuals, especially before exposure to a person known to have Ebola virus disease, funeral attendance, or health-care consultations and asthenia and abdominal pain (on days 0–2), and asthenia, conjunctivitis, and headache (on day 3 or later).

Our study was limited by its specific epidemiological context and by an operational dataset including some variables potentially affected by recall bias. Comparisons and generalisations should be made with care. Additionally, we used vaccination data to confirm that the specificity of identified symptoms and bias related to the clinical presentation of patients who were vaccinated might exist: before vaccination, these individuals were listed as direct or indirect contacts of an individual with Ebola virus disease, vaccinated, and followed-up, and therefore might have been identified more quickly than the unvaccinated after developing their first symptoms. This bias could also explain the lower intensity of symptomatology among vaccinated individuals without Ebola virus disease compared with unvaccinated individuals without Ebola virus disease (appendix pp 10–13). Nevertheless, our analyses were stratified by elapsed time from disease

onset. When restricted to the period days 3 and 4, the same decrease in symptoms was observed.

We describe two stages of Ebola virus disease symptomatology and the effect of vaccination on clinical presentation in a specific epidemiological setting (appendix p 17). This analysis can improve health workers' understanding of Ebola virus disease and provide guidance when assessing patients matching an Ebola virus disease case definition. During an Ebola outbreak response, the use of a broad, sensitive case definition is useful but also carries important drawbacks for patients. The burden of lengthy time to diagnosis should not be underestimated, and long isolation periods while awaiting test results can lead many to not comply with quarantine and other protective public health measures. Overly broad case definitions can also negatively affect the health system (eg, testing and quarantine costs and nosocomial infection risks). Conversely, a case definition too specific for Ebola would leave some individuals with Ebola virus disease outside the response network and hamper outbreak control.[22] Our analyses clarify who the most at-risk individuals for Ebola could be.

Contributors

D-LA, KP, and SA-M contributed to the conception and design of the work. D-LA, MA, and FG accessed and verified all data. D-LA performed the analyses of the database with the help of MA and FL. D-LA and JN interpreted the data and wrote the article with the support of KP, RMC, and EG. All authors substantially contributed to the acquisition of data, critically contributed to the early and final drafts of the manuscript, and are accountable for all aspects of the work. D-LA had full access to all study data and final responsibility for the decision to submit for publication following Ministry of Health validation.

Declaration of interests

We declare no competing interests.

Data sharing

All data belong to the Ministry of Health of the Democratic Republic of the Congo who, in accordance with an established Memorandum of Understanding between the Ministry of Health and Epicentre, authorised access to the dataset for this collaborative research. Any further access to and analysis of data must be presented to and approved by the Ministry of Health.

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