

Enhancing Health Risk Surveillance: Integrating Molecular Biology, Epidemiology, and Geography for Infectious Disease Prevention and Control

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- Home of Connaught Laboratories
- Extended by integrating with the Institute for Health Policy, Management & Evaluation (IHPE) in 2018
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Prof. Howard Hu



Prof. Steini Brown





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Notice of Upcoming Funding Opportunity: Avian Influenza Interdisciplinary Research

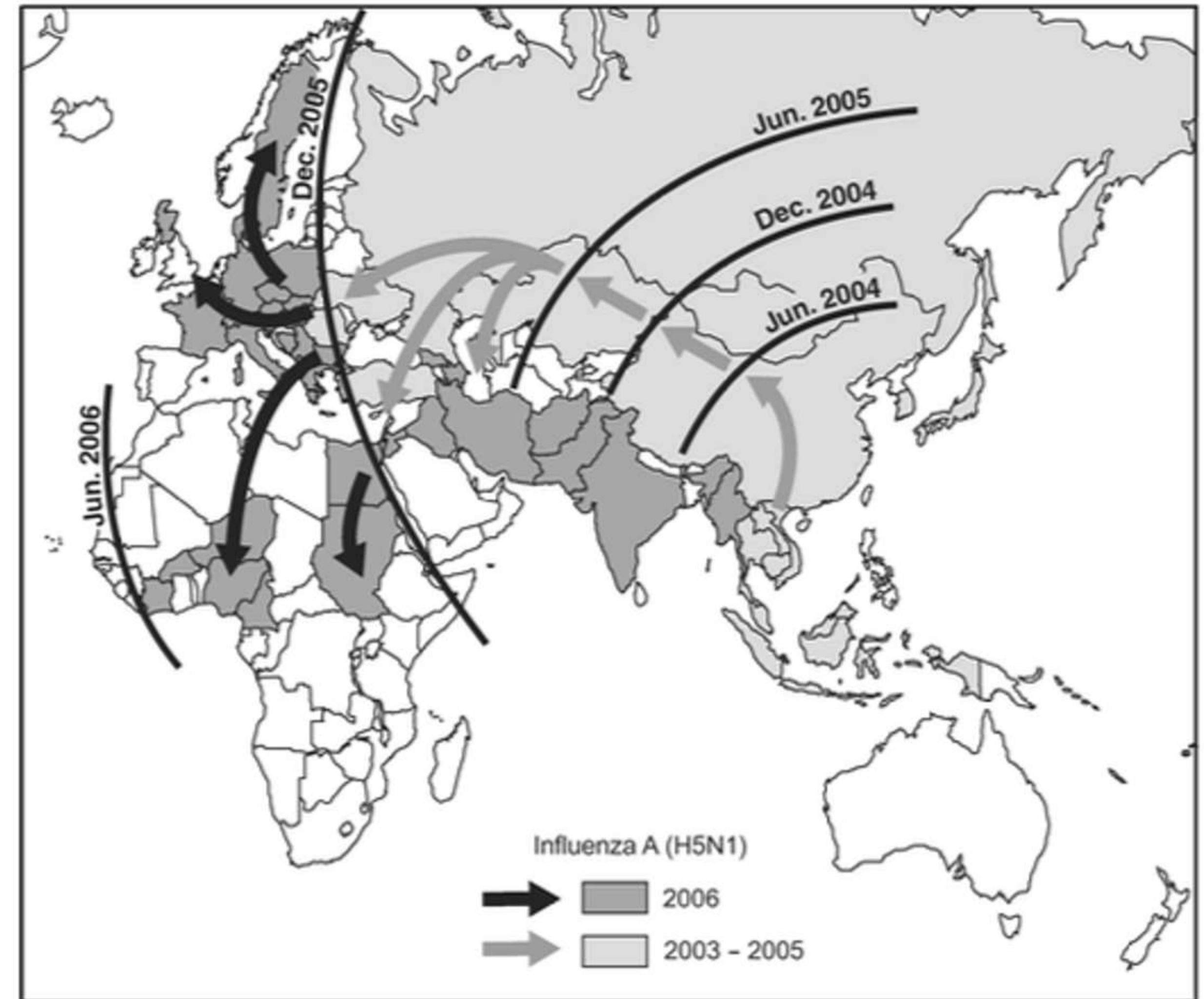
Introduction

The Canadian Institutes of Health Research (CIHR) is pleased to announce the upcoming launch of the Avian Influenza Interdisciplinary Research Funding Opportunity.

This funding opportunity is led by the CIHR Centre for Research on Pandemic Preparedness and Health Emergencies (CRPPHE) in partnership with the CIHR Institute of Infection and Immunity (III), and the Public Health Agency of Canada (PHAC).

Avian influenza

- Avian influenza Type A virus
- Spread among wild aquatic birds worldwide
- Can infect domestic poultry and other birds and animal species
- The first human cases by the highly pathogenic H5N1 infection in Guangdong, South China, 1996.

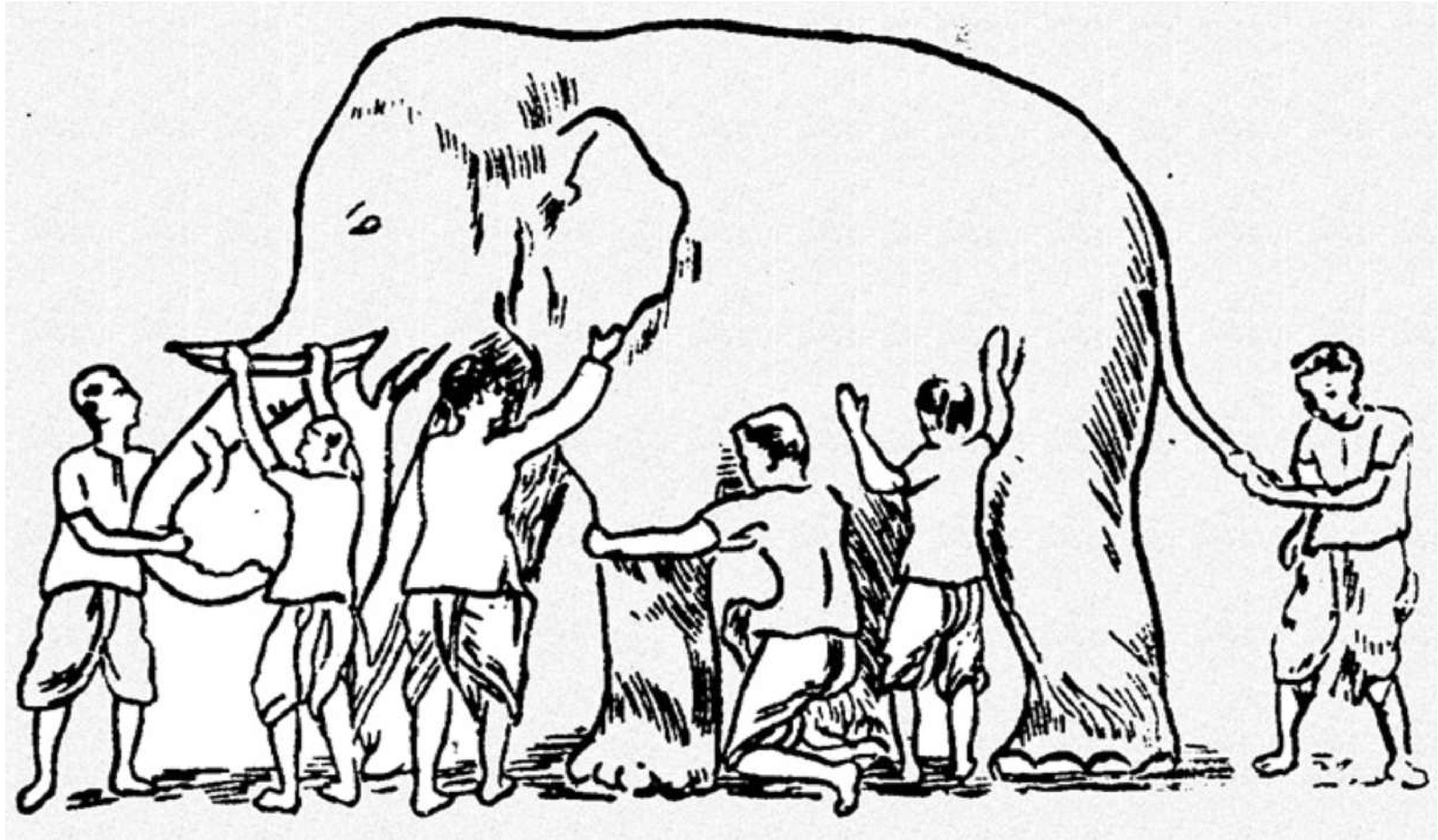


Smallman-Raynor M. & Cliff A.D., (2008) *Annals of AAG* 98(3): 553-582

Earlier studies in avian influenza

- Virology & Molecular Biology
 - ✦ R.G. Webster & Y. Guan
- Phylogeography
 - ✦ R.G. Wallace & M.W. Fich
- Health Geography
 - ✦ A.D. Cliff, J.K. Ord, R. Haining, & P. Diggle
- Spatial Epidemiology
 - ✦ M. Gilbert

Mistake a part for a whole



How can we integrate these different pieces of information to gain a more accurate understanding of the whole picture?

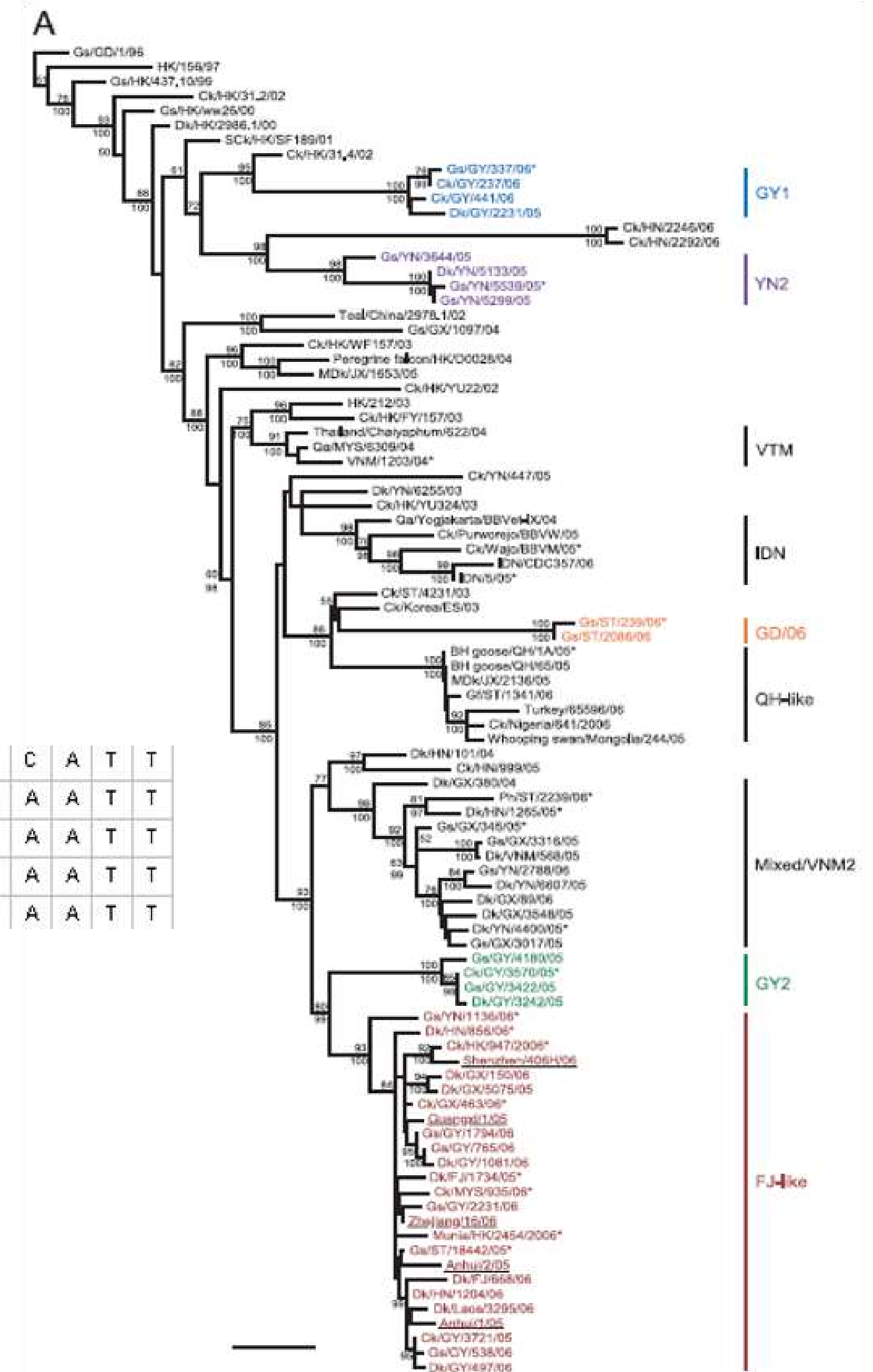
Phylogenetic analysis

- A/Gs/GD/1/1996
 - Gs - goose; GD - Guangdong
- Genetic sequences (GenBank)

PB2, PB1, HA, NP, NA, M1, M2, NS

✓ 1. A/Goose/Guangdong/1/96	C	T	C	T	G	C	G	A	T	C	T	A	A	A	T	G	G	A	G	T	G	A	A	G	C	C	T	C	T	C	A	T	T
✓ 2. A/Thailand/NK165/2005	C	T	C	T	G	T	G	A	T	C	T	A	G	A	T	G	G	A	G	T	G	A	A	G	C	C	T	C	T	A	A	T	T
✓ 3. A/cat/Thailand/KU-02/04	C	T	C	T	G	C	G	A	T	C	T	A	G	A	T	G	G	A	G	T	G	A	A	G	C	C	T	C	T	A	A	T	T
✓ 4. A/tiger/Thailand/CU-T4/04	C	T	C	T	G	C	G	A	T	C	T	A	G	A	T	G	G	A	G	T	G	A	A	G	C	C	T	C	T	A	A	T	T
✓ 5. A/Thailand/NBL1/2006	C	T	C	T	G	C	G	A	T	C	T	A	G	A	T	G	G	A	G	G	G	A	A	G	C	C	T	C	T	A	A	T	T

- Evolution model
- Length of branch



Quantification of phylogenetic tree

- Individual + Family at stage i

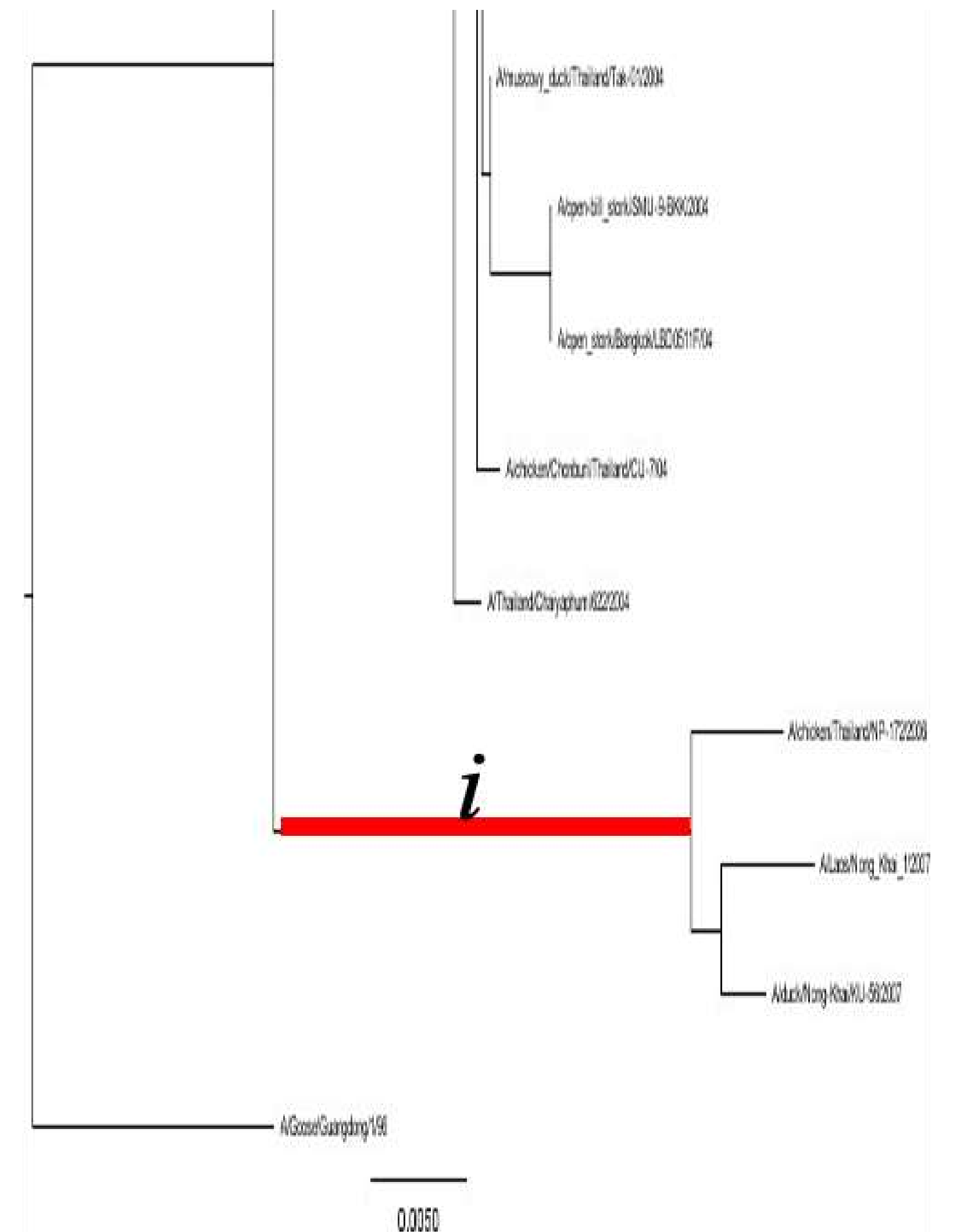
$$cap_i = w_{1i} \times e_i + w_{2i} \times s_i + w_{3i} \times t_i$$

e_i , s_i , and t_i are viral evolution, spatial dispersion, and time span; w_{1i} , w_{2i} , w_{3i} are weights.

- Capability of a virus to spread can be quantified as

$$Capability = \sum_{i=1}^n cap_i$$

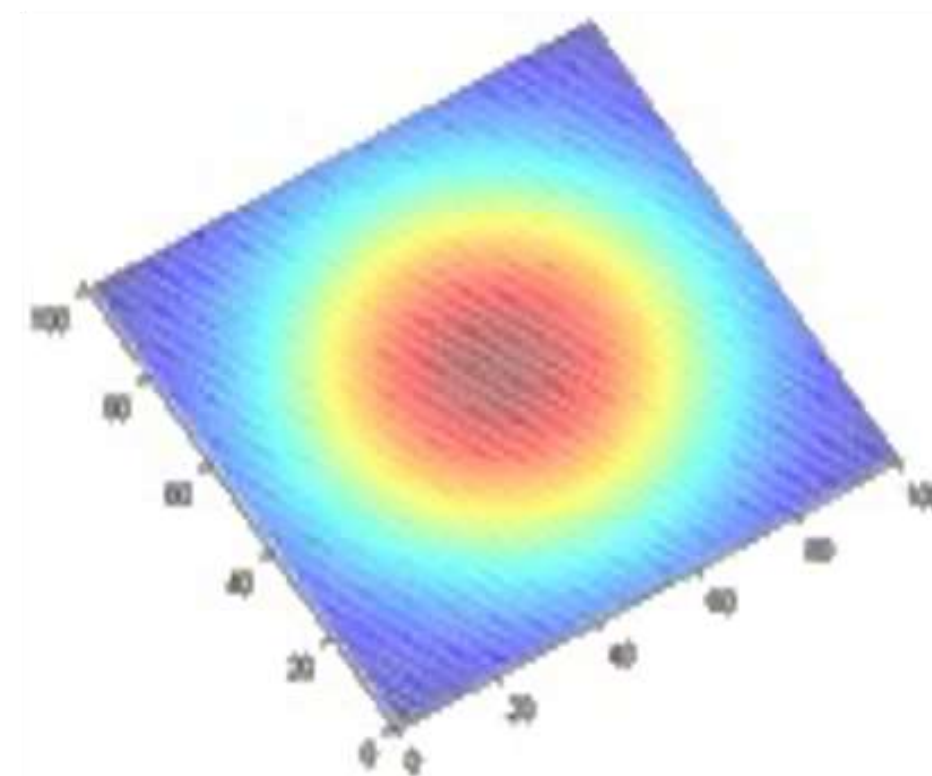
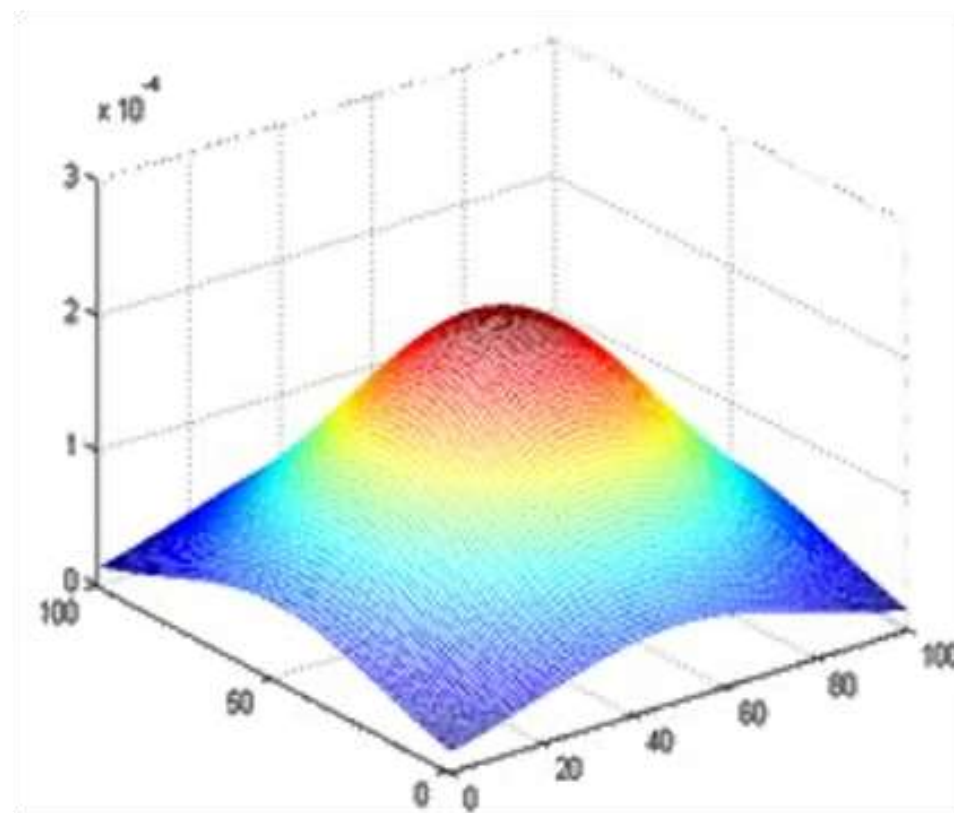
n is the number of evolution stages of a virus.



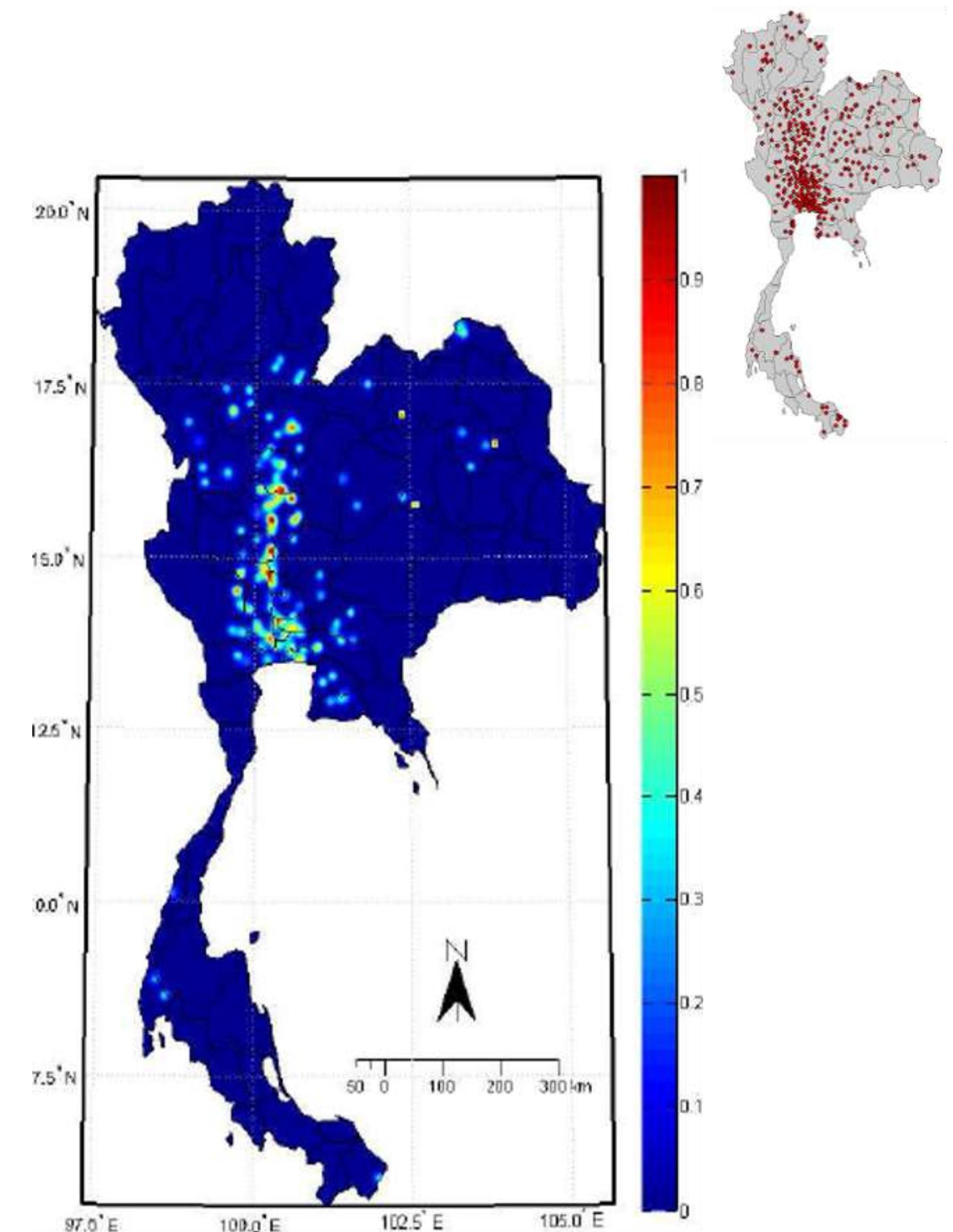
Gaussian Kernel Function

$$G(x, \delta) = \frac{1}{2\pi \times \delta^2} e^{-\frac{x^2}{2\delta^2}}$$

Where δ is *capability* and x refers to the range within which a pathogen might reach.



Here $x = 113 \text{ km}$, this scale was used by Viboud et al. in characterizing the local pattern of influenza spreading (Science, 2006).



Modified local K function

$$\hat{K}_i(h) = \frac{\sum_{j=1}^n w_{ij} I(d_{ij} < h)}{\lambda c_i}$$

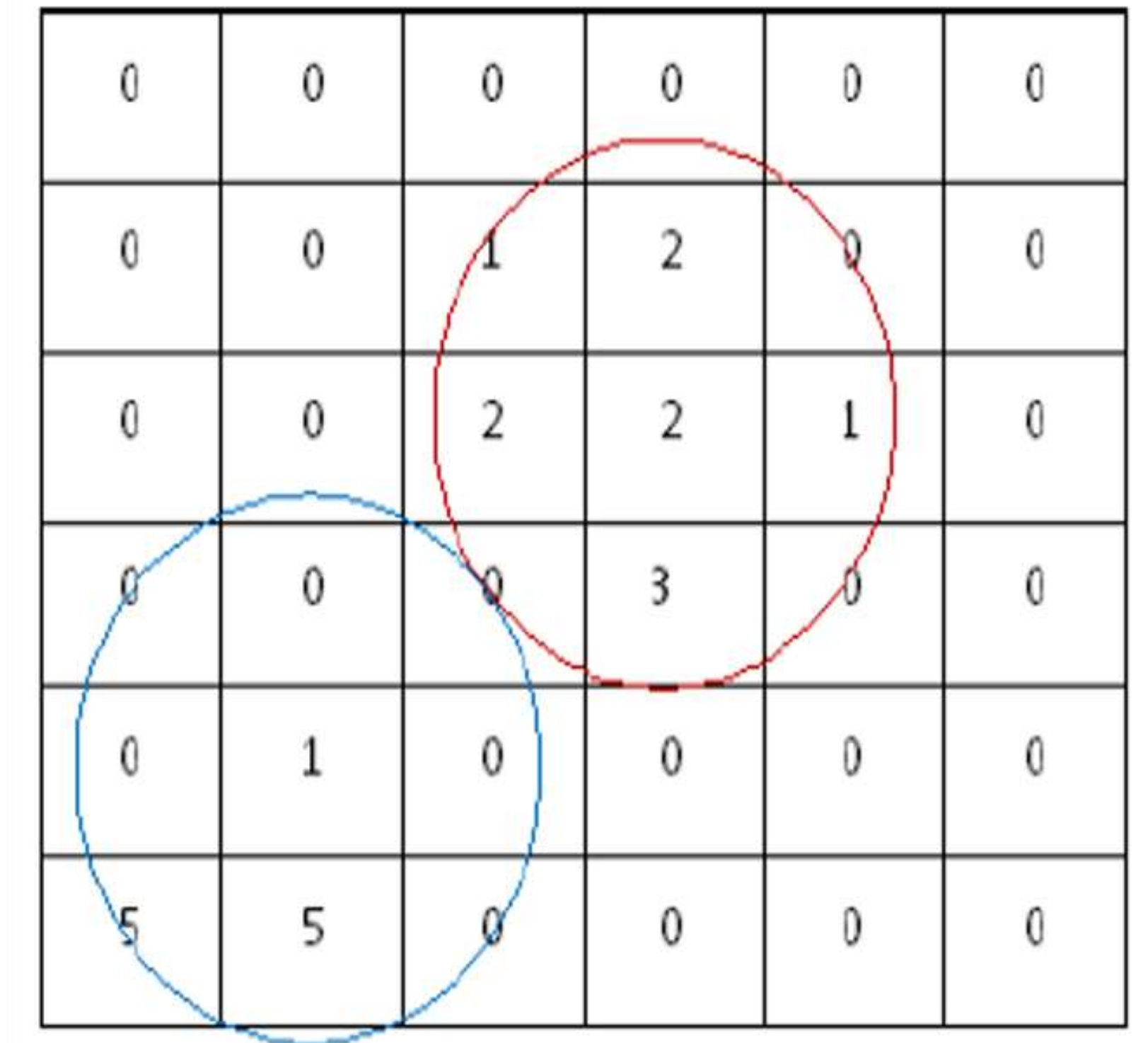
λ : The overall density of outbreaks.

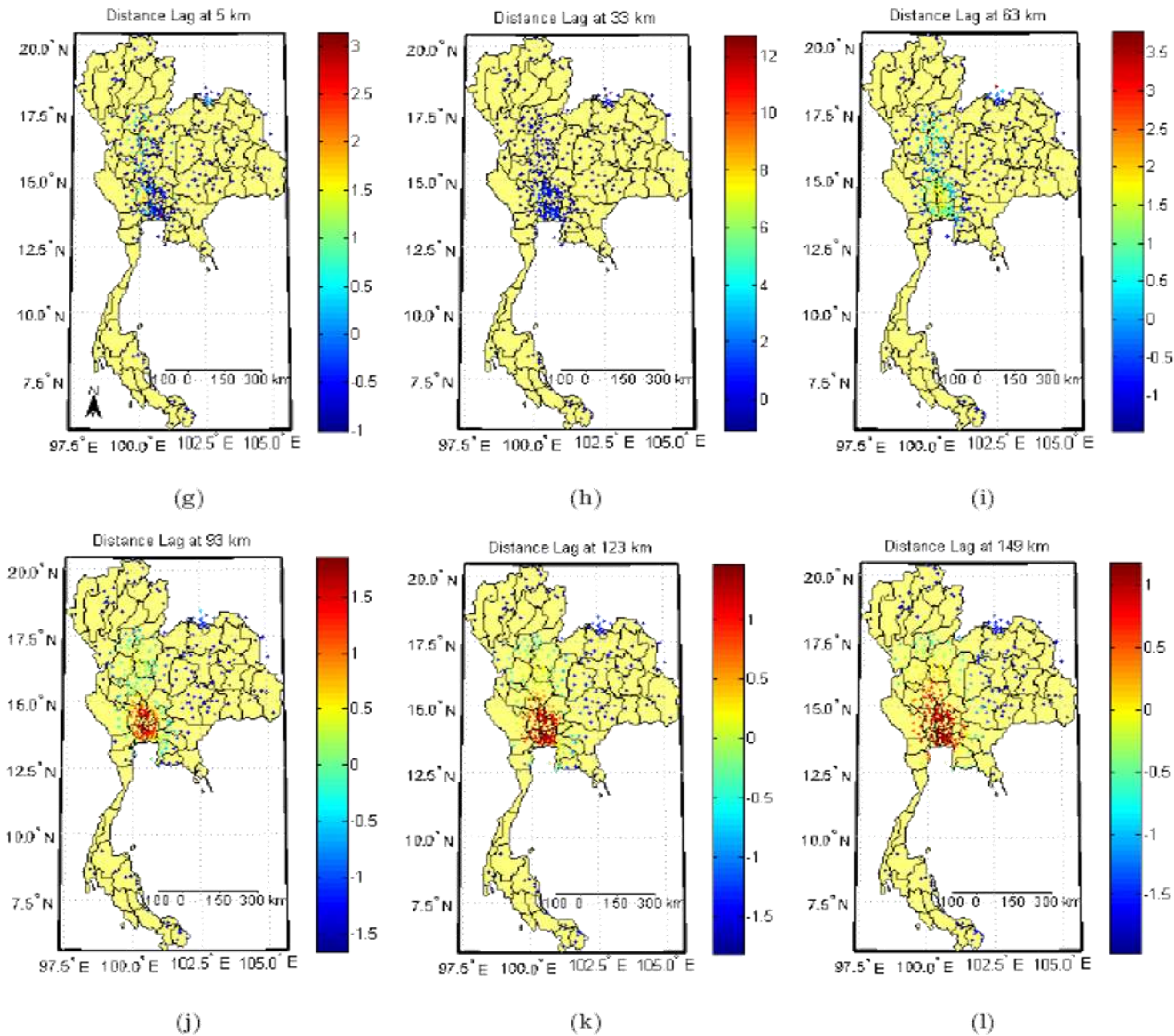
d_{ij} : The distance between location i and j .

I : Indicator function with 1 for $d_{ij} < h$ and 0 for a larger d_{ij} .

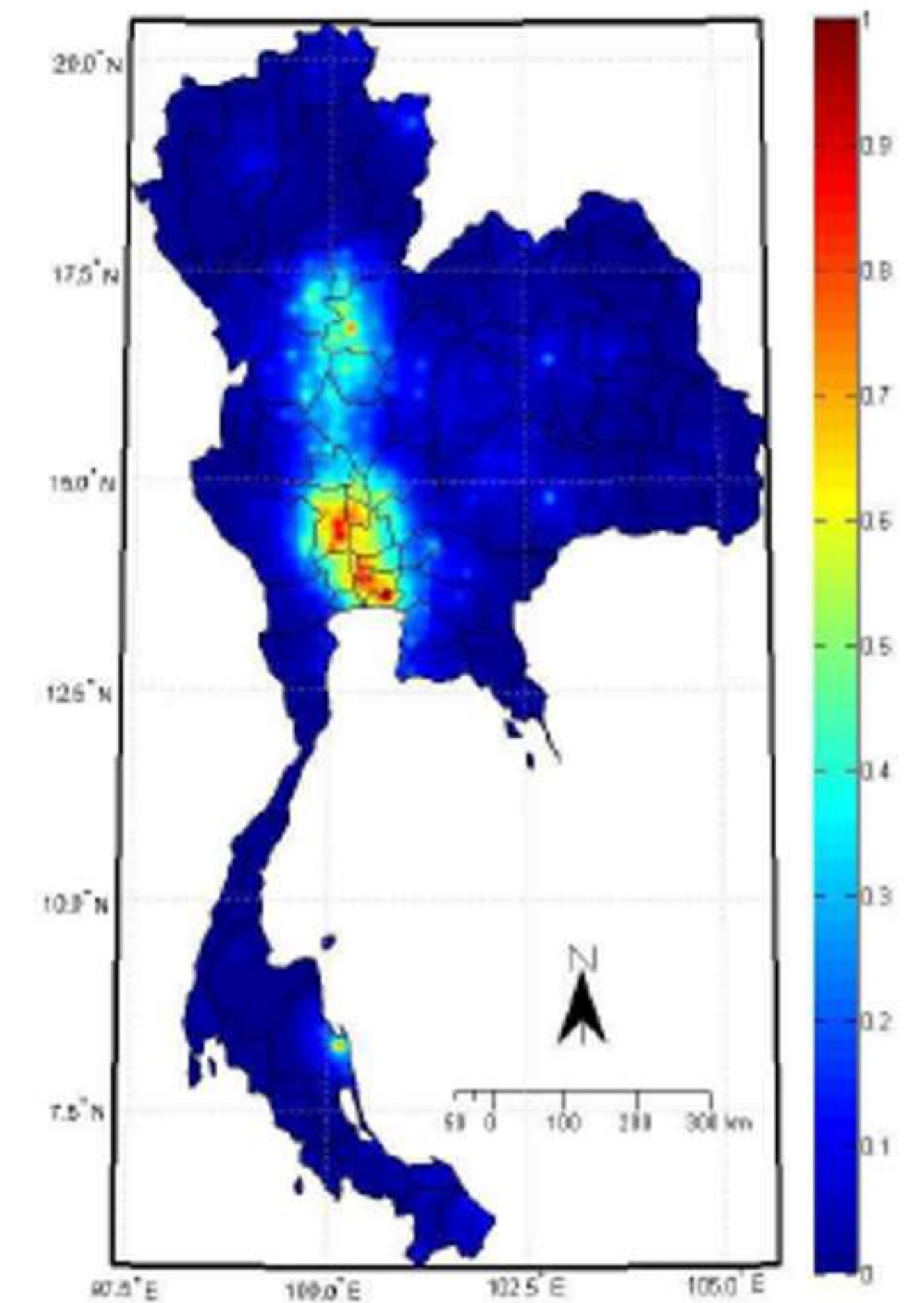
h : Distance threshold; 113 *km* was adopted here as it was in the Gaussian Kernel Function.

w_{ij} : A distance-inverse weight, specified as $w_{ij} = \frac{1}{d_{ij}}$.





Results of modified local K function analysis in varying distance thresholds

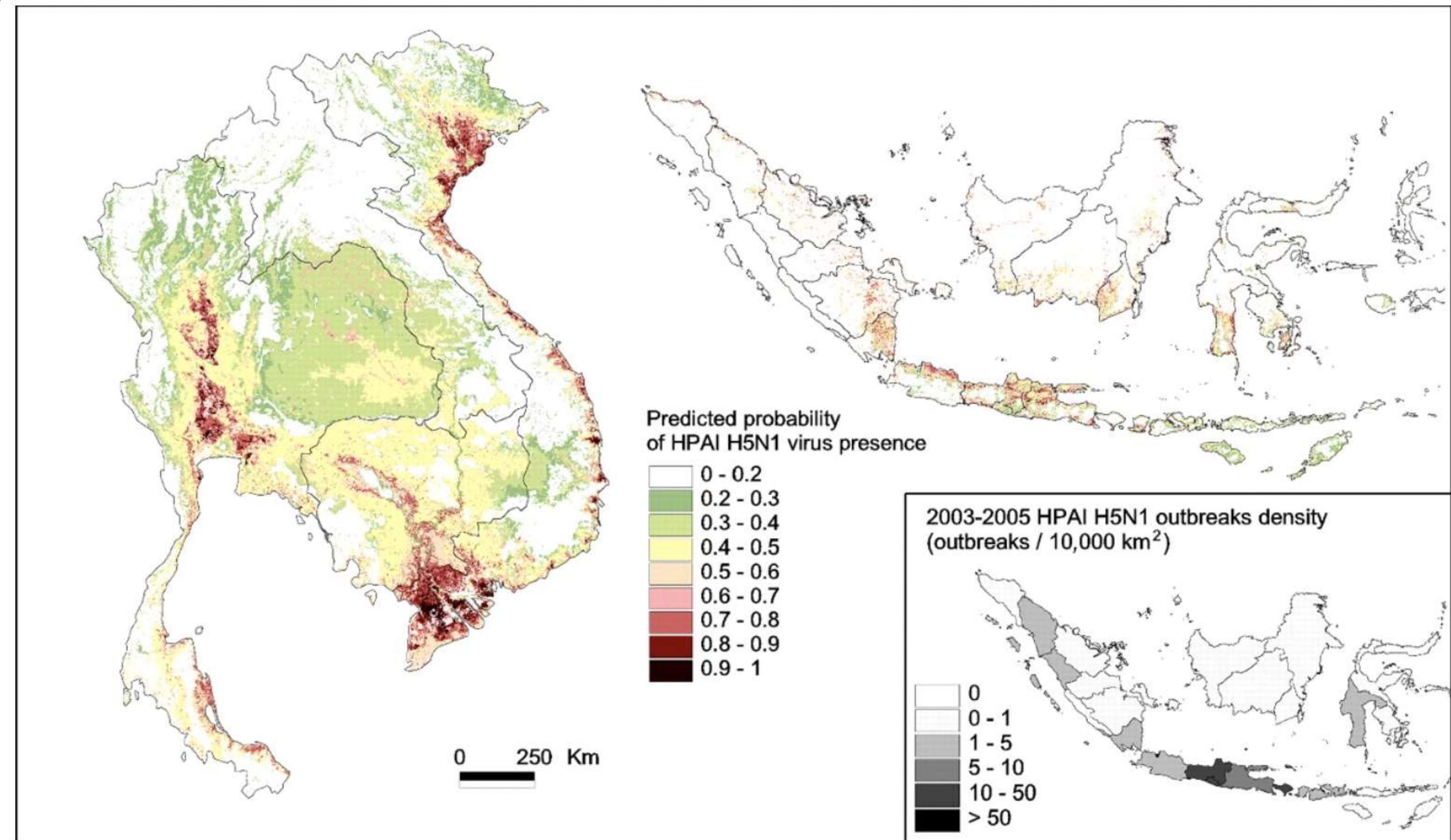


The Gaussian Kernel estimates based on the modified local K function with the threshold $h = 113$ km

Epidemiological studies

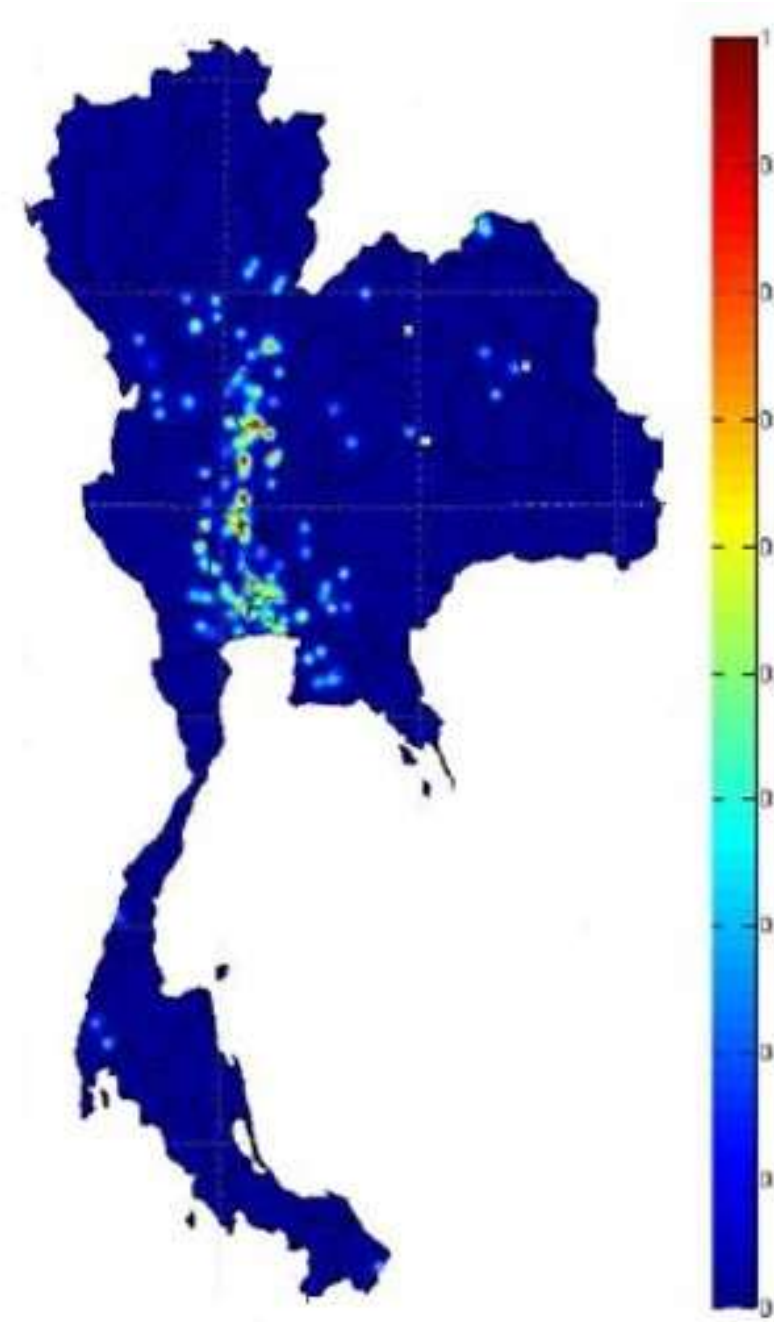
Predictors

- Elevation
- Population density
- Chicken density
- Duck density
- Annual number of rice crop harvest

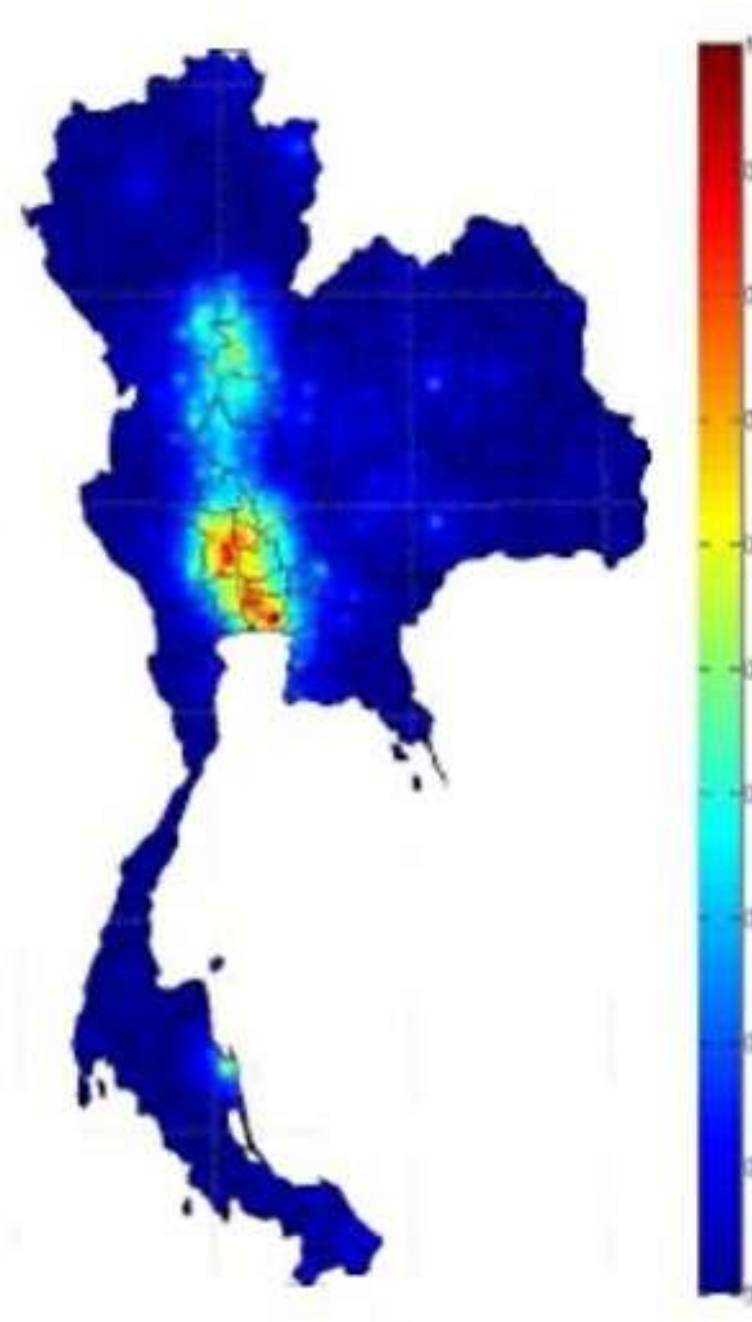


Predictions of HPAI H5N1 virus relative risk of presence in Thailand, Laos, Cambodia, and Vietnam based on the Thailand wave II model using the following parameters: $\text{Logit}(p) = -0.903 - 3.11 \cdot 10^{-3} \text{Alt} - 1.62 \cdot 10^{-4} \text{HpopDn} - 2.47 \cdot 10^{-5} \text{ChDn} + 5.40 \cdot 10^{-4} \text{DuDn} + 0.968 \text{Cropl}$, where Alt, HpopDn, ChDn, DuDn, and Cropl are the elevation, human population density, chicken density, duck density, and annual number of rice crop harvest, respectively, in each 500-m pixel. (Inset) Shown is the density of HPAI H5N1 outbreaks recorded in Indonesia in 2003-2005 expressed as number of outbreaks per 10,000 km².

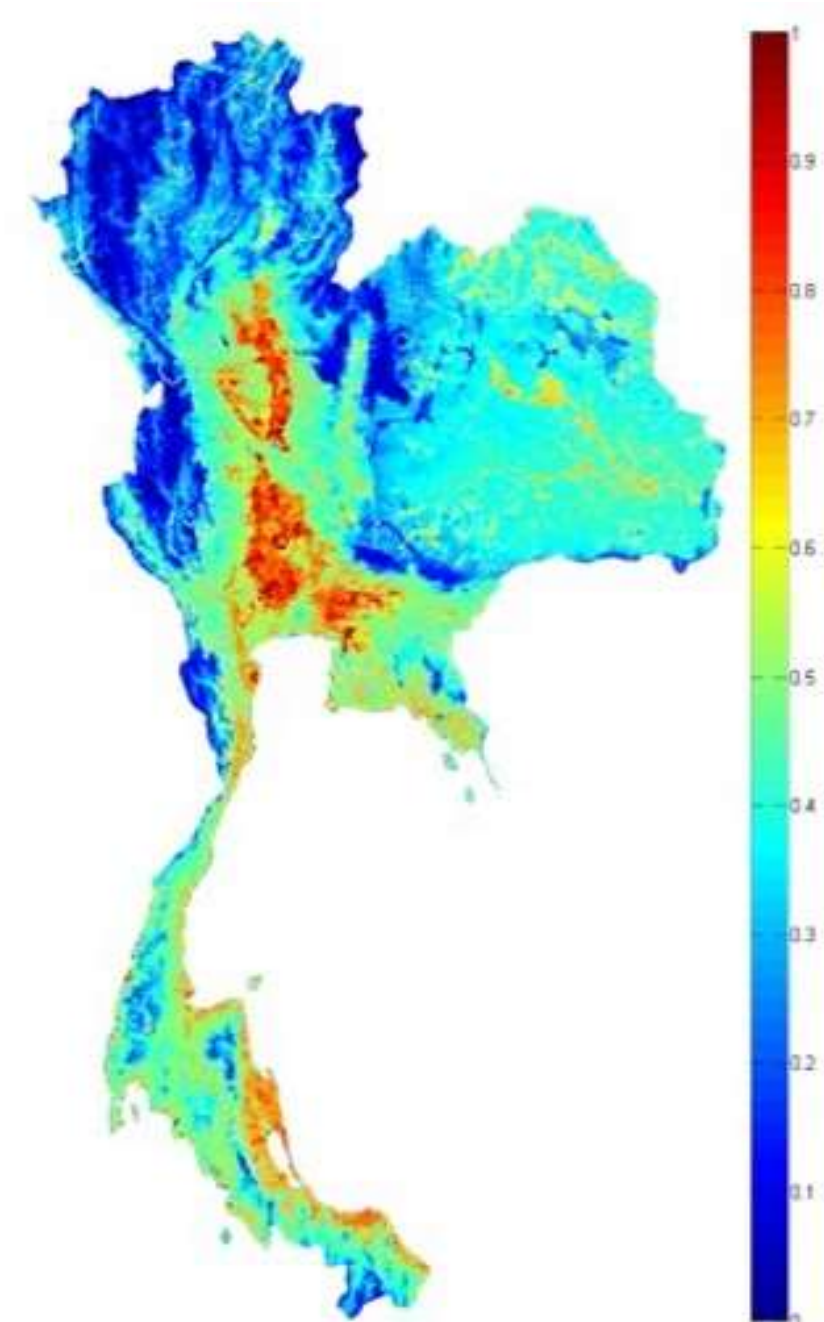
How can we integrate these results if this can improve avian influenza surveillance and prediction?



The spatial distribution of viral evolution



Clustering of outbreaks



Environmental factor-associated risks for outbreaks (Gilbert et al., 2008, *PNAS*)

Dempster-Shafer Theory of Evidence

- The D-S Theory was proposed to quantify and reason with imprecise, uncertain, and /or weak information (Dempster A.P, 1967; Shafer, G., 1976, *Annals of Mathematical Statistics*).
- Three steps of the D-S inference procedure
 - Set up frame of discernment (FOD)
 - Each subset is assigned a belief value by evidence, called probability mass function, $m(\cdot)$
$$m(\{\phi\}) = 0 \text{ and } \sum_{H \subseteq \Theta} m(H) = 1, 0 < m(H) < 1$$
 - Dempster's rule of combination.

- Frame of Discernment (FOD)

$\{\{\phi\}, \{\text{yes}\}, \{\text{no}\}, \{\text{yes, no}\}\}$, $\{\text{yes, no}\}$ – unknown;

- *Mass functions:*

$$m_1(\{\text{yes}\}) = p_1; \quad m_1(\{\text{yes, no}\}) = 1 - p_1$$

$$m_2(\{\text{yes}\}) = p_2; \quad m_2(\{\text{yes, no}\}) = 1 - p_2$$

$$m_3(\{\text{yes}\}) = p_3 * q; \quad m_3(\{\text{no}\}) = (1 - p_3)(1 - q);$$

$$m_3(\{\text{yes, no}\}) = 1 - m_3(\{\text{yes}\}) - m_3(\{\text{no}\}).$$

Note: q is an index assessing the predictive power of the statistical models;

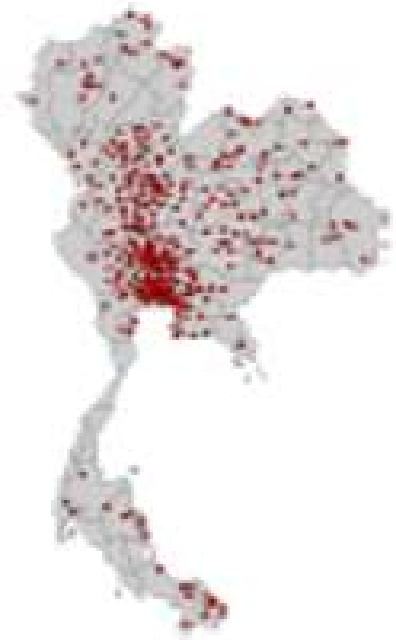
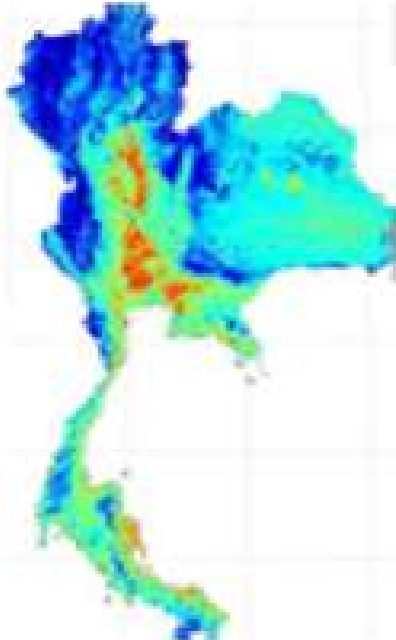
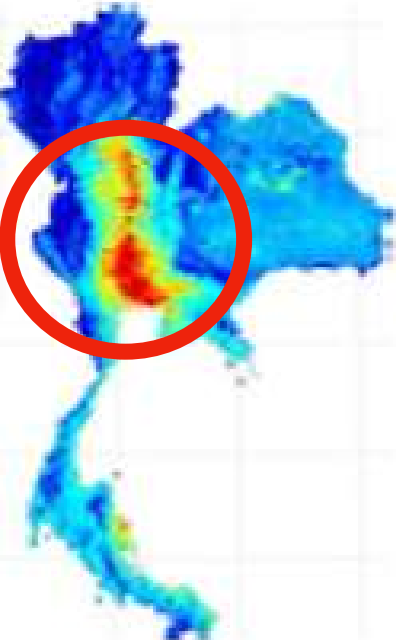
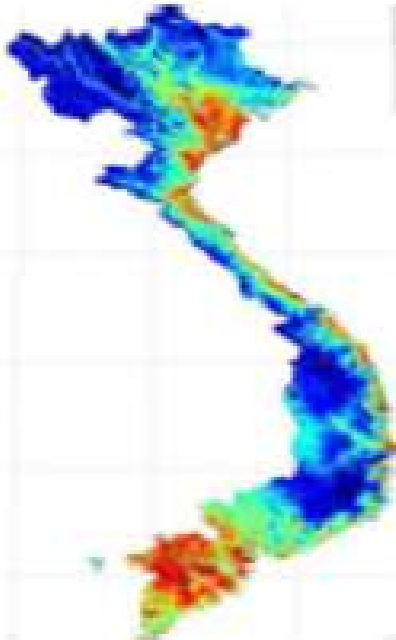
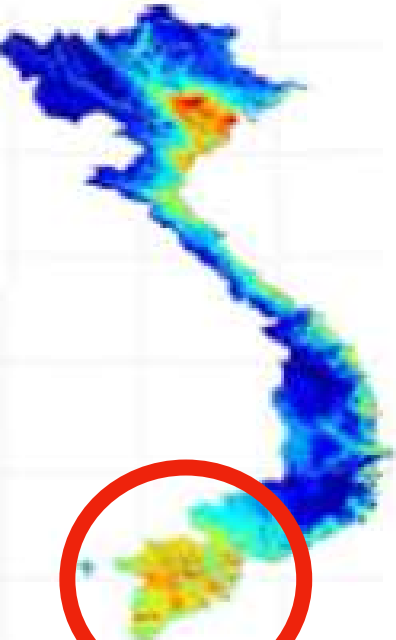
- Dempster Combination

$$m(\{\text{yes}\}) = (m_1 \oplus m_2)(\{\text{yes}\}) = \frac{1}{k} \sum_{s_1 \cap s_2 = \{\text{yes}\}} m_1(s_1) m_2(s_2)$$

Where

$$k^{-1} = 1 - \sum_{s_1 \cap s_2 = \{\text{yes}\}} m_1(s_1) m_2(s_2) > 0$$

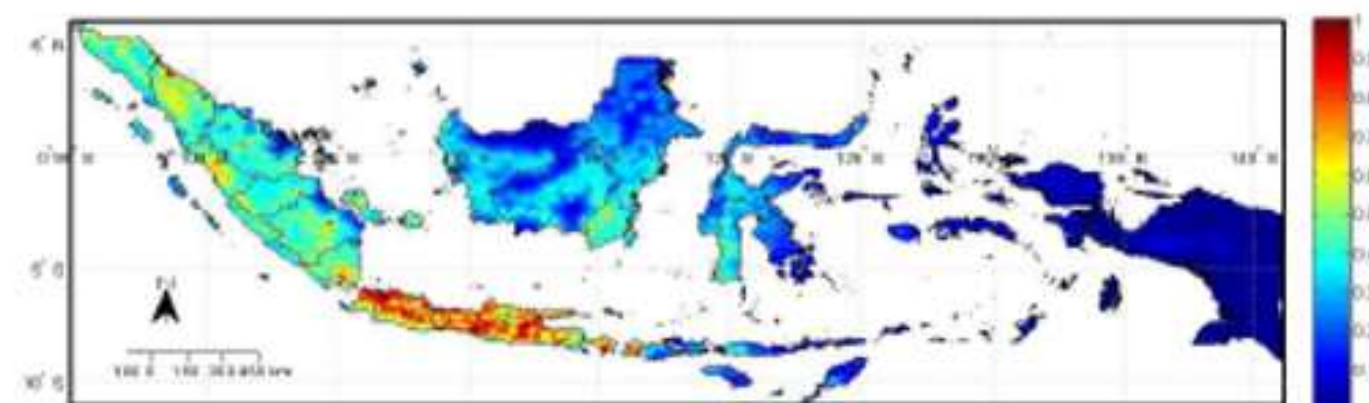
Table 1: Test for spatial correspondence of H5N1 outbreaks and the empirical patterns

			Assessment of Bivariate Spatial Association							
Country	OBK	ALM	KF	Pattern	Group Size	R	n	Adj N'	DF	p -value
Thailand				OBK-ALM	60x60	.2035	1508	85	83	.050
				OBK-KF	60x60	.2871	1508	84	82	.010
				OBK-ALM	50x50	.1870	2170	99	97	.050
				OBK-KF	50x50	.2630	2170	99	97	.010
				OBK-ALM	40x40	.1487	3432	141	139	.075
				OBK-KF	40x40	.2159	3432	142	140	.010
				OBK-ALM	30x30	.1178	5974	178	176	.100
				OBK-KF	30x30	.1778	5974	182	180	.010
Vietnam				OBK-ALM	60x60	.1206	1770	263	261	.050
				OBK-KF	60x60	.1530	1770	265	263	.010
				OBK-ALM	50x50	.1012	2485	305	303	.070
				OBK-KF	50x50	.1320	2485	306	304	.020
				OBK-ALM	40x40	.0903	3872	324	322	.100
				OBK-KF	40x40	.1179	3872	325	323	.025
				OBK-ALM	30x30	.0598	6962	537	535	.150
				OBK-KF	30x30	.0811	6962	539	537	.050

OBK: outbreaks; ALM: Auto-logistic model; KF: Knowledge Fusion; R : Pearson's correlation coefficient; n : sample size; Adj N' : adjusted sample size; DF: degree of freedom; Group sizes: the number of lattice points grouped as an experiment unit in assessing the spatial correspondence between outbreaks and experimental patterns: ALM and KF.



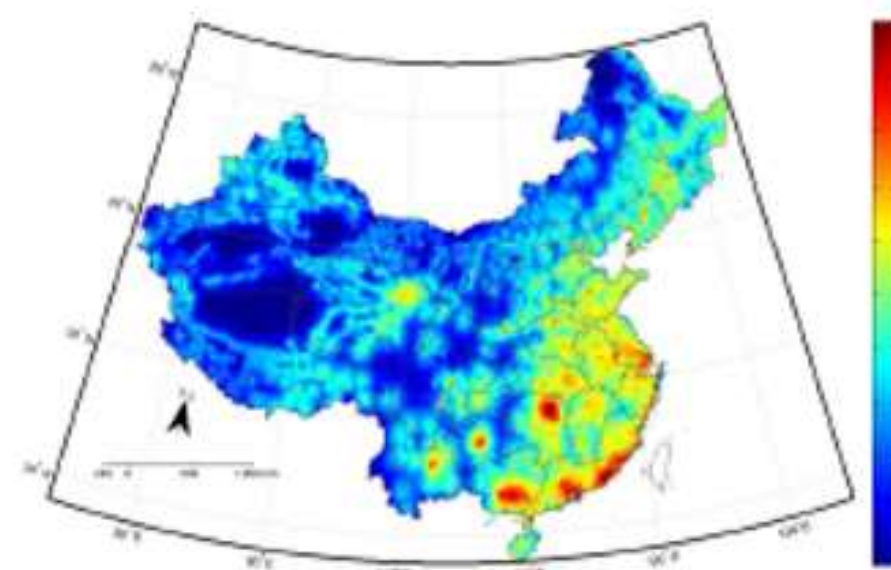
(a)



(b)



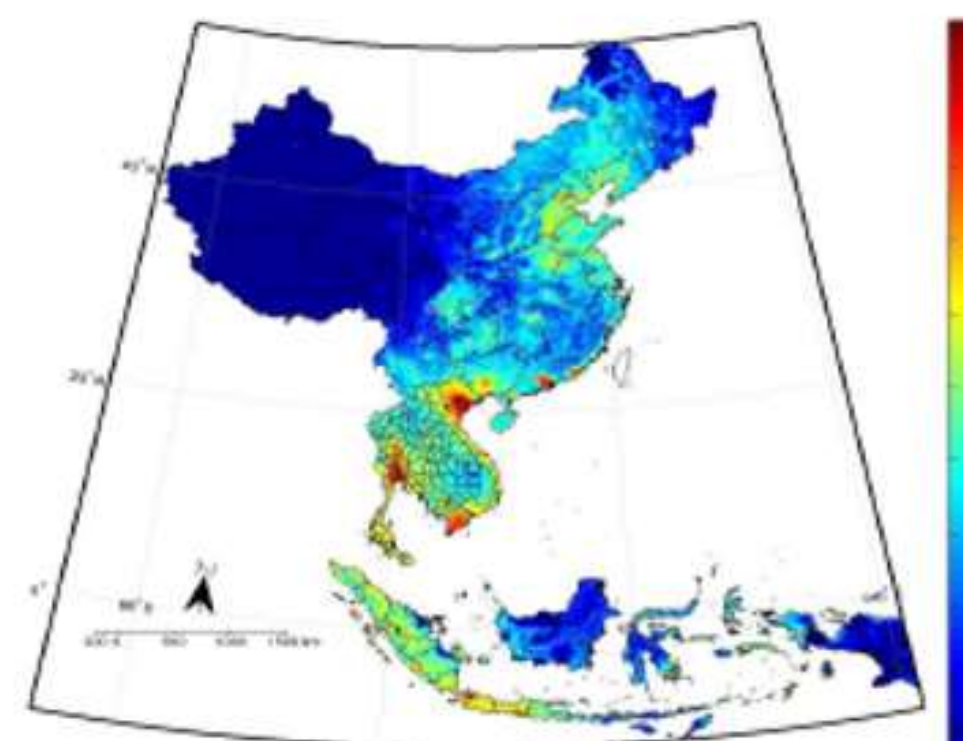
(c)



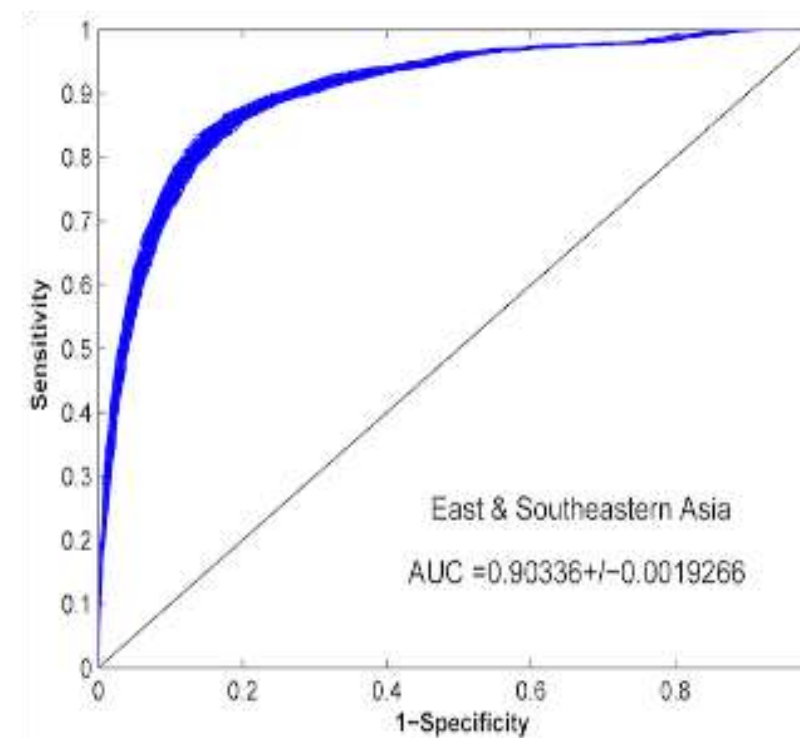
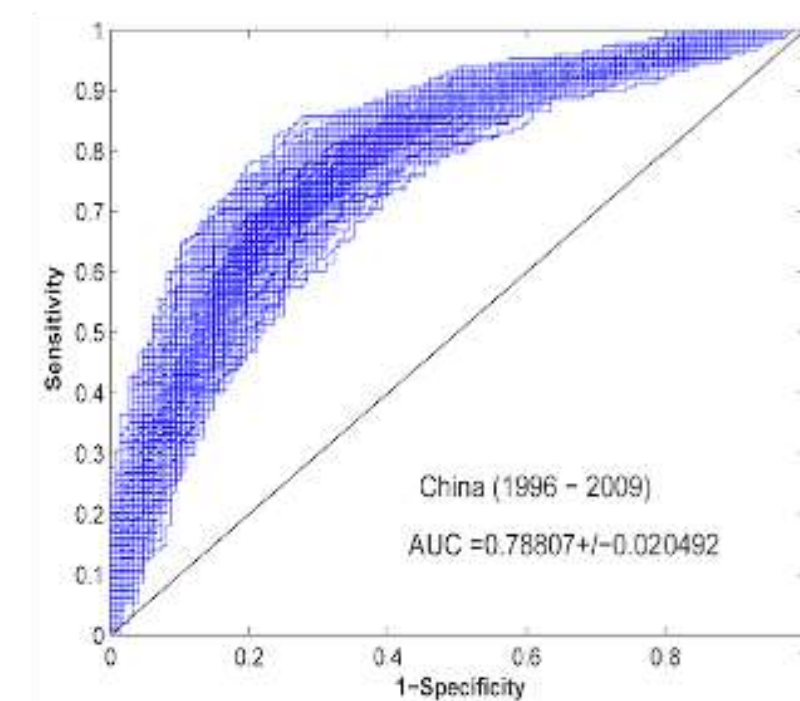
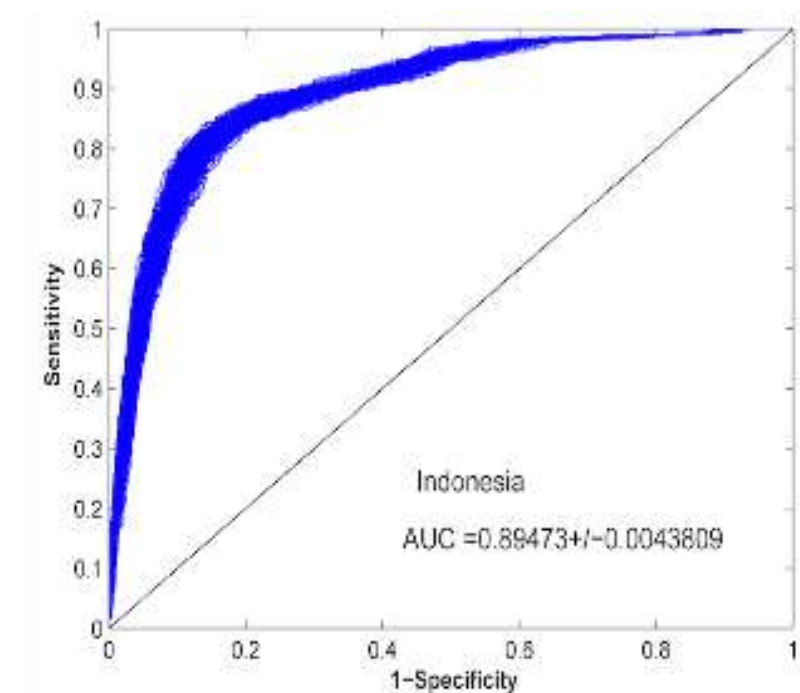
(d)



(e)



(f)

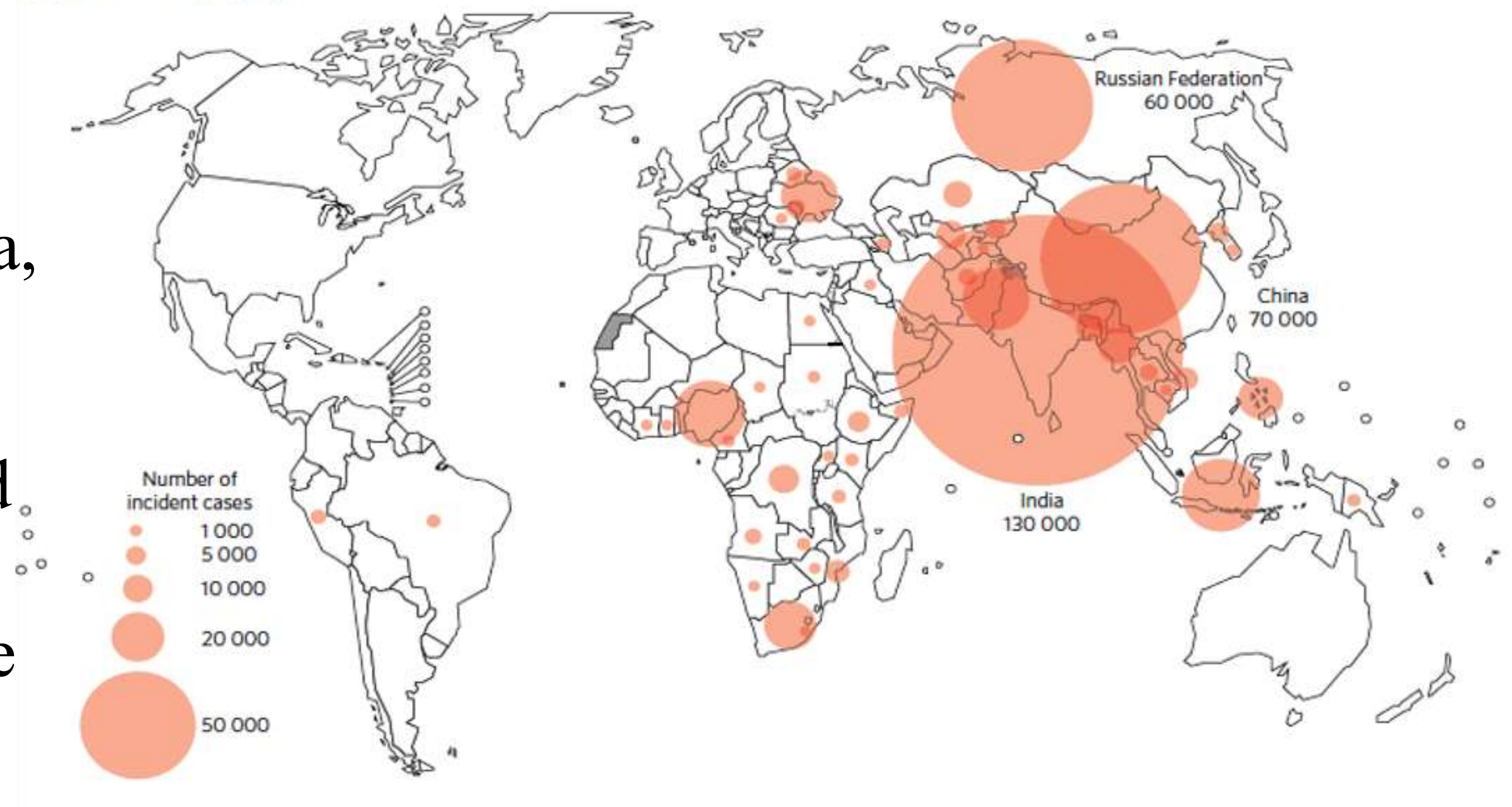


Transmission of Multidrug-Resistant Tuberculosis (MDR-TB): Roles of Internal Migrants and Local Residents in Shanghai, China

Multidrug resistant tuberculosis (MDR-TB)

- MDR-TB is caused by a strain of *Mycobacterium Tuberculosis* resistant to at least isoniazid and rifampicin, the two most effective first-line anti-TB drugs.
- **Treatment** needs at least **18 months** and costs up to **\$10 000**.
- Treatment success < **50%**
- An estimate of **490 000** MDR-TB cases globally, of which **47%** were in China, India, and Russia.
- **Transmission** of MDR-TB has been listed as one of the most dangerously pathogen and become an important public health issue worldwide (WHO, 2016).

Estimated incidence of MDR/RR-TB in 2015, for countries with at least 1000 incident cases. Areas that are not applicable are in grey.

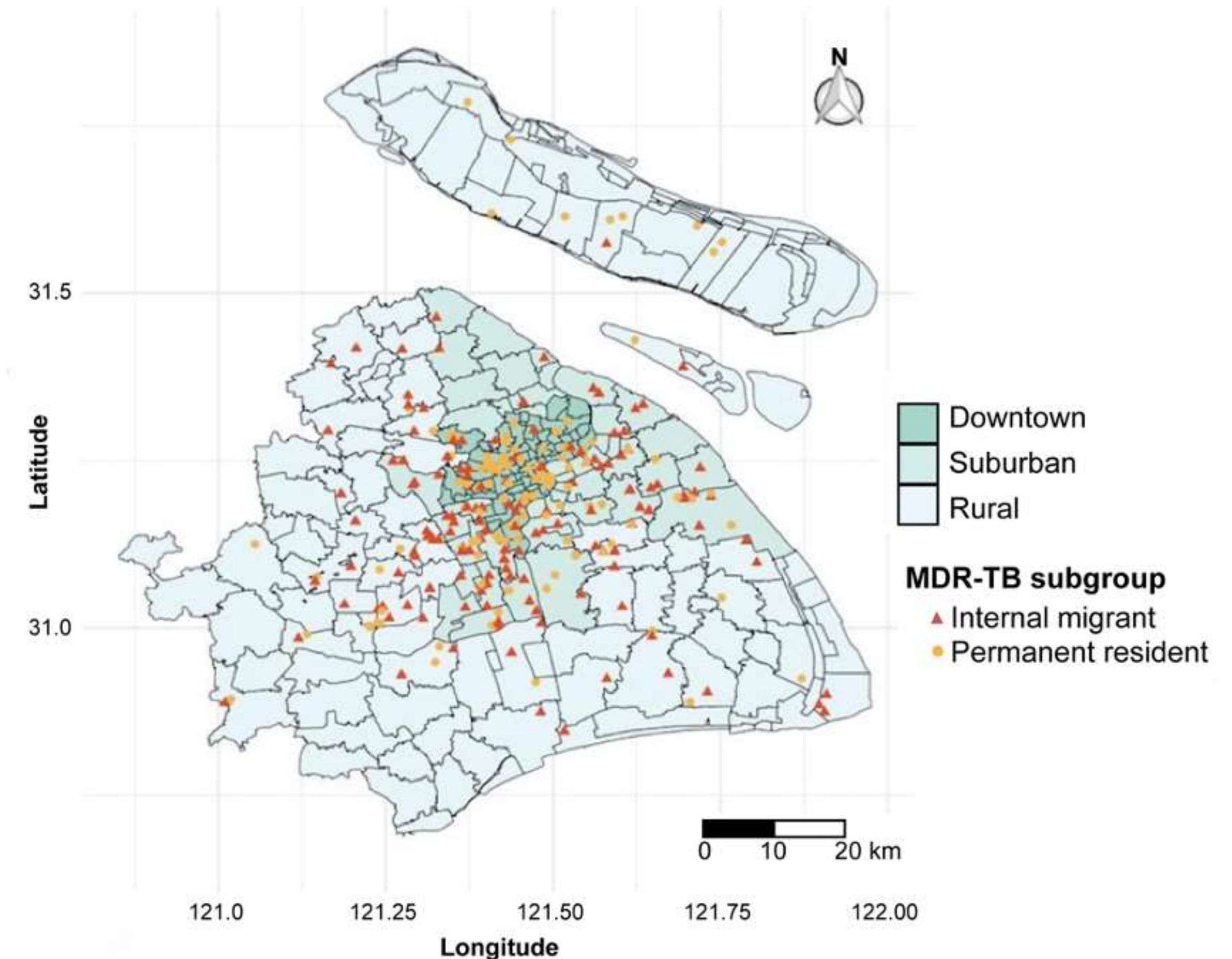


Questions

- Who played a primary roles in the **recent transmission** of MDR-TB: migrants or local residents?
- Did the two groups exhibit similar **spatial patterns** in disease transmission?
- What are the **risk factors** associated with the recent transmission of MDR-TB?

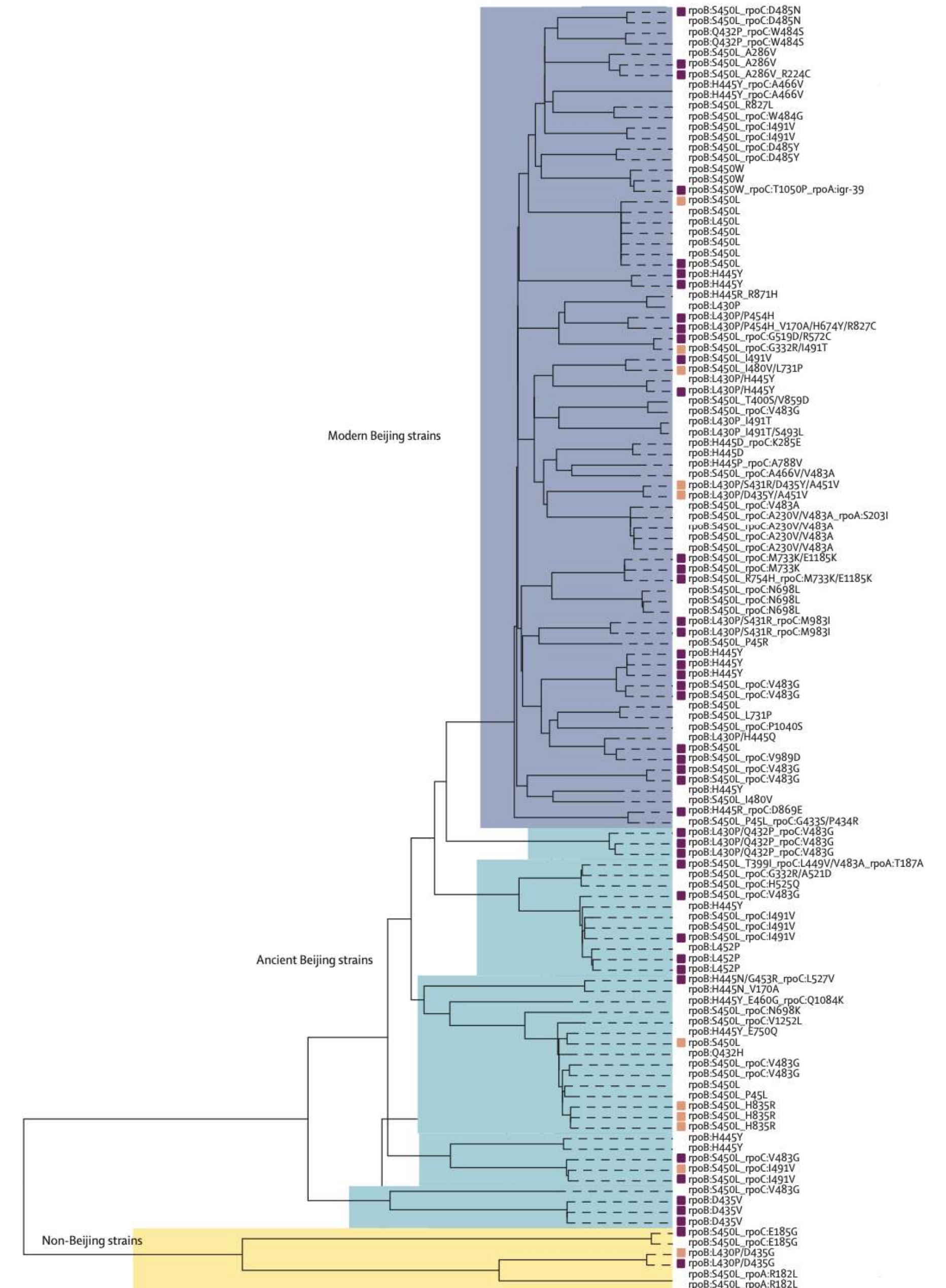
Setting

- There were 367 patients diagnosed with MDR TB in 2009-2012, accounting for **4.6% of the total TB cases**.
- **299 cases** with complete individual and genotypic information **were included** for the analyses.
- Among the cases, there were 213 (71%) in **male**, 170 cases (57%) aged **45 years** and below, and **53%** were **migrants**.
- **29%** cases in **downtown**, **45%** in **suburban**, and **25%** in **rural areas**.



Genotyping analysis

- Bacterial genomic DNA from each MDR-TB patient was genotyped using 12 VNTR loci (Yang et al, 2017 *Lancet Infectious diseases*).
- Cases whose *Mycobacterium tuberculosis* strains had an **identical genotypic pattern** were considered genotypic clustering, indicating **primary resistant** (i.e. **recent transmission**).
- Cases with a different genotypic pattern indicated reactivation of exogenous factors, suggesting **acquired resistance**.
- Strains with **cross-contamination** were **excluded**.



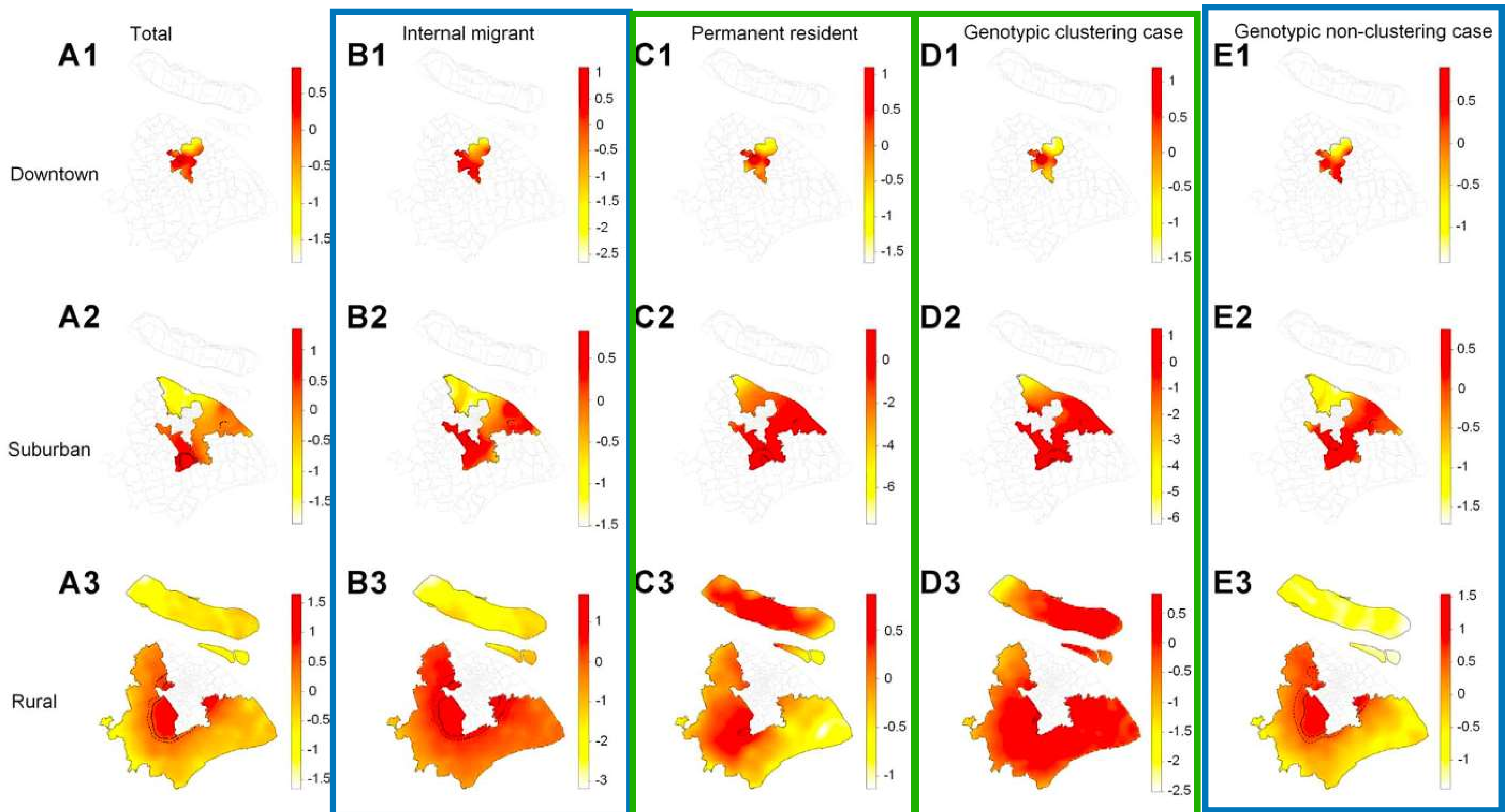


Figure A.3 Adaptive kernel smoothing estimates for log-relative risks of MDR-TB, with asymptotic tolerance contours at 0.05 [dashed] and 0.01 [solid], among **A)** the total population, **B)** internal migrants, **C)** permanent residents, **D)** genotypic clusters and **E)** genotypic non-clusters in the downtown, suburban and rural areas of Shanghai. MDR-TB = multidrug-resistant tuberculosis.

Table. Univariate analysis of risk factors associated with genotypic clustering MDR tuberculosis in migrants, local residents, and the total population.

	Total (n ₁ =115, n ₂ =184)	OR (95% CI)	Internal migrant (n ₁ = 34, n ₂ =124)	OR (95% CI)	Permanent resident (n ₁ = 81, n ₂ = 60)	OR (95% CI)
Sex						
female	n ₁ =27, n ₂ =59	1.00 (ref)	n ₁ =12, n ₂ =52	1.00 (ref)	n ₁ =15, n ₂ =7	1.00 (ref)
male	n ₁ =88, n ₂ =125	1.54 (0.88, 2.73)	n ₁ =22, n ₂ =72	1.32 (0.57, 3.21)	n ₁ =66, n ₂ =53	0.58 (0.19, 1.66)
Age, years						
15 - 34	n ₁ =33, n ₂ =90	1.00 (ref)	n ₁ =20, n ₂ =81	1.00 (ref)	n ₁ =13, n ₂ =9	1.00 (ref)
35 - 44	n ₁ =18, n ₂ =29	1.69 (0.77, 3.63)	n ₁ =9, n ₂ =20	1.83 (0.63, 4.97)	n ₁ =9, n ₂ =9	0.70 (0.17, 2.89)
45 - 64	n ₁ =47, n ₂ =51	2.50 (1.38, 4.59)	n ₁ =4, n ₂ =21	0.77 (0.17, 2.67)	n ₁ =43, n ₂ =30	0.99 (0.33, 2.89)
> 65	n ₁ =17, n ₂ =14	3.28 (1.36, 8.10)	n ₁ =1, n ₂ =2	2.01 (0.03, 40.4)	n ₁ =16, n ₂ =12	0.93 (0.26, 3.30)
Living area						
Rural	n ₁ =41, n ₂ =47	1.00 (ref)	n ₁ =6, n ₂ =40	1.00 (ref)	n ₁ =16, n ₂ =14	1.00 (ref)
Suburban	n ₁ =52, n ₂ =83	1.53 (0.81, 2.97)	n ₁ =24, n ₂ =64	2.48 (0.89, 8.09)	n ₁ =19, n ₂ =28	1.29 (0.46, 3.58)
Downtown	n ₁ =22, n ₂ =54	2.13(1.07, 4.33)	n ₁ =4, n ₂ =20	1.33 (0.25, 6.36)	n ₁ =37, n ₂ =27	1.20 (0.46, 3.13)
Neighbourhoods						
< 50,000 people	n ₁ =32, n ₂ =74	1.00 (ref)	n ₁ =12, n ₂ =53	1.00 (ref)	n ₁ =20, n ₂ =21	1.00 (ref)
≥ 50,000 people	n ₁ =83, n ₂ =110	1.74 (1.03, 2.99)	n ₁ =22, n ₂ =71	1.37 (0.59, 3.32)	n ₁ =61, n ₂ =39	1.64 (0.74, 3.64)
Migrant proportion						
< 50%	n ₁ =82, n ₂ =132	1.00 (ref)	n ₁ =17, n ₂ =83	1.00 (ref)	n ₁ =65, n ₂ =49	1.00 (ref)
≥ 50%	n ₁ =33, n ₂ =52	1.02 (0.59, 1.76)	n ₁ =17, n ₂ =41	2.01 (0.87, 4.69)	n ₁ =16, n ₂ =11	1.10 (0.43, 2.86)
Beijing strains						
No	n ₁ =7, n ₂ =26	1.00 (ref)	n ₁ =1, n ₂ =21	1.00 (ref)	n ₁ =6, n ₂ =5	1.00 (ref)
Yes	n ₁ =108, n ₂ =158	2.53 (1.02, 7.16)	n ₁ =33, n ₂ =103	6.68 (1.00, 28.6)	n ₁ =75, n ₂ =55	1.14 (0.26, 4.72)

n₁: counts of genetic clustering case.

n₂: counts of non-genetic clustering case.

Conclusion

- In Shanghai, **permeant residents** were significantly associated with **primary transmission** of MDR-TB in **downtown** area.
- **Migrants'** cases clustering in **suburban** and **rural** areas were more likely to obtain MDR-TB through **acquired resistance**.
- In summary, effective intervention should be meticulously tailored, accounting for the diverse demographics of **population**, the unique geographic characteristics of each **region**, and the intricate **mechanisms** underlying the transmission and spread of the disease.

Reference

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Thank you!

Questions & Comments?