Assessing spatial heterogeneity of MDR-TB in a high burden country – Appendix

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Appendix methods

Model construction of individual level models

We used logistic regression models to identify factors associated with multidrug-resistant tuberculosis (MDR-TB) at initial diagnosis. Several potentially explanatory variables were included in the full model and then removed used a backwards elimination method as follows. Variables were removed from the multivariable model sequentially by size of p-value for association with MDR-TB (beginning with the largest). As each variable was removed, the estimated parameters in the new model were compared with those in the model before removal. If removal of the variable altered any of the estimated parameters by at least 10%, then we retained that variable in the model to ensure appropriate adjustment. If the removed variable contained missing data, when comparing the parameter estimates for confounding, we ran the two models based on identical datasets (i.e. both excluding the missing data). The final models included all variables that were statistically significantly associated with odds of MDR-TB ($p<0.05$ by likelihood ratio test) and other variables that helped to adjust for probable confounding.

Construction of maps of spatially smoothed MDR-TB burden

We used inverse distance weighting (IDW) to smooth the risk and incidence of MDR-TB spatially. This method divides the country into cells of a pre-specified area and interpolates the value of interest, u (for example MDR-TB notified incidence) in each cell, x, based on samples $u_i=u_i(x)$ for i=0,1,….,N as follows:

$$u(x) = \sum_{i=0}^{N} \left(\frac{w_i(x) u_i}{\sum_{j=0}^{N} w_j(x)} \right) \qquad \text{where} \quad w_i(x) = \frac{1}{d(x, x_i)^p}$$ with x denoting the interpolated

point, x_i denoting an interpolating point, d being the distance between x and x_i, N being the

number of points used in each interpolation and p being a positive real number (the power parameter).

As described in the main text, our data cover all notified TB cases in Moldova and drug susceptibility testing is carried out for more than 95% of all culture positive cases. Therefore, it was not necessary to interpolate any "missing" values in any localities since data were considered to be virtually complete. As such, our aim here was to create a visualization of the MDR-TB burden and so to keep our estimates in each locality as close to that observed as possible, we set N=4 (i.e. a small value) and p=2 (to minimize the impact of more distant points).

Identifying statistically significant spatial clusters of disease

We used Anselin's Local Moran's I statistic[1] to identify areas of statistically clustering of MDR-TB and localities which were outliers, i.e. with high proportions of TB case with MDR-TB compared to localities around them. The statistic I_i is calculated for each locality, i as follows:

$I_i = \frac{Z_i}{m_2}\sum_j W_{ij} Z_j$ where $m_2 = \frac{\sum_i Z_i^2}{N}$, Zi is the deviation of the variable of interest from the mean, N is the number of localities and W_{ij} is a matrix of weights with ones in the positions i,j if locality i is a neighbour of locality j and 0 otherwise.

Locality-level regression analysis

We used logistic regression to model the number of notified MDR-TB as a proportion of the total number of TB cases with sufficient DST to diagnose MDR-TB by locality for new and previously treated cases separately. The unit of observation here was a locality. Our aim was to examine if a local concentration of TB cases with characteristics identified as individual-level risk factors in the individual-level regression analyses above (Table 2, main text) was sufficient to explain the

marked spatial heterogeneity observed in the proportion of TB cases with MDR-TB. For each individual risk factor identified above, we created an explanatory variable for the proportion of all TB cases in the locality which had that risk factor. For age, we calculated the proportion of TB cases that were less than 40 years old. Before inclusion in the model, all explanatory variables were log-transformed (natural logarithm). Since the value of the explanatory variables could be zero for which a natural logarithm does not exist, we added 0.5 to each count before creating a proportion and log-transforming to minimize bias in the resulting covariates[2] (i.e. for the proportion with characteristic x of N TB cases we entered the value $\ln[(x+0.5)/N]$ into the model).

Table 1 Potential risk factors for multidrug-resistant tuberculosis (MDR-TB) at the individual level and percentage of cases for which data were missing. Variables were only considered if less than 10% of data were missing

Variable	Possible forms[c]	Percentage of new cases for which data were missing	Percentage of previously treated cases for which data were missing
Age	a) linear, b) categorical (10 year groups)	0.0	0.0
Living in urban/rural area	Binary (urban or rural)	0.0	0.0
Homeless	Binary (yes or no)	3.2	3.5
Gender	Binary (male or female)	0.0	0.0
Citizenship	Binary (Moldovan or other)	0.0	0.0
Occupation[a]	a) categorical (employed, disabled, retired, student, unemployed), b) disabled or other, c) unemployed or other	0.3	1.3
Salaried[a]	Binary (yes or no)	0.9	1.8
Education[a]	a) categorical (primary, secondary, specialized secondary, higher, no education), b) binary (education or no education)	0.6	1.6
Living conditions[b]	Binary (satisfactory or unsatisfactory)	11.1	9.3
Was outside Moldova for >3 months in last 12 months	Binary (yes or no)	1.2	1.7
Previously in detention	Binary (yes or no)	1.9	2.6
In detention at time of diagnosis	Binary (yes or no)	0.0	0.0
Household size	a) linear, b) categorical, c) binary (lives alone or not alone)	0.0	0.0
Number of children in the household	a) linear, b) categorical, c) binary (some or none)	0.0	0.0
Known TB contact in the household	Binary (yes or no)	0.0	0.0
Smear status	Categorical (positive, negative,	0.0	0.0

	tested but no result, not tested)		
HIV status	a) categorical (positive, negative, tested but unknown result, not tested), b) binary (positive or other)	1.7	3.0
Presence of alcoholism	Binary (yes or no)	36.8	43.1
Presence of drug abuse	Binary (yes or no)	40.7	50.7
Presence of mental illness	Binary (yes or no)	40.5	50.7
Presence of neoplasia	Binary (yes or no)	37.2	46.8
Taking steroids	Binary (yes or no)	46.4	55.6
Any other comorbidity	Binary (yes or no)	46.6	55.6
Has diabetes	Binary (yes or no)	28.3	27.7

[a]The majority of "missing" are not applicable (e.g. children); [b]Missing includes both those in the category "unknown living conditions" and those with no result in this field; [c]Where variables could be entered into the model in more than one way, univariable models of each form were compared using maximum likelihood to choose the most appropriate form.

Table 2 Number of tuberculosis (TB) cases and usage of diagnostic tools by case type, 2007-2010. DST=drug susceptibility testing sufficient to diagnose multidrug-resistant TB. Any notable annual trends from the entire dataset are indicated in the footnotes and shown in full in Appendix Tables 3-9. Results for the entire country and the subset of those diagnosed within the penitentiary system (sub-divided into Transnistria and the rest of Moldova) are shown. Ten cases which initiated treatment abroad and were diagnosed in the penitentiary system are included in the total but not shown separately.

Indicator	Entire dataset				Penitentiary system					
	New	Previously treated	Initiated treatment abroad	Total	Rest of Moldova			Transnistria		
					New	Previously treated	Total*	New	Previously treated	Total
Number of TB cases										
Notified TB cases[a]	15574	7469	109	23152	619	747	1376	164	149	313
Pulmonary TB cases	13697	7241	102	21040	587	739	1336	146	147	293
Diagnostics										
Number of pulmonary TB cases that received microscopy (% of all pulmonary TB cases)	13307 (97.2)	7122 (98.4)	101 (99.0)	20530 (97.6)	587 (100.0)	739 (100.0)	1336 (100.0)	146 (100.0)	147 (100.0)	293 (100.0)
Number of pulmonary TB cases with positive smear (% of those receiving microscopy)[b]	5713 (42.9)	4445 (62.4)	43 (42.6)	10201 (49.7)	176 (30.0)	481 (65.1)	660 (49.4)	88 (60.3)	126 (85.7)	214 (73.0)
Number of pulmonary TB cases that received culture (% of all pulmonary TB cases)[c]	12523 (91.4)	6728 (92.9)	95 (93.1)	19346 (91.9)	566 (96.4)	714 (96.6)	1288 (96.4)	80 (54.8)	92 (62.6)	172 (58.7)
Number of pulmonary TB cases with positive culture (% of those cultured)	5741 (45.8)	3734 (55.5)	36 (37.9)	9511 (49.2)	220 (38.9)	397 (55.6)	619 (48.1)	13 (16.3)	26 (28.3)	39 (22.7)
Number of cases receiving DST, including non-pulmonary (% of all cases with positive culture)[d]	5442 (94.8)	3488 (93.4)	36 (100.0)	8966 (94.3)	225 (99.1)	379 (95.2)	606 (96.7)	9 (69.2)	22 (84.6)	31 (79.5)
Number of pulmonary TB cases with both negative smear and culture (of all pulmonary TB cases)	2957 (21.6)	1007 (13.9)	19 (18.6)	3983 (18.9)	210 (35.8)	110 (14.9)	322 (24.1)	6 (4.1)	4 (2.7)	10 (3.4)

[a]The number of notified TB cases fell year-on-year as did TB incidence per capita; [b] The percentage of cases with positive smear decreased over the study period and was 44.5% in 2010; [c]The percentage of pulmonary TB cases that received culture rose each year; the overall figure for 2010 was 97.7%; [d] The percentage of culture positive TB cases receiving DST increased 2007-9 and remained constant between 2009 and 2010; the overall figure for 2010 was 95.6%; *Includes 10 cases that initiated treatment abroad

Table 3 Number of tuberculosis (TB) cases by case type (new/previously treated and previously treated type) diagnosed between January 2007 and December 2010.

Case type	Previously treated type	Number of TB cases				Number of pulmonary TB cases			
		2007	2008	2009	2010	2007	2008	2009	2010
New		4135	3926	3782	3731	3627	3444	3311	3315
Previously treated	Smear microscopy negative relapse	524	462	474	467	521	462	473	467
	Smear microscopy positive relapse	590	482	420	382	586	481	418	381
	Chronic	152	93	82	64	151	91	74	57
	Default	457	451	407	467	450	444	401	465
	Extrapulmonary relapse	38	41	42	30	2	1	0	1
	Failure	416	342	320	266	411	337	311	256
Total previously treated		2177	1871	1745	1676	2121	1816	1677	1627
Initiated treatment abroad		21	22	42	24	17	21	40	24
Total		6333	5819	5569	5431	5765	5281	5028	4966

Table 4 Number of pulmonary tuberculosis (TB) cases sent for microscopy and with positive smear by case type (new/previously treated and previously treated type) diagnosed between January 2007 and December 2010.

Case type	Previously treated type	Number of pulmonary TB cases sent for microscopy (% of all pulmonary TB cases)				Number of pulmonary TB cases with positive smear (% of cases sent for microscopy)			
		2007	2008	2009	2010	2007	2008	2009	2010
New		3506 (96.7)	3344 (97.1)	3223 (97.3)	3234 (97.6)	1607 (45.8)	1527 (45.7)	1314 (40.8)	1265 (39.1)
Previously treated	Smear microscopy negative relapse	498 (95.6)	431 (93.3)	451 (95.3)	443 (94.9)	5 (1.0)	14 (3.2)	10 (2.2)	7 (1.6)
	Smear microscopy positive relapse	586 (100.0)	480 (99.8)	417 (99.8)	379 (99.5)	586 (100.0)	476 (99.2)	402 (96.4)	371 (97.9)
	Chronic	150 (99.3)	91 (100.0)	74 (100.0)	57 (100.0)	139 (92.7)	83 (91.2)	70 (94.6)	44 (77.2)
	Default	446 (99.1)	441 (99.3)	397 (99.0)	464 (99.8)	313 (70.2)	307 (69.6)	270 (68.0)	300 (64.7)
	Extrapulmonary relapse	2 (100.0)	1 (100.0)	0 (NA)	1 (100.0)	0 (0.0)	0 (0.0)	0 (NA)	0 (0.0)
	Failure	410 (99.8)	337 (100.0)	311 (100.0)	255 (99.6)	365 (89.0)	279 (82.8)	239 (76.8)	165 (64.7)
Total previously treated		2092 (98.6)	1781 (98.1)	1650 (98.4)	1599 (98.3)	1408 (67.3)	1159 (65.1)	991 (60.1)	887 (55.5)
Initiated treatment abroad		17 (100.0)	20 (95.2)	40 (100.0)	24 (100.0)	8 (47.1)	6 (30.0)	18 (45.0)	11 (45.8)
Total		5615 (97.4)	5145 (97.4)	4913 (97.7)	4857 (97.8)	3023 (53.8)	2692 (52.3)	2323 (47.3)	2163 (44.5)

Table 5 Number of pulmonary tuberculosis (TB) cases sent for culture and with positive culture by case type (new/previously treated and previously treated type) diagnosed between January 2007 and December 2010.

Case type	Previously treated type	Number of pulmonary TB cases sent for culture (% of all pulmonary TB cases)				Number of pulmonary TB cases with positive culture (% of cases sent for culture)			
		2007	2008	2009	2010	2007	2008	2009	2010
New		3019 (83.2)	3064 (89.0)	3200 (96.6)	3240 (97.7)	1428 (47.3)	1410 (46.0)	1360 (42.5)	1543 (47.6)
Previously treated	Smear microscopy negative relapse	413 (79.3)	394 (85.3)	451 (95.3)	438 (93.8)	110 (26.6)	118 (29.9)	125 (27.7)	140 (32.0)
	Smear microscopy positive relapse	525 (89.6)	443 (92.1)	413 (98.8)	377 (99.0)	344 (65.5)	309 (69.8)	284 (68.8)	296 (78.5)
	Chronic	146 (96.7)	87 (95.6)	74 (100.0)	57 (100.0)	98 (67.1)	68 (78.2)	55 (74.3)	37 (64.9)
	Default	388 (86.2)	413 (93.0)	391 (97.5)	460 (98.9)	225 (58.0)	241 (58.4)	227 (58.1)	282 (61.3)
	Extrapulmonary relapse	1 (50.0)	1 (100.0)	0 (NA)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (NA)	0 (NA)
	Failure	383 (93.2)	319 (94.7)	300 (96.5)	254 (99.2)	255 (66.6)	204 (63.9)	161 (53.7)	155 (61.0)
Total previously treated		1856 (87.5)	1657 (91.2)	1629 (97.1)	1586 (97.5)	1032 (55.6)	940 (56.7)	852 (52.3)	910 (57.4)
Initiated treatment abroad		16 (94.1)	17 (81.0)	38 (95.0)	24 (100.0)	4 (25.0)	7 (41.2)	14 (36.8)	11 (45.8)
Total		4891 (84.8)	4738 (89.7)	4867 (96.8)	4850 (97.7)	2464 (50.4)	2357 (49.7)	2226 (45.7)	2464 (50.8)

Table 6 Number of tuberculosis (TB) cases with drug susceptibility testing (DST) for multidrug-resistant tuberculosis (MDR-TB) by case type (new/previously treated and previously treated type) diagnosed between January 2007 and December 2010.

Case type	Previously treated type	Number of cases with DST for MDR-TB, including non-pulmonary (% of all cases with positive culture)			
		2007	2008	2009	2010
New		1246 (85.3)	1335 (93.3)	1340 (96.8)	1521 (96.6)
Previously treated	Smear microscopy negative relapse	101 (91.0)	110 (93.2)	123 (98.4)	136 (97.1)
	Smear microscopy positive relapse	309 (89.3)	300 (96.8)	280 (98.6)	281 (94.9)
	Chronic	89 (90.8)	59 (86.8)	54 (98.2)	33 (86.8)
	Default	207 (91.6)	230 (95.0)	216 (95.2)	262 (92.9)
	Extrapulmonary relapse	2 (33.3)	1 (50.0)	1 (100.0)	3 (100.0)
	Failure	221 (86.3)	182 (89.2)	143 (88.8)	145 (91.8)
Total previously treated		929 (89.1)	882 (93.4)	817 (95.8)	860 (93.8)
Initiated treatment abroad		5 (100.0)	7 (100.0)	14 (100.0)	10 (90.9)
Total		2180 (86.9)	2224 (93.4)	2171 (96.4)	2391 (95.6)

Table 7 Number of pulmonary tuberculosis (TB) cases with both negative smear and culture results by case type (new/previously treated and previously treated type) diagnosed between January 2007 and December 2010.

Case type	Previously treated type	Number of cases with both negative smear and culture results (% of all pulmonary TB cases)			
		2007	2008	2009	2010
New		685 (18.9)	544 (15.8)	791 (23.9)	937 (28.3)
Previously treated	Smear microscopy negative relapse	186 (35.7)	145 (31.4)	180 (38.1)	185 (39.6)
	Smear microscopy positive relapse	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
	Chronic	4 (2.6)	1 (1.0)	0 (0.0)	7 (12.3)
	Default	45 (10.0)	45 (10.1)	31 (7.7)	74 (15.9)
	Extrapulmonary relapse	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
	Failure	17 (4.1)	17 (5.0)	33 (10.6)	35 (13.7)
Total previously treated		252 (11.9)	209 (11.5)	245 (14.6)	301 (18.5)
Initiated treatment abroad		2 (11.8)	3 (14.3)	7 (17.5)	7 (29.2)
Total		939 (16.3)	756 (14.3)	1043 (20.7)	1245 (25.1)

Table 8 Number and percentage of tuberculosis (TB) cases with multidrug-resistant tuberculosis (MDR-TB) by case type (new/previously treated and previously treated type) diagnosed between January 2007 and December 2010.

Case type	Previously treated type	Number of MDR-TB cases, including non-pulmonary				% MDR-TB of all with DST for MDR-TB including non-pulmonary			
		2007	2008	2009	2010	2007	2008	2009	2010
New		251	341	315	372	20.1	25.5	23.5	24.5
Previously treated	Smear microscopy negative relapse	56	59	77	80	55.4	53.6	62.6	58.8
	Smear microscopy positive relapse	139	155	152	139	45.0	51.7	54.3	49.5
	Chronic	74	55	46	27	83.1	93.2	85.2	81.8
	Default	123	135	147	168	59.4	58.7	68.1	64.1
	Extrapulmonary relapse	2	0	0	1	100.0	0.0	0.0	33.3
	Failure	172	128	106	105	77.8	70.3	74.1	72.4
Total previously treated		566	532	528	520	60.9	60.3	64.6	60.5
Initiated treatment abroad		3	5	10	4	60.0	71.4	71.4	40.0
Total		820	878	853	896	37.6	39.5	39.3	37.5

Table 9 Notified and estimated multidrug-resistant tuberculosis (MDR-TB) incidence by case type (new/previously treated and previously treated type) diagnosed between January 2007 and December 2010.

Case type	Previously treated type	Notified MDR-TB incidence per 100,000 population				Estimated MDR-TB incidence per 100,000 (based on smear and/or culture +)				Estimated MDR-TB incidence per 100,000 population (based on all TB cases)			
		2007	2008	2009	2010	2007	2008	2009	2010	2007	2008	2009	2010
New		6.07	8.27	7.66	9.06	9.80	12.18	10.25	11.08	20.10	24.28	21.61	22.27
Previously treated	Smear microscopy negative relapse	1.35	1.43	1.87	1.95	1.50	1.59	1.92	2.02	7.02	6.01	7.21	6.69
	Smear microscopy positive relapse	3.36	3.76	3.70	3.39	6.42	6.04	5.51	4.58	6.42	6.04	5.55	4.61
	Chronic	1.79	1.33	1.12	0.66	2.91	1.99	1.49	1.00	3.05	2.10	1.70	1.28
	Default	2.97	3.27	3.57	4.09	4.88	4.86	5.17	5.56	6.56	6.42	6.74	7.29
	Extrapulmonary relapse	0.05	0.00	0.00	0.02	0.22	0.00	0.00	0.02	0.92	0.00	0.00	0.24
	Failure	4.16	3.10	2.58	2.56	7.22	5.20	4.72	3.74	7.83	5.83	5.77	4.69
Total previously treated		13.68	12.90	12.84	12.67	23.26	19.60	18.68	16.83	32.06	27.37	27.41	24.71
Initiated treatment abroad		0.07	0.12	0.24	0.10	0.13	0.17	0.38	0.14	0.30	0.38	0.73	0.23
Total		19.83	21.30	20.74	21.83	32.77	31.80	28.73	27.52	57.57	55.75	53.22	49.62

Table 10 Potential risk factors for multidrug-resistant tuberculosis (MDR-TB) at the individual level which were not significantly associated with odds of having MDR-TB. Variables were only considered if more less than 10% of data were missing (Appendix Table 1). Odd ratios, 95% confidence intervals (CI) and p-values are shown adjusting for all other variables included in the final models as presented in Table 2 (see Main Text)

Variable	Final form used*	Odds ratio (95% CI) and, p-value in model for MDR-TB risk among new TB cases.	Odds ratio (95% CI) and, p-value model for MDR-TB risk among previously treated TB cases.
Age	Linear	Significantly associated, included in final model (see Table 3)	Significantly associated, included in final model (see Table 3)
Urban/rural location	Binary (urban vs rural)	Significantly associated, included in final model (see Table 3)	Significantly associated, included in final model (see Table 3)
Homeless	Binary (yes vs no)	1.15 (0.94, 1.41), p=0.18	Borderline significantly associated, included in final model (see Table 3)
Gender	Binary (male vs female)	0.94 (0.83, 1.05), p=0.28	0.94 (0.87, 1.01), p=0.074
Citizenship	Binary (Moldovan vs other)	1.07 (0.62, 1.85), p=0.79	0.92 (0.58, 1.48), p=0.74
Occupation	Binary (disabled vs other)	0.81 (0.62, 1.05), p=0.096	Significantly associated, included in final model (see Table 3)
Salaried	Binary (yes vs no)	1.08 (0.96, 1.22), p=0.19	0.99 (0.41, 2.40), p=0.85
Education	Binary (education vs no education)	1.24 (0.87, 1.78), p=0.27	0.90 (0.70, 1.17), p=0.43
Living conditions	Binary (satisfactory vs unsatisfactory)	Excluded, >10% missing data	0.98 (0.93, 1.04), p=0.60
Was outside Moldova for >3 months in last 12 months	Binary (yes vs no)	Significantly associated, included in final model (see Table 3)	0.97 (0.90, 1.05), p=0.49
Previously in detention	Binary (yes vs no)	Significantly associated, included in final model (see Table 3)	Significantly associated, included in final model (see Table 3)
In detention at time of diagnosis	Binary (yes vs no)	Not significantly associated, included as a confounder (see Table 3)	Significantly associated, included in final model (see Table 3)
Household size	Binary (lives alone vs not	1.00 (0.87, 1.15), p=0.96	Not significantly associated, included as a

	alone)		confounder (see Table 3)
Number of children in the household	Binary (some vs none)	1.13 (0.91, 1.12), p=0.82	0.95 (0.89, 1.02), p=0.15
Known TB contact in the household	Binary (yes vs no)	Significantly associated, included in final model (see Table 3)	0.99 (0.89, 1.11), p=0.92
Smear status	Categorical (positive, negative, tested but no result, not tested)	P-value for variable = 0.094	P-value for variable = 0.25
	Positive (reference group)	1.00	1.00
	Negative	0.91 (0.82, 1.01)	1.00 (0.94, 1.07)
	Tested but no result	1.24 (0.64, 2.39)	1.22 (0.96, 1.54)
	Not tested	1.53 (0.99, 2.35)	0.59 (0.25, 1.39)
HIV status	Binary (positive vs other)	Significantly associated, included in final model (see Table 3)	Not significantly associated, included as a confounder (see Table 3)
Presence of alcoholism	Binary (yes or no)	Excluded, >10% missing data	Excluded, >10% missing data
Presence of drug abuse	Binary (yes or no)	Excluded, >10% missing data	Excluded, >10% missing data
Presence of mental illness	Binary (yes or no)	Excluded, >10% missing data	Excluded, >10% missing data
Presence of neoplasia	Binary (yes or no)	Excluded, >10% missing data	Excluded, >10% missing data
Taking steroids	Binary (yes or no)	Excluded, >10% missing data	Excluded, >10% missing data
Any other comorbidity	Binary (yes or no)	Excluded, >10% missing data	Excluded, >10% missing data
Has diabetes	Binary (yes or no)	Excluded, >10% missing data	Excluded, >10% missing data

*Where variables could be entered into the model in more than one way, univariable models of each form were compared using maximum likelihood to choose the most appropriate form (see Table S1).

Figure 1 Culture use and positivity by rayon. Percentage of pulmonary TB cases that received culture (A) and percentage culture positive of those that received culture (B) by rayon, 2007-2010.

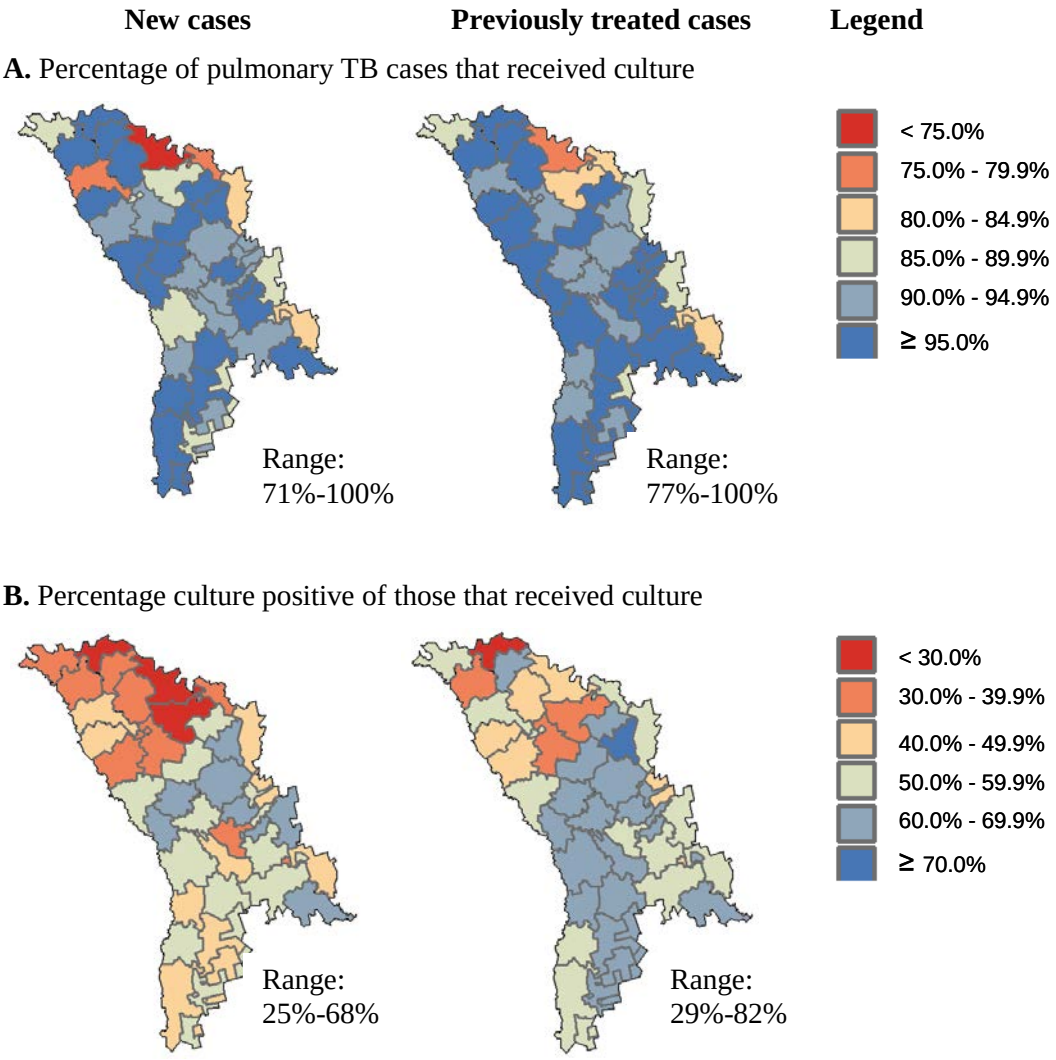
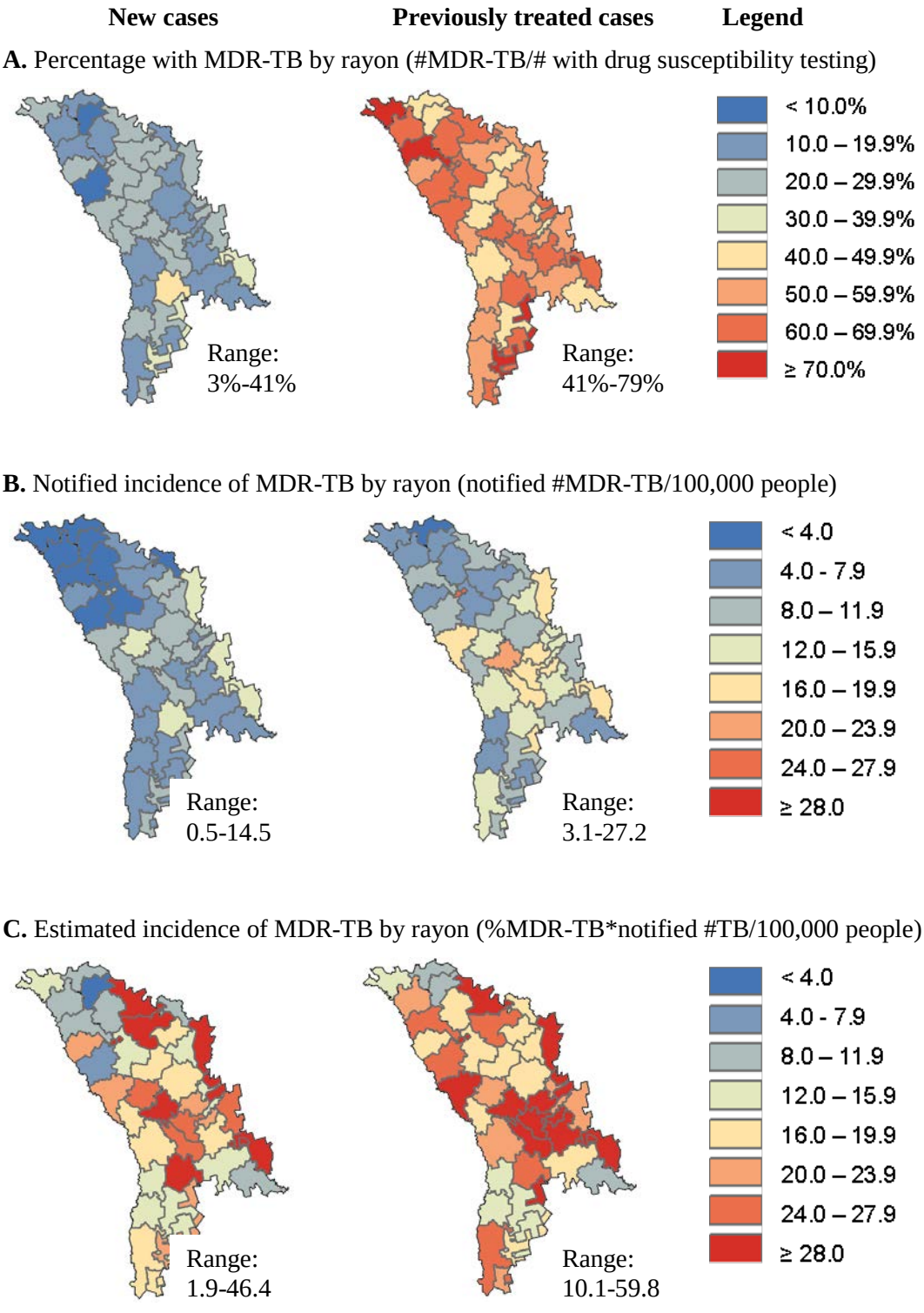


Figure 2 Percentage with and notified and estimated incidence of MDR-TB by rayon, 2007-2010.



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