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REGULAR ARTICLES

Seroprevalence and risk factors of *Coxiella burnetii* infection in cattle in northeast Algeria

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Abstract

A cross-sectional study was conducted to determine the seroprevalence and the risk factors associated with *C. burnetii* infection in cattle in the state of Setif in northeastern Algeria from March 2016 to April 2018. A total of 678 cows animals aged at least 24 months and belonging to 90 herds were randomly selected. A serum sample from each cow was tested for antibodies against *C. burnetii* using an indirect enzyme-linked immunosorbent assay (ELISA). A structured questionnaire focusing on risk factors for *C. burnetii* infection was administered to farm owners involved in the study. The individual animal prevalence was 11.36% (77/678) (95%CI 8.97–13.75%), the herd prevalence was 45.56% (41/90) (95%CI 35.27–55.84%), and the within-herd prevalence ranged from 9.09 to 57.14% (mean 23.71%; Q1 11.11%, Q2 or median 20%, Q3 30%). Multivariable logistic regression analysis revealed that contact with other herds (odds ratio (OR) 1.95, 95 CI 1.12–3.42) and purchased animals (OR 2.05, 95 CI 1.14–3.68) was identified as risk factors for seropositivity to *C. burnetii*, while the use of disinfectants (OR 0.32, 95 CI 0.14–0.72) was identified as protective factor. The results from the present study indicate that *C. burnetii* is circulating into cattle herds in the region of Setif in Northeastern of Algeria. It is recommended to implement good hygienic practices and measures of biosecurity to reduce the spread of infection between cattle herds and possible exposure of humans.

Keywords *Coxiella burnetii* · Cows · Seroprevalence · Risk factors · ELISA · Setif

Introduction

Q fever in humans or coxiellosis in animals is a ubiquitous worldwide zoonosis with the exception of New Zealand. The causal agent is *Coxiella burnetii*, which is a Gram-negative obligate intracellular bacterium, belonging to Coxiellaceae family, order Legionellales of the gamma subdivision of Proteobacteria (Bielawska-Drózd et al. 2013).

C. burnetii can infect a wide range of animals, including mammalian and non-mammalian animals (Parker et al. 2006). Domestic ruminants are recognized as the primary reservoirs of *C. burnetii* for human infection (Kirkan et al. 2008; Roest et al. 2011; Alvarez et al. 2012), which shed the bacteria mainly with birth products, vaginal discharges, urine, milk, and feces (Guatteo et al. 2006, 2007; Rousset et al. 2009; Angelakis and Raoult 2010; EFSA 2010). *C. burnetii* transmits mainly to humans or animals through inhalation of infected aerosols or dust, while its oral transmission remains controversial (Porter et al. 2011). Furthermore, ticks play a role in the maintenance of *C. burnetii* infection among wildlife and in the transmission of *C. burnetii* from wildlife to domestic ruminants (EFSA 2010). However, its role in transmission of Q fever to humans is rarely documented (Porter et al. 2011). The infection is mostly asymptomatic in ruminants. However, during clinical expression, it is mainly manifested by reproductive disorders including abortion, stillbirth, premature delivery, and delivery of weak offspring, particularly in small ruminants, as well as, infertility, metritis, and mastitis in cattle (Agerholm 2013; Porter et al. 2011). In humans, Q fever can be asymptomatic, as an acute form with fever, atypical pneumonia, and hepatitis, or it can progress to chronic form with long-term sequelae including fatigue, abortion, and heart disease (Vanderburg et al. 2014; Wielders et al. 2014).

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Several surveys have been performed in many countries to evaluate the prevalence of *C. burnetii* in cattle, which ranges from 0 to 100% for animal level and from 4.4 to 100% for herd level (Guatteo et al. 2011). Limited serological studies on bovine coxiellosis were carried out in different Algerian regions targeting a small number of cows and adopting different sampling strategies (Dechicha et al. 2010; Abdelhadi et al. 2015; Agag et al. 2017; Derdour et al. 2017). To date, no epidemiological survey has targeted the Setif region in Algeria. However, Lacheheb and Raoult (2009) showed a high seroprevalence among the human inhabitants of Setif (15.5%) with a significantly higher seroprevalence among inhabitants of rural areas (20%). Therefore, the main objectives of this study are to estimate the apparent seroprevalence of *C. burnetii* infection in cows at herd and animal levels and to identify risk factors associated with *C. burnetii* seropositivity in the Setif region of Algeria.

Material and methods

Study area

The present study was conducted from March 2016 to April 2018 in the Setif high plains in northeastern Algeria. The region covers about 6550 km^2, lies between eastern longitudes of 4° 73′–6° 02′ and northern latitudes of 35° 61′–36° 59′, and has an altitude that vary between 900 and 2000 m above sea level. The climate is semi-arid Mediterranean, characterized by cold rainy winters and hot dry summers. The temperatures often exceed 40 °C in summer and fall below 0 °C in winter, with frequent snowfall and frequent frost. The mean annual rainfall was of 350 mm from 1984 to 2014. The study area contains about 161,952 cattle, of which 79,354 are dairy cows, distributed across 4465 dairy herds (Agricultural Services direction of Setif 2015) (Fig. 1).

Study design and sampling

The study was designed as cross-sectional targeting a convenient sample of cows aged 24 months old and over selected by simple random sampling method from a cattle population that exists in the Setif area. Firstly, to estimate the number of sampled animals, we used the formula for simple random samples recommended by Thrusfield (2007):

$$N = \frac{(1.96)^2\ P(1-P)}{L^2}$$

where N was the sample size, 1.96 was the Z value for the selected confidence level (95%), P was the individual disease prevalence, and L is the desired absolute precision. A minimum sample size of 600 animals was obtained using 50% expected individual prevalence (since there was no previous study in this area), an absolute precision of 4%, and a confidence level of 95%. However, a total of 678 animals were included in this study to increase the precision.

Secondly, to determine the minimal number of cows to be selected within each dairy herd, we adopted the formula described by Thrusfield (2007):

$$n = \left[1-(1-p)^{1/d}\right] \times \left(N-{}^{d}/_{2}\right) + 1$$

where "n" is the sample size, "p" is the probability of detection of at least one seropositive cow, "N" is the herd size, and "d" is the number of seropositive cows in the herd. The probability of detection of at least one seropositive cow in a herd was determined at 95% ($P = 0.95$), and the number of seropositive cows in each herd "d" was calculated assuming within-herd prevalence of 25% (Carbonero et al. 2015;

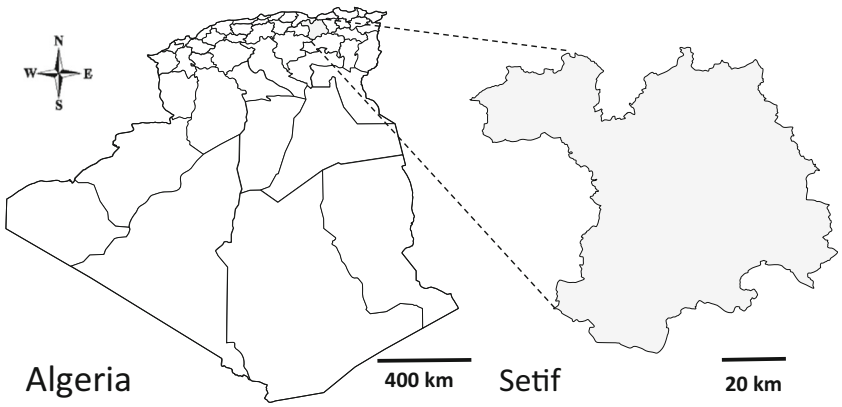

Fig. 1 Map of the region of Setif in the northeastern Algeria (gray area) where blood samples were collected from cows during the period between March 2016 and April 2018 to determine the seroprevalence of antibodies against *C. burnetii* and risk factors associated with seropositivity

Guatteo et al. 2011). For this purpose, a minimum sample size of 11 animals per herd was used. On farms with a herd size up to 11 animals, all animals were included. Finally, a total of 678 female cows from 90 herds were randomly selected. The herds and animals within herds were randomly selected using the RAND function of Microsoft Excel® 2013. In the case, where the owner of the selected herd refused to participate, we looked for the closest neighbor herd. The blood samples were collected from the coccygeal vein of each cow into plain vacutainer tubes using disposable needles, and immediately transported on ice to the laboratory. The sera were separated by centrifuging the tubes at 1000×*g* for 10 min and stored at − 20 °C until use.

Data collection

A structured questionnaire focusing on risk factors for *C. burnetii* infection was administered to farm owners on the day of sample collection. The questionnaire was divided into two parts:

1. The first part involved farm characteristics and herd management: management system (intensive or semi-intensive), herd size (≤ 11 cows or > 11 cows), breeding type (dairy or mixed), use of disinfectants (yes or no), contact with other herds (yes or no), source of water (well water or groundwater or tap water), presence of ticks (yes or no), presence of small ruminants (yes or no), presence of horses (yes or no), presence of dogs (yes or no), presence of cats (yes or no), type of reproduction (only natural or only artificial insemination or both types), use of calving pens (yes or no) and milking (mechanic or manual).
2. The second part involved individual characteristics and reproduction disorders collected from each cow such as breed (imported breeds; Prim'holstein, Montbeliarde, and Fleckvieh, or local breeds mainly brown of atlas, or crossed breeds between imported and local breeds), age in years (> 2 to ≤ 5 or > 5 to ≤ 8 or > 8), animal origin (homebred or purchased), history of abortion in previous year (yes or no), history of stillbirths in previous year (yes or no), and history of infertility in previous year (yes or no).

Laboratory analysis

Serological analysis

Determination of antibodies against phase I and phase II antigens of *C. burnetii* from each serum sample was screened by employing a commercial ELISA "ID Screen Q Fever Indirect Multi-species Kit" (IDvet, Grabels, France) following the protocol prescribed by the manufacturer. This test uses native antigens isolated from an aborted bovine placenta and purified from culture of phases I and II *C. burnetii*. The manufacturer's internal validation report indicates a specificity of 100% based on the negative serological results obtained by this assay on 167 bovine serum from free Breton herds (no abortion was recorded for 3 years, and no positive result was obtained, either by ELISA or fixation complement over the last 3 years), and a 100% sensitivity based on positive serological results on 52 sera of aborted cows and positive for *C. burnetii* by complement fixation or by PCR on placenta. The optical density percent (% OD) was calculated according to the formula:

$$\%\mathrm{OD} = 100 \times (\mathrm{OD}\ \textit{sample} - \mathrm{OD}\ \textit{negative control}) / (\mathrm{OD}\ \textit{positive control} - \mathrm{OD}\ \textit{negative control})$$

Samples with a % OD greater than 50% were considered positive; % OD between 40 and 50% were considered as doubtful, and those less than 40% were determined to be negative. Doubtful results were considered negative in this study.

Statistical analysis

The apparent prevalence (AP) of antibodies to *C. burnetii* at individual level was estimated from the ratio of seropositive cows to the total number of cows examined. Prevalence of positive herds was estimated from the ratio of positive herds to the total number of herds investigated; herds that contain at least one seropositive cow were considered positive, with the exact binomial CI of 95% (Thrusfield 2007). Analysis of risk factors potentially associated with *C. burnetii* seropositivity was evaluated in two steps. Firstly, we conducted a univariable analysis of each variable using a chi-square test and those variables that presented $P \leq 0.25$ were subjected to multivariable logistic regression analysis. The multivariable analysis was then performed using backward stepwise selection using a likelihood ratio test at each step with a significance level of 0.05 for entry and 0.1 for removal. All variable with a $P < 0.05$ was considered statistically significant. The fit of the model was assessed using the Hosmer and Lemeshow goodness-of-fit (Hosmer and Lemeshow 2000). Spearman's correlation test was used to check a correlation among the independent variables, and if higher collinearity (correlation coefficient > 0.9) was found between those variables, one of them was excluded from the multivariable analysis according to the biological plausibility (Dohoo et al. 1996). A variable is considered as a confounding factor if its removal changed the regression coefficient of the other variables by more than 25%. Finally, all pairwise interactions were tested for significance ($P \leq 0.05$). The statistical analysis was performed using SPSS v25.0 software (SPSS Inc., Chicago, IL, USA).

Results

Seroprevalence of *Coxiella burnetii*

Out of the 678 cows tested, 77 were found positive for *C. burnetii* phase I and phase II antigens antibodies with an individual seroprevalence of 11.36% (95%CI 8.97–13.75%). At the herd level, 41 of 90 selected cattle herds had at least one seropositive cow to *C. burnetii* infection, giving a herd seroprevelence of 45.56% (95%CI 35.27–55.84%). Regarding the within-herd prevalence, the prevalence of seropositive cows per herd ranged from 9.09 to 57.14% (mean 23.71%, Q1 11.11%; median 20%, Q3 30%).

Risk factor analysis

Regarding the risk factor analysis, the six factors herd size, contact with other herds, presence of small ruminants in farm, use of disinfectants, origin of cows, and history of infertility in previous year were all significant on the univariable analyses ($P < 0.25$) and were selected for multivariable logistic regression analysis (Table 1). When these independent variables were subjected to the multivariable analysis, contact with other herds (OR 1.95, 95 CI 1.12–3.42) and purchased animals (OR 2.05, 95 CI 1.14–3.68) were identified as risk factors for seropositivity to *C. burnetii*, while the use of disinfectants (OR 0.32, 95 CI 0.14–0.72) was identified as a protective factor (Table 2). The final model had a good fit (Hosmer and Lemeshow test: $\chi 2 = 5.006$; $P = 0.287$).

Discussion

Our work is the first study conducted with an appropriate sampling design to determine the individual and cattle herd prevalence, as well as, risk factors for the infection of *C. burnetii* in the state of Setif in the northeastern of Algeria. In this study, we chose the ELISA test instead of other serological tests to detect reactive antibodies to *C. burnetii* in serum samples for its higher sensitivity and for practical reasons because it is rapid, inexpensive, easy to perform in laboratories, and has higher throughout (OIE 2018). ELISA is a method of indirect diagnosis that highlights a past exposure to *C. burnetii* by the detection of their specific antibodies; therefore, a positive result does not confirm an active infection because this requires the use of direct diagnostic methods such as ELISA antigen or PCR (Muskens et al. 2011; Alvarez et al. 2012). The sensitivity and specificity of the commercial kit ELISA used are 100% (Seo et al. 2017; IDvet, internal validation report), which indicates an identical value of apparent and true seroprevalence. Since the vaccination against *C. burnetii* is not practiced in Algeria, the results of this serological study are a response to the natural infection.

The individual prevalence of 11.36% obtained in this study is similar to the 10.6% reported in Bejaïa state northern of the study area (Agag et al. 2017), but lower than a value of 23.91% reported in the region of Tiaret located in western Algeria (Abdelhadi et al. 2015), and 29% observed in one farm that suffered an abortion problem, located in the state of Blida in the center of the country (Dechicha et al. 2010). On the other hand, our seroprevalence was higher than that found in control case study between infectious causes of abortion seropositivity and cow abortion in Algiers, capital of Algeria, 1.66% (Derdour et al. 2017). This difference in prevalence between these regions might be partially attributed to the sampling strategies that are different.

Bovine coxiellosis has been reported in many countries with different prevalence rates (Guatteo et al. 2011). Compared with other serological investigations carried out in some African and Mediterranean countries, our individual seroprevalence seems to be lower than 14.5% in Nigeria (Tukur et al. 2014), 16.21% in Tunisia (Elandalousi et al. 2015), 16.3% in the East of Turkey (Ceylan et al. 2009), 14.4% in Italy (Capuano et al. 2001), 19.3% in Egypt (Klemmer et al. 2018), 29.92% in Sudan (Hussien et al. 2017), and 31.3% in Cameroon (Scolamacchia et al. 2010). Nevertheless, it was comparable with 10.5% in Kenya (Wardrop et al. 2016). Our study showed a higher seroprevalence than those observed 6.8% in another study in Nigeria (Adamu et al., 2018), 4% in Chad (Schelling et al. 2003), 3.6% in Senegal (Kamga-Waladjo et al. 2010), and 6.76% in Spain (Alvarez et al. 2012). This variation in prevalence rates between regions and countries may be linked to several factors such as local ecological factors and type of management which may influence the transmission of *C. burnetii* (Hussien et al. 2017).

This study concluded that 45.56% of herds had at least one seropositive animal. This result is higher than 22% in the state of Bejaïa (Agag et al. 2017), which demonstrates the widespread of *C. burnetii* among herds in the examined area. Several studies reported considerable variation in the seroprevalence of *C. burnetii* in herd cattle such as Spain (30%) (Alvarez et al. 2012), Nigeria (57.1%) (Tukur et al. 2014), Cameroon (68.1%) (Scolamacchia et al. 2010), and Italy (68%) (Capuano et al. 2001).

The within-herd prevalence obtained in the current work that ranged from 9.09 to 57.14% with mean of 23.71% (Q1 11.11%, median 20%, Q3 30%) is close to the mean values estimated from many studies in the whole world by Guatteo et al. (2011) (median 26.3%, Q1 21.8%, Q3 38.2%).

In the risk factor analysis, a positive association exists between seropositivity of *C. burnetii* and contact with other herds through the sharing of the same grazing fields and or the same source of water ($P < 0.01$). This can be explained on the one hand by the facts that contact with other herds increases the chance of meeting with infected cattle favoring

Table 1 Univariable analysis of risk factors associated with *C. burnetii* seropositivity among cows sampled in Setif in northeastern Algeria during the period from March 2016 to April 2018

Independent variables	Categories	No. of animal sampled	No. of positive animals	Prevalence %	*P* value
Management system	Intensive	159	20	12.57	0.579
	Semi-intensive	519	57	10.98	
Herd size	≤ 11 cows	436	43	9.86	0.102*
	> 11 cows	242	34	14.04	
Breeding type	Dairy	579	63	10.88	0.345
	Mixed	99	14	14.14	
Use of disinfectants	Yes	131	7	5.34	0.016*
	No	547	70	12.79	
Contact with other herds	Yes	280	47	16.78	< 0.001*
	No	398	30	7.53	
Presence of ticks	Yes	129	17	13.17	0.469
	No	549	60	10.92	
Source of water	Well water	395	39	9.87	0.307
	Groundwater	116	21	18.10	
	Tap water	167	17	10.17	
Presence of small ruminants	Yes	213	34	15.96	0.011*
	No	465	43	9.24	
Presence of horses	Yes	111	14	12.61	0.648
	No	567	63	11.11	
Presence of dogs	Yes	252	32	12.69	0.397
	No	426	45	10.56	
Presence of cats	Yes	175	21	12.00	0.756
	No	503	56	11.13	
Type of reproduction	Only natural service	387	43	11.11	0.385
	Only artificial insemination	202	27	13.36	
	Natural service And artificial insemination	89	7	7.86	
Use of calving pens	Yes	100	10	10.00	0.643
	No	578	67	11.59	
Milking	Manual	146	18	12.32	0.676
	Mechanic	532	59	11.09	
Breed	Imported	237	27	11.39	0.581
	Local	90	13	14.44	
	Crossed	351	37	10.54	
Age in years	> 2 to ≤ 5	310	31	10	0.573
	> 5 to ≤ 8	299	38	12.70	
	> 8	69	8	11.59	
Cow origin	Homebreed	538	48	8.92	< 0.001*
	Purchased	140	29	20.71	
History of abortion in previous year	Yes	43	7	16.27	0.293
	No	635	70	11.02	
History of stillbirths in previous year	Yes	16	3	18.75	0.346
	No	662	74	11.17	
History of infertility in previous year	Yes	74	13	17.56	0.074*
	No	604	64	10.59	

* $P \leq 0.25$ and offered to the multivariable logistic regression model

the direct transmission of *C. burnetii* between animals, and on the other hand, by the contamination of the grazing and watering environment. Especially this bacterium is characterized by a very high stability towards environmental conditions and can stay infectious for many months (Gürtler et al. 2014). The environment can be contaminated either by abortion and birth products, feces, urine, milk, and vaginal mucus from infected animals at the time of grazing or watering (Guatteo et al. 2006, 2007; Angelakis and Raoult 2010; EFSA 2010; Astobiza et al. 2011) or by dissemination of *C. burnetii* from

Table 2 Multivariable logistic regression analysis of risk factors associated with *C. burnetii* seropositivity among cows sampled in Setif in northeastern Algeria, during the period from March 2016 to April 2018

Variables	B[a]	ES[b]	OR[c]	CI[d] 95% (OR)	*P* value
Contact with other herds	0.670	0.285	1.95	1.12–3.42	0.019
Use of disinfectants	− 1.143	0.41	0.32	0.14–0.72	0.006
Cow purchased	0.719	0.298	2.05	1.14–3.68	0.016

Model chi-square 27.885 with df of 5

Model-2 log likelihood 479.907

Chi-square goodness to fit = 5.006, *p* value = 0.287

[a] Logistic regression coefficient

[b] Standard error

[c] Odds ratio

[d] Confidence interval

contaminated farms through soil, animal skin, and wastewater (Kersh et al. 2013; Villari et al. 2018), as well as by wind (Nusinovici et al. 2015).

In this study, the purchased cows were also identified as a risk factor for *C. burnetii* infection. The seroprevalence of purchased cows (20.71%) was significantly higher than for cows whose origin was the farm (8.92%) ($P < 0.05$). This is in agreement with the study of Obaidat and Kersh (2017), who reported a significant association between the addition of new cattle to the herd and *C. burnetii* antibody positivity in bulk milk tank (BTM) of Jordanian dairy cattle herds (Obaidat and Kersh 2017), and the study of van Engelen et al. (2014), who showed that the purchase of cattle from at least two addresses in 2009 in the Netherlands was significantly correlated with the presence of both *C. burnetii* antibodies and DNA in BTM of dairy cattle herds (van Engelen et al. 2014). Furthermore, it has been revealed that the lack of quarantine of newly purchased animals is a factor that increased the risk of *C. burnetii* seropositivity for dairy cows in Denmark (Paul et al. 2012). This emphasizes the importance of taking biosecurity measures like quarantine and screening of newly purchased animals to prevent the introduction of infected animals into the herds.

In fact, both risk factors identified in this study whether the contact between herds or the introduction of new cows in the herd support the spread of infection from one herd to the other, which explains the high herd seroprevalence obtained in this study (45.56%).

However, the use of disinfectants was identified as the factors that protect against bovine coxiellosis. A similar result was reported recently in domestic ruminants in Lebanon (Dabaja et al. 2019). In addition, it was revealed that the prevalence of *C. burnetii* antibodies in cattle decreases in farms where the cleaning and disinfection of equipment after use (Tukur et al. 2014), the cleaning of the bedding in the cubicles at least once per day (van Engelen et al. 2014), and the frequent cleaning of the feeders (Obaidat and Kersh 2017) were realized, hence, the interest of good hygiene practices in the reduction of exposure to *C. burnetii* in livestock. *C. burnetii* or more precisely its infectious form small cell variant (SCV) is known to be resistant to environmental factors and chemical disinfectants (Cantas et al. 2011; Pexara et al. 2018). However, it is completely inactivated following exposure to Quaternary ammonium or 70% ethanol during 30 min contact time (Plummer et al. 2018). It has been revealed also that exposure to 1% Peroxygen or 1:100 dilution of hypchlorite during 30 min contact time reduced more than 90% of infectivity (Plummer et al. 2018). The disinfectant can destroy a wide range of pathogens and minimize the risk of infection in cattle; therefore, it indirectly helps the immune system of animals to fight against pathogens resistant to disinfectants like *C. burnetii*, in particular, the destruction of pathogens with immunosuppressive effects such as bovine herpesvirus-1 (BHV-1) and bovine viral diarrhea virus (BVDV) that predispose cattle to secondary infections (Potgieter 1995; Srikumaran et al. 2007; Biswas et al. 2013; Molina et al. 2013; Lanyon et al. 2014).

In conclusion, the results from the current study indicate the presence and circulation of *C. burnetii* infection in cattle herd in Setif state of Northeastern Algeria. Consequently, some hygiene and biosecurity measures must be implemented mainly focusing on risk factors identified in this work, such as limiting contact between herds, quarantine of newly purchased animals, and the use of disinfectants that can reduce the spread of infection and possible transmission to humans. Finally, more epidemiological surveys in animals and human are needed to better understand and control of this disease in Algeria.

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Compliance with ethical standards

Ethical statement All animal owners declared their oral consent before the collection of the blood samples as well to the related survey questions. The cattle were sampled by a qualified veterinarian following all applicable guidelines for the care and use of animal.

Conflict of interest The authors declare that they have no conflict of interest.

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