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Changing livestock vaccination policy alters the epidemiology of human anthrax, Georgia, 2000–2013

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ABSTRACT

Anthrax is a widely spread zoonotic disease found on nearly every continent. To control the disease in humans and animals, annual livestock vaccination is recommended. However, in 2007, the country of Georgia ended its policy of compulsory annual livestock anthrax vaccination. Our objective was to assess how the epidemiology of human anthrax has evolved from 2000–2013 in Georgia, in the wake of this cessation. We used passive surveillance data on epidemiological surveys of human anthrax case patients. Risk factors and rates of self-reported sources of infection were compared, before and after the change in livestock vaccination policy. We mapped ethnicity-adjusted incidence during the two periods and assessed changes in the spatial pattern of risk. The overall risk of human anthrax increased >5-fold, from 0.7 cases per 100,000 in 2000 to 3.7 cases per 100,000 by 2013. Ethnic disparities in risk became pronounced; from 2000 to 2013, incidence increased >60-fold in Azerbaijanis from 0.35 to 21.1 cases/100,000 Azerbaijanis compared to 0.61 to 1.9 cases/100,000 among ethnic Georgians. Food-borne exposures from purchasing meat increased from 11% in 2000–2006 to 21% in 2007–2013. Spatial analyses revealed a shift from a random pattern of reporting pre-policy change to clustering among district municipalities following the change in policy. Our findings indicate there were unintended human health consequences associated with changing livestock vaccination policy. Following a reduction in the immunizations administered, there was a major shift in the epidemiology of human anthrax in Georgia. Current infection risk is now highest among ethnic minorities. Increased reporting among individuals uncharacteristically at risk for anthrax from foodborne exposures suggests spillover from modes of agricultural production. Given the importance of human-livestock health linkages, careful evaluations of policy need to be undertaken before changes to animal vaccination are made.

1. Introduction

Anthrax is a zoonotic disease that is found on nearly every continent (except Antarctica) [1,2]. The causative agent, *Bacillus anthracis*, is a soil-borne Gram-positive bacterium with the remarkable ability to survive in the environment for long periods of time, perhaps years, and infect a wide range of hosts [2,3]. Herbivorous animals are most often infected [2–4]. Human infections are typically a result of contact with infected animals or their byproducts (e.g. meat or hides) during activities such as livestock slaughtering [1,4].

Targeting livestock with annual vaccination is the most effective method to control anthrax in both humans and animals in endemic regions [1,5]. The most widely used vaccine is the live attenuated Sterne strain (34F2) [5]. In the former Soviet Union (FSU), livestock anthrax vaccination combined with improvements in occupational safety produced a nearly 10-fold reduction in animal cases with a concomitant decline in human incidence [6]. Similar decreases were observed in Europe and the United States following mass vaccination of livestock [7]. However, despite the effectiveness of vaccination, anthrax persists in areas with weakened health infrastructures and long-term vaccination strategies may be needed in endemic areas [1,8]. Countries of the FSU, sub-Saharan Africa, and southeast Asia have (re)emerged as foci for transmission [9].

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The country of Georgia has experienced repeated outbreaks of human anthrax with a recent increase in human incidence (2010–2012) [10]. Reports of an anthrax-like disease in humans dates to the 17th century [11] and >500 locations have been registered as foci (permanent locations of anthrax risk) in Georgia since 1881 [12]. During Soviet governance, anthrax was a mandatory reportable infectious disease in both humans and livestock. Following the dissolution of the Soviet Union in 1991, and Georgian independence in December of the same year, anthrax reporting remained mandatory. To combat the spread of anthrax, from 1995 through 2006, the government carried out annual compulsory livestock vaccination. In 2007, Georgia ended this policy, placing the responsibility of vaccination on private livestock owners [13].

Yet, little is known about how the alteration in livestock immunization policy and the concomitant decline in the number of anthrax vaccine doses administered affected the epidemiology of human anthrax. In the context of >90% private livestock ownership in Georgia, and the high risk associated with agricultural production, identifying changes in anthrax epidemiology are crucial for implementing control strategies and limiting its spread. Our objective was to assess how the change in livestock vaccination policy impacted the epidemiologic characteristics of human anthrax in Georgia from 2000–2013 by identifying changes in risk factors and rates of self-reported sources of infection.

2. Methods

We obtained passive surveillance data on epidemiological surveys of human anthrax case patients and the annual number of livestock vaccine doses administered from the National Centers for Disease Control and Public Health (NCDC) during 2000–2013. We estimated national incidence rates per 100,000, using population data from the Georgian national census (Georgian State Statistical Committee, GeoStat). To describe the trend in human anthrax incidence and identify trend breakpoints if present, we used segmented regression (JoinPoint 4.4.0.0, https://surveillance.cancer.gov/joinpoint/) [14]. Breakpoints in a trend are characterized by an inflection point in the line segment indicating an increasing or decreasing rate of change [14]. We defined the dependent variable as the annual crude incidence rate and independent variable was the year. To adjust for heteroscedastic errors, we used a weighted least squares approach with weights applied to each observation [14]. We allowed for between 0 and 2 breakpoints in the regression line. For each possible regression line segment provided by the best fit model, the rate of change is given by the average annual percent change (AAPC).

Risk ratios and incidences per 1 million were estimated for age, sex, ethnicity, region, self-reported source of exposure, season, and occupation. Season was defined as: winter (December January, and February); spring (March, April, and May); summer (June, July, and August); fall (September, October, and November). We derived a binary dummy variable for each region with ethnic enclaves defined as district municipalities with $\geq$30% of the population reporting as non-Georgian. Statistical analyses (Fig. S1) and accompanying 95% confidence intervals of estimates were performed in R v3.3.1 (R Core Development Team).

Human anthrax data were aggregated to district municipality, and we mapped crude average annual human incidence per 100,000 persons (total cases/population) for each district during 2000–2006 and 2007–2013. The ethnic composition (percent of non-Georgian population) of each district was derived from the Georgian census (http://www.geostat.ge/).

We used classifications of four main ethnic groups defined in the census data: Georgian, Azerbaijani, Armenian, and other (Russian, Ukrainian, Greek, and Yazidi). We calculated ethnicity adjusted incidence rates per municipality before and after the policy change using the indirect standardization method with an internal standard, a best practice in age- or ethnicity-adjusted spatial analyses [15,16].

To test for changes in the spatial dependence in human anthrax incidence among district municipalities between the two time periods, we used the global Moran's *I* statistic (OpenGeoDa 1.0.1, GeoDa Center, ASU, Arizona). This statistic is a measure of spatial autocorrelation or similarity among spatial units with values close to +1.0 indicating clustering and values close to -1.0 indicating dispersion [17]. To characterize the spatial relationship among district municipalities, we used a queen contiguity matrix with row standardization [18]. We tested the null hypothesis of no spatial association in incidence rates of human anthrax among district municipalities before and after the change in policy for both crude and ethnicity adjusted rates.

3. Results

3.1. Temporal trends

From 2000 to 2013, 736 human anthrax cases (annual range: 15–143) were reported in Georgia (Fig. 1). During this 14-year period, the trend in rates was characterized by a breakpoint in the regression line in the year 2010 (95% CI: 2008, 2011) indicating an increasing rate of reporting post-policy change with an AAPC = 10.2% (95% CI: 9.3, 10.9; p = .02) (Fig. 1). The annual human incidence per 100,000 increased from 0.6 cases (95% CI: 0.4, 0.8) in 2000 to 3.7 cases (95% CI: 3.1, 4.4) in 2013. Following the policy change in 2007, there was a precipitous decline in the average annual number of livestock anthrax vaccine doses administered: 2 million (95% CI: 1.2, 2.8) doses were administered during 2000–2006 compared to 201 thousand (95% CI: 32, 436) doses during 2007–2013 (Fig. 1).

Persons age 40–64 years had higher rates of human anthrax nearly every year except in 2010 when they were surpassed by rates in persons age 65 years and older (Fig. 2). Prior to 2007, annual incidence rates were not consistently higher among any ethnic group. In 2007, when the compulsory livestock vaccination program supported by the government ended, incidence rates increased among all ethnic groups (Georgians, Azerbaijanis, and Armenians). Rates began to diverge in 2010 with a rapid increase in the risk of human anthrax among ethnic Azerbaijanis; rates among ethnic Azerbaijanis ranged from 0 to 25.3 cases per 100,000 (Fig. 3).

3.2. Risk before and after policy change

When comparing time periods before and after the policy change, males were two times more likely to have reported human anthrax compared to females during 2000–2006; by 2007–2013 males were at least four times more likely to have reported compared to females (Table 1). Persons age 40–64 were at higher risk of infection compared to all other age groups during 2000–2006 and remained so following the policy change. From 2000–2006, Azerbaijanis accounted for 8% of cases, increasing to 30% during 2007–2013; the relative risk compared to Georgians increased from 1.3 to 6.1 (Table 1). Azerbaijanis and Armenian ethnicities comprised approximately 8% of the total Georgia population while accounting for 35% (187) of all anthrax cases during 2007–2013. Notably during 2012–13, these ethnicities accounted for 48% of all cases (Fig. 3). Regionally, ethnic enclaves were two and a half times more likely to report anthrax cases compared to other district municipalities prior to the policy change, increasing to six

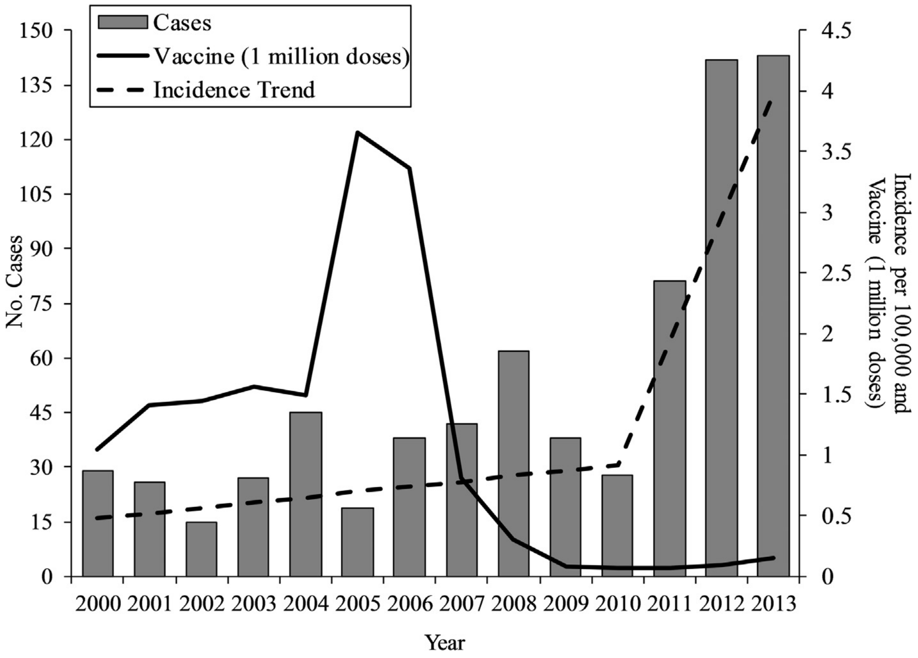

Fig. 1. Annual number human anthrax cases in Georgia, 2000–2013 (grey bars). Total annual number of livestock anthrax vaccine doses administered (1 million doses) in Georgia, 2000–2013 (solid black line). The modeled incidence per 100,000 trend in humans (black dotted line) displaying the breakpoint in the rate of change at 2010 (95% CI: 2008, 2011).

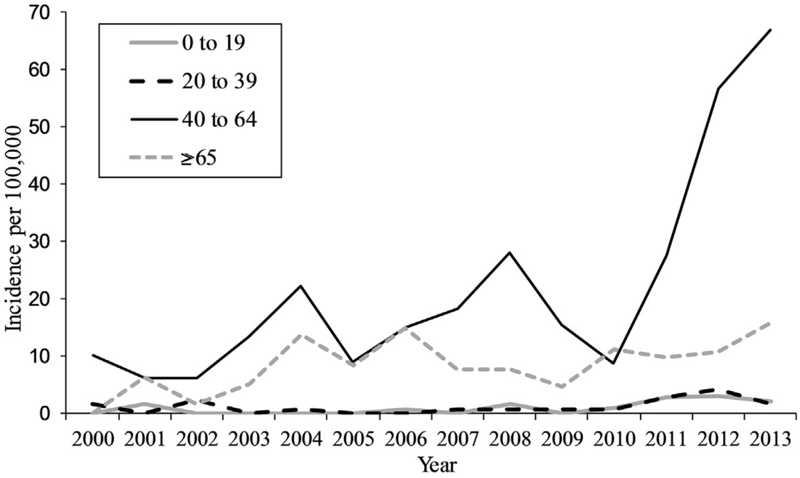

Fig. 2. Incidence per 100,000 of human anthrax by age group during 2000–2013 in Georgia.

times more likely after the change in vaccination policy. Seasonal patterns of reporting indicated that cases were essentially split between summer (38%) and fall (41%) during 2000–2006; by 2007–2013 summer seasonality became more pronounced and it was 1.5 times more likely for a case to be reported during the summer than the fall.

The self-reported source of infection was disclosed for 709 (709/736, 96%) cases during 2000–2013; most cases reported slaughtering/butchering livestock before (108;61%) and after (300;56%) the policy change, 2000–2006 and 2007–2013 respectively (Table 2). Of the cases that reported slaughtering/butchering, 46 (23%) confirmed the animal was sick or dead during 2000–2006 compared to 49 (9%) during 2007–2013. Prior to the policy change, purchasing meat was reported as source of infection in 21 (11%) cases compared to 114 (21%) cases after the policy change; this increase reflects an increase in persons buying meat rather than handling the sick animal carcass directly.

Occupation was available for 415 (56%) cases (Table 2). Working with animals or handling animal by-products during 2000–2006 was documented in 8 (4%) cases during 2000–2006 compared to 149 (28%) cases during 2007–2013. After the policy change in 2007, there was an increase in the number of housewives that reported anthrax: from 8 (4%) cases to 61 (11%). (Table 2).

3.3. Geographic patterns of anthrax cases

The spatial distribution of ethnicity-adjusted and crude rates changed with the vaccination policy (Fig. 4). Ethnic composition of the district population ranged from 0.2 to 90.4%. There was no discernable pattern in the distribution of rates during 2000–2006 indicated by the absence of clustering for both the crude (Moran's $I = -0.03$, z-score = −0.23, p = .80) and adjusted (Moran's $I = 0.06$, z-score = −0.94, p = .40) rates (Fig. 4A and C). Following the change in policy, areas of high rates appeared to coincide with ethnic

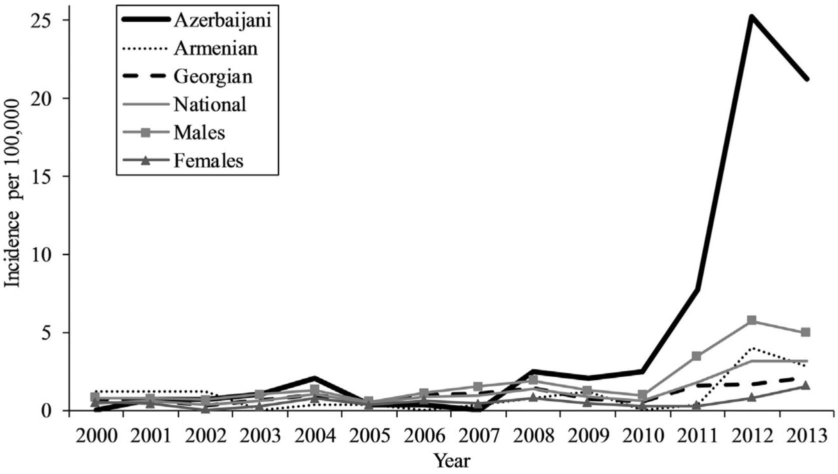

Fig. 3. Incidence of human anthrax cases/100,000 by ethnicity, and by gender in Georgia during 2000–2013.

Table 1
Demographic characteristics of human anthrax cases and relative risk estimates before (2000–2006) and after (2007–2013) a change in vaccine policy.

Demographic characteristics	2000–2006 (n = 200)			2007–2013 (n = 536)		
	No. cases (% of cases)	Average annual incidence per 1,000,000 (95% CI)[†]	Relative risk (95% CI)[†]	No. cases (% of cases)	Average annual incidence per 1,000,000 (95% CI)[†]	Relative risk (95% CI)[†]
Overall	200 (100)	6.5 (5.7, 7.5)	–	536 (100)	17.7 (16.3, 19.3)	–
Gender						
Female	70 (35)	4.3 (3.4, 5.5)	Reference	113 (21)	7.1 (5.9, 8.6)	Reference
Male	130 (65)	9 (7.5, 10.7)	2.1 (1.6, 2.8)	423 (79)	27.5 (25, 30.2)	3.9 (3.1, 4.8)[*]
Age (years)						
1–19	9 (5)	1.1 (0.5, 2)	0.1 (0.04, 0.2)	26 (5)	3.5 (2.3, 5.1)	0.1 (0.1, 0.2)
20–39	53 (26)	6 (4.5, 7.9)	0.5 (0.4, 0.7)	177 (33)	20 (17.1, 23.1)	0.6 (0.5, 0.8)
40–64	108 (54)	11.8 (9.7, 14.3)	Reference	292 (54)	31.3 (27.8, 35.1)	Reference
≥65	30 (15)	0.6 (0.4, 0.9)	0.6 (0.4, 0.9)	41 (8)	9.6 (6.9, 13)	0.5 (0.3, 0.7)[*]
Ethnicity						
Georgian	153 (76)	6 (5.1, 7)	Reference	338 (63)	13.3 (12.2, 15.1)	Reference
Azerbaijani	15 (8)	7.7 (4.3, 12.6)	1.3 (0.7, 2.2)	163 (30)	83.3 (71, 97.1)	6.1 (5.1, 7.4)[*]
Armenian	14 (7)	8 (4.4, 13.7)	1.4 (0.8, 2.3)	24 (4)	15.8 (10, 23.6)	1.2 (0.8, 1.8)
Other	4 (2)	3.3 (0.4, 12)	0.6 (0.1, 1.9)	9 (2)	16.2 (7.4, 3)	1.2 (0.6, 2.3)
Unknown	14 (7)	–	–	2 (0.4)	–	–
Region						
Ethnic enclaves[¥]	61 (31)	14.3 (10.9, 18.4)	2.4 (1.8, 3.3)	281 (52)	65.8 (58.3, 74)	6.1 (5.1, 7.2)[*]
Other	139 (70)	5.9 (5, 7)	Reference	255 (48)	10.9 (9.6, 12.3)	Reference
Season						
Winter	10 (5)	0.3 (0.2, 0.6)	0.1 (0.1, 0.2)	32 (6)	1.1 (0.7, 1.5)	0.2 (0.1, 0.3)
Spring	32 (16)	1.0 (0.7, 1.5)	0.4 (0.3, 0.6)	79 (15)	2.7 (2.1, 3.3)	0.5 (0.4, 0.6)
Summer	75 (38)	2.5 (1.9, 3.1)	0.9 (0.7, 1.2)	258 (48)	8.7 (7.7, 9.9)	1.5 (1.3, 1.9)[*]
Fall	83 (41)	2.7 (2.2, 3.4)	Reference	167 (31)	5.6 (4.8, 6.6)	Reference

[†] 95% Confidence Intervals (CI).
[*] Significant difference between relative risk in 2000–2006 and 2007–2013, based on the lack of overlap between the 95% CI.
[¥] Ethnic enclaves represent municipalities with ≥30% of the population comprised of ethnic groups.

enclaves; high rates were observed in the west along the Black Sea and in the southeast near the border with Azerbaijan and Armenia. The spatial distribution of cases shifted from being randomly distributed during 2000–2006 to spatially clustered during 2007–2013 for both the crude (Moran's $I = 0.3$, z-score = 4.0, $p < .001$) and adjusted (Moran's $I = 0.19$, z-score = 2.5, $p = .01$) rates (Fig. 4B and D). The significance of the Moran's I test in both the adjusted and crude rates indicates that the presence of clustering was not due to the underlying spatial distribution of the ethnic population.

4. Discussion

During Soviet governance (1950–1980), the incidence of human anthrax declined, in part, due to widespread livestock vaccination mirrored by reductions worldwide [5–8,9,19]. However, in endemic areas, long-term livestock vaccination may not be tenable due to costs and there is a paucity of evidence regarding the impact of cessation policies [9]. Our findings show that following changes to livestock vaccination policy in Georgia, which reduced immunizations administered, there was a major shift in the epidemiology of human anthrax. Ethnic minorities (Azerbaijanis) now appear at highest risk for anthrax, as this demographic is more often employed in high-risk occupations such as shepherding, with ethnic enclaves situated in intensive agricultural production zones [20]. Interestingly, the epidemiology of brucellosis in Georgia has also shifted to a disease primarily of Azerbaijani ethnicity, supporting the hypothesis of increased ethnically-biased occupational exposures [20]. Concomitantly, a rise in foodborne exposures and infections amongst groups uncharacteristically at risk for anthrax is consistent with spillover transmission from agricultural modes

Table 2
Reported risk factors for human anthrax before (2000–2006) and after (2007–2013) a change in vaccine policy in Georgia.

Anthrax risk factors	2000–2006 (n = 200)		2007–2013 (n = 536)	
	No. cases	% of cases (95% CI)[†]	No. cases	% of cases (95% CI)[†]
Self-reported source of infection				
Slaughter or butcher livestock	108	54 (47, 61)	313	58 (54, 63)
Yes/animal was sick or dead[‡]	46	23 (17, 29)	49	9 (7, 12)[*]
Process, cook, or handle meat	51	26 (19, 32)	160	30 (26, 34)
Yes/animal was sick or dead[‡]	5	2 (0, 3)	4	1 (0.01, 2)
Yes/purchased meat[¥]	21	11 (6, 15)	114	21 (18, 25)[*]
Soil	30	15 (10, 20)	47	9 (6, 11)
Unknown	11	6 (2, 9)	16	3 (2, 4)
Occupational risks				
Handle animals/animal by-products	8	4 (1, 7)	149	28 (24, 32)[*]
Housewife	8	4 (1, 7)	61	11 (9, 14)[*]
Student/teacher	2	1 (0, 2)	14	3 (1, 4)
Unemployed	12	6 (3, 9)	76	14 (11, 17)[*]
Other	13	7 (3, 10)	74	14 (11, 17)[*]
Unknown	157	79 (73, 84)	162	30 (26, 34)[*]

[†] 95% Confidence Intervals (CI).

[*] Significant difference between relative risk in 2000–2006 and 2007–2013, based on the lack of overlap between the 95% CI.

[‡] Number of case patients that answered yes to butchering/slaughtering livestock or processing/cooking/handling meat and that the animal was also sick or dead.

[¥] Number of case patients that processing/cooking/handling meat and answered to purchasing the meat.

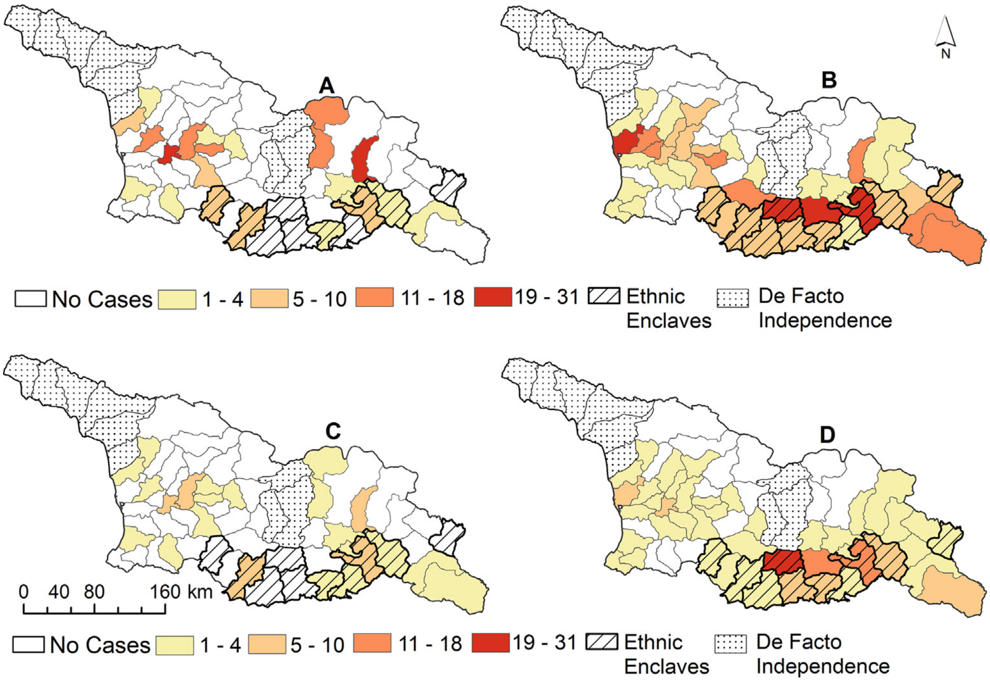

Fig. 4. Spatial distribution on crude human anthrax incidence rates in Georgia during (A) 2000–2006 (B) 2007–2013 and ethnicity-adjusted incidence rates during (C) 2000–2006 and (D) 2007–2013. Ethnic enclaves represent districts where ≥30% of the population is non-Georgian. De facto independent regions are autonomous self-governing entities not officially recognized as being independent.

of production [21]. The change in policy, from compulsory anthrax livestock immunizations to voluntary participation, has had unintended consequences, facilitating the increasing incidence of anthrax.

In general, vaccination of all susceptible animals is recommended for three years or greater in response to anthrax outbreaks [22]. Prior to the policy change, vaccine coverage among livestock in Georgia was relatively high (70–90%) (Fig. 1) (http://www.geostat.ge/). However, evidence for ending livestock anthrax vaccination in endemic areas is mixed. In an area of the Middle East a 10-year livestock anthrax vaccination campaign was carried out and after cessation of the program no new cases were reported [23]. Conversely, the cessation of livestock vaccination in Azerbaijan was associated with a dramatic rise in the incidence of both human and livestock anthrax [24]. Whereas, livestock vaccination in Ukraine has been continuous for decades, even in light of recent declines [25]. Given the variation in vaccination results, regionally and worldwide, dictating policy remains a challenge that should be based on local surveillance [9,22]. Recent evidence in Georgia indicated low-levels of anthrax vaccination (<50%) among private livestock owners during a 2012 outbreak [13]. Additionally, Azerbaijanis living in Georgia are also less likely to vaccinate livestock due to a belief that anthrax livestock vaccination permanently disrupts milk output (pers. comm. Zviadi Asanishvili; National Food Agency, Tbilisi, Georgia), suggesting suboptimal levels of voluntary vaccine adoption among high-risk groups. This underscores the challenges of trying to reinstitute vaccination campaigns in the wake of the policy cessation.

Consistent with previous studies, we found that the majority of anthrax cases were associated with agriculture [1,26–28].

However, we also found an increased proportion of cases that reported foodborne transmission following the change in policy. Historically, >85% of human anthrax cases occurred in the rural population, with the vast majority (>90%) of those involving occupations that handled animals on government collective farms [19]. In contrast, our findings suggest that the spread of infection has been, in part, facilitated by the illegal slaughter and sale of infected meat, as documented in previous epidemiological trace-back investigations [13,21]. These findings are in keeping with a hypothesis of spillover from rural and peri-urban areas into urban markets used to recoup economic losses from livestock mortality [21].

Interestingly, by 2007–2013, the risk of anthrax had increased among males, and those aged 40–64 years old. While gender differences in anthrax risk are not typically observed [1,26,28], our findings suggest the high risk among males is related to occupational risks [29]. The high risk among the 40–64 age group is consistent with a cohort effect, as these individuals would have been the typical age of livestock tenders (15–40 years of age) twenty-five years ago during the extensive agricultural production of the Soviet Union, and it is plausible that they have maintained this agrarian lifestyle.

Clustering of anthrax risk among districts replaced the random pattern of reporting observed during the early part of the last decade. Risk increased among ethnic enclaves during 2007–2013 to >6 times that of all other district municipalities, with evidence of spatial clustering not uniquely driven by the underlying distribution of the ethnic population. Previous studies also documented high rates of zoonotic disease among ethnic enclaves in the United States [30] and Germany [31]. Following decollectivization in the 1990s, livestock ownership was privatized across the FSU. Subsequently, in Georgia, agriculture was grouped into two categories: subsistence farming and private enterprises (http://www.geostat.ge/). One plausible explanation for this clustering is that enterprise agriculture (higher livestock density) is more common among ethnic enclaves in the southeast, compared to the west where subsistence agriculture predominated and the ethnic composition is low (≤10%) (Fig. S1). These changes, in conjunction with the alteration to livestock immunization, have exacerbated the risk associated with areas of agricultural production. Furthermore, these may also overlap with ecological zones, such as alkaline soils, which can support *B. anthracis* [3–10].

The data we used in this study were obtained through passive surveillance and are subject to systematic error; changes in surveillance techniques may have affected reporting from earlier to later years. Our epidemiological questionnaire-based surveys relied on the ability of case patients to accurately recall information and may be prone to recall bias. In addition, a large proportion of occupational responses from the epidemiological questionnaires were missing, limiting our inference regarding differences in this category. There may be also an unwillingness to admit to illegally slaughtering sick livestock, and thus the underreporting of livestock anthrax cases has likely skewed the true sources for the occurrence of the disease. Conversely, areas with better access to healthcare facilities may be overrepresented in our sample. Future studies should focus on collecting better livestock case data and vaccination records for use in cost-effectiveness analyses.

5. Conclusion

The change in livestock vaccination policy has dramatically affected the epidemiology of human anthrax in Georgia. In addition to the increasing rates of transmission, the epidemiology of the disease has shifted such that ethnic enclaves, and in particular, Azerbaijanis, are now at highest risk. Furthermore, the likely spillover of contaminated meat and animal by-products from agriculture into markets has increased the frequency of infections among occupations uncharacteristically at risk for anthrax. Thus, consumers should be warned to only purchase meat from licensed vendors. Indemnity programs that provide compensation for vaccine and livestock losses should be considered as an approach for interrupting transmission and enhancing reporting. The change in policy highlights the need for weighing the costs and benefits of ending policies that can have substantial human health impacts. Public health programs that focus on 'One Health' preventative measures would be beneficial, as they can integrate awareness of disease among high-risk populations such as agricultural workers of Azerbaijani ethnicity. Integrated human and veterinary health regulations and livestock vaccination campaigns are needed to address the evolving epidemiology of anthrax.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2017.09.081.

References

[1] Turnbull P, Böhm R, Hugh-Jones M, Melling J. Guidelines for the surveillance and control of anthrax in humans and animals, 4th ed.; 2008. p. 219.

[2] Hugh-Jones M, De Vos V. Anthrax and wildlife. Rev Sci Tech Int Off Epizoot 2002;21:359.

[3] Hugh-Jones M, Blackburn J. The ecology of *Bacillus anthracis*. Mol Aspects Med 2009;30:356–67.

[4] Beyer W, Turnbull P. Anthrax in animals. Mol Aspects Med 2009;30:481–9.

[5] Turnbull PC. Anthrax vaccines: past, present and future. Vaccine 1991;9:533–9.

[6] Shlyakhov EN, Rubinstein E. Human live anthrax vaccine in the former USSR. Vaccine 1994;12:727–30.

[7] Velimirovic B. Anthrax in Europe [Bacillus anthracis]. Rev Sci IOIE n.d.;3:527–59.

[8] Fasanella A, Galante D, Garofolo G, Jones MH. Anthrax undervalued zoonosis. Vet Microbiol 2010;140:318–31.

[9] Hugh-Jones M. 1996–97 global anthrax report. J Appl Microbiol 1999;87:189–91.

[10] Kracalik I, Malania L, Tsertsvadze N, Manvelyan J, Bakanidze L, Imnadze P, et al. Human cutaneous anthrax, Georgia 2010–2012. Emerg Infect Dis 2014;20:261–4. https://doi.org/10.3201/eid2002.130522.

[11] Imnadze P, Bakanidze L, Manrikyan M, Kukhalashvili T, Zangaladze E, Kekelidze M, et al. Anthrax in southern Caucasus. Antibiot Monit 2002;18:17–8.

[12] Kukhalashvili T. Anthrax foci in Georgia; n.d.

[13] Navdarashvili A, Doker TJ, Geleishvili M, Haberling DL, Kharod GA, Rush TH, et al. Human anthrax outbreak associated with livestock exposure: Georgia, 2012. Epidemiol Infect 2016;144:76–87. https://doi.org/10.1017/S0950268815001442.

[14] Kim H, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335–51.

[15] Pickle LW, White AA. Effects of the choice of age-adjustment method on maps of death rates. Stat Med 1995;14:615–27.

[16] Waller LA, Gotway CA. Applied spatial statistics for public health data. vol. 368. Wiley-Interscience; 2004.

[17] Moran PA. Notes on continuous stochastic phenomena. Biometrika 1950:17–23.

[18] Anselin L, Syabri I, Kho Y. GeoDa: an introduction to spatial data analysis. Geogr Anal 2006;38:5–22.

[19] Makarov N. Incidence and prevention of anthrax in the cis-Caucasian and trans-Caucasian Republics. J Microbiol Epidemiol Immunobiol 1962;9:105–11.

[20] Akhvlediani T, Clark DV, Chubabria G, Zenaishvili O, Hepburn MJ. The changing pattern of human brucellosis: clinical manifestations, epidemiology, and treatment outcomes over three decades in Georgia. BMC Infect Dis 2010;10:346.

[21] Kracalik I, Malania L, Imnadze P, Blackburn JK. Human anthrax transmission at the urban-rural interface, Georgia. Am J Trop Med Hyg 2015;93:1156–9.

[22] Turnbull PCB, Nations F and AO of the U, International Office of E, World Health O. Anthrax in humans and animals, 4th ed. Geneva, Switzerland: World Health Organization; 2008.

[23] Elad D. An unholy disease in the Holy Land: the history of anthrax between the Jordan River and the Mediterranean Sea (1909–2012). Vet J 2013.

[24] Kracalik I, Abdullayev R, Asadov K, Ismayilova R, Baghirova M, Ustun N, et al. Changing patterns of human anthrax in Azerbaijan during the post-Soviet and

preemptive livestock vaccination eras. PLoS Negl Trop Dis 2014;8:e2985. https://doi.org/10.1371/journal.pntd.0002985.

[25] Bezymennyi M, Bagamian KH, Barro A, Skrypnyk A, Skrypnyk V, Blackburn JK. Spatio-temporal patterns of livestock anthrax in Ukraine during the past century (1913–2012). Appl Geogr 2014;54:129–38.

[26] Woods CW, Ospanov K, Myrzabekov A, Favorov M, Plikaytis B, Ashford DA. Risk factors for human anthrax among contacts of anthrax-infected livestock in Kazakhstan. Am J Trop Med Hyg 2004;71:48.

[27] Thapa NK, Tenzin Wangdi K, Dorji T, Migma Dorjee J, et al. Investigation and control of anthrax outbreak at the human-animal interface, Bhutan, 2010. Emerg Infect Dis 2014;20:1524–6. https://doi.org/10.3201/eid2009.140181.

[28] Doganay M, Metan G. Human anthrax in Turkey from 1990 to 2007. Vector-Borne Zoonotic Dis 2009;9:131–40.

[29] Gurbanov S, Akhmedova S. Especially dangerous infections in Azerbaijan. In: Emerg. endem. pathog. Springer; 2010. p. 39–43.

[30] Fosgate GT, Carpenter TE, Chomel BB, Case JT, DeBess EE, Reilly KF. Time-space clustering of human brucellosis, California, 1973–1992. Emerg Infect Dis 2002;8:672–8. https://doi.org/10.3201/eid0807.010351.

[31] Al Dahouk S, Neubauer H, Hensel A, Schöneberg I, Nöckler K, Alpers K, et al. Changing epidemiology of human brucellosis, Germany, 1962–2005. Emerg Infect Dis 2007;13:1895–900. https://doi.org/10.3201/eid1312.070527.