

THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Liu y, Chan T-C, Yap L-W, et al. Resurgence of scarlet fever in China: a 13-year population-based surveillance study. *Lancet Infect Dis* 2018; published online May 29. [http://dx.doi.org/10.1016/S1473-3099\(18\)30231-7](http://dx.doi.org/10.1016/S1473-3099(18)30231-7).

Supplementary Web Appendix

Supplement 1: Diagnostic Criteria for Scarlet Fever Issued by Ministry of Health, People's Republic of China released on February 28, 2008 (WS 282-2008)

1 Scope

This standard specifies the diagnostic basis, diagnostic principles, diagnosis and differential diagnosis for scarlet fever.

This standard applies to nationwide medical institutions and their staff to diagnose and report scarlet fever.

2 Terms and definitions

The following terms and definitions apply to this standard.

2.1 White strawberry tongue

The tongue has a white coating on it, while the papillae of the tongue are swollen and reddened, standing out on the white coating, making the tongue resemble a strawberry.

2.2 Red strawberry tongue

White strawberry tongue following the desquamating process, or the shedding of the tissue which created the white coating) the whiteness disappears while the red and enlarged papillae give it the "red strawberry" appearance.

2.3 Pastia's lines

Lines of petechiae which appear as pink/red areas located in arm pits and elbow pits.

2.4 Circumoral pallor

Obvious facial hyperemia compared to hyperemia of the nose and mouth, appearing to be white.

3 Diagnostic basis

3.1 Epidemiology history

Local occurrence and prevalence of the disease, with exposure to scarlet fever patients or to tonsillitis, angina, otitis media, erysipelas or other streptococcal infected patients.

3.2 Clinical manifestations

3.2.1 Common scarlet fever

Abrupt onset with fever, angina, and rash. Rash is observed on the second day of fever; the skin has disseminated hyperemia and flushing, among which congestive rash as small as a needle's point can be seen that fades with pressing, accompanied by itching. A small number of patients can have a rash with yellow-white pustules, which do not break easily. Pastia's lines may form on skin creases. Facial hyperemia emerges without rash, accompanied by "circumoral pallor". In early onset of the disease, "white strawberry tongue" is seen and is more severe toward the edge of the tongue. After 2-3 days the white coating begins to fall off, forming a "red strawberry tongue". After 2-5 days the rash subsides, after which the skin has desquamation or furfur.

3.2.2 Mild scarlet fever

Fever, angina and rash are mild and short of duration; desquamation is also mild.

3.2.3 Toxic type

The main clinical manifestation is toxemia, with obvious poisoning symptoms, like fever, headache, vomiting, hemorrhagic rash, confusion, etc. Angina is not severe. Toxic myocarditis, toxic hepatitis and septic shock can occur.

3.2.4 Sepsis type

Pharyngeal swelling with exudation of pus or even ulcers, causing cervical lymphadenitis, acute otitis media, acute sinusitis, etc. Can also cause sepsis.

3.2.5 Surgical and obstetric type

Pathogenic bacteria invade from the wound or birth canal. Local rash at first, which extends to the whole body with no pharyngitis. Systemic symptoms are mostly mild.

3.3 Laboratory testing

3.3.1 The total number of leukocytes and neutrophils increases, with possible toxic granulation for severe patients.

3.3.2 Group A *Streptococcus* by rapid antigen detection is positive.

3.3.3 The result of bacteria identification is the β hemolytic streptococcus by bacterial culture and by microscopy.

3.3.4 The result of a bacitracin-sensitive test is positive.

3.3.5 The result of biochemical identification is *Streptococcus pyogenes*.

3.3.6 Throat swab or other focal secretion is identified as Group A β hemolytic streptococcus by bacteria serotyping.

4 Diagnostic principles

Comprehensive diagnosis should be based on epidemiological data, clinical manifestations and laboratory tests. Confirmation must be based on etiological examination.

5 Diagnosis

5.1 Probable cases

Satisfying clinical manifestations in 3.2 and 3.3.1.

5.2 Clinical diagnosis of cases

Meeting any of the following for diagnosis:

5.2.1 Probable cases satisfying 3.1.

5.2.2 Probable cases satisfying at least one of 3.3.2, 3.3.3, 3.3.4, or 3.3.5.

5.3 Confirmed cases

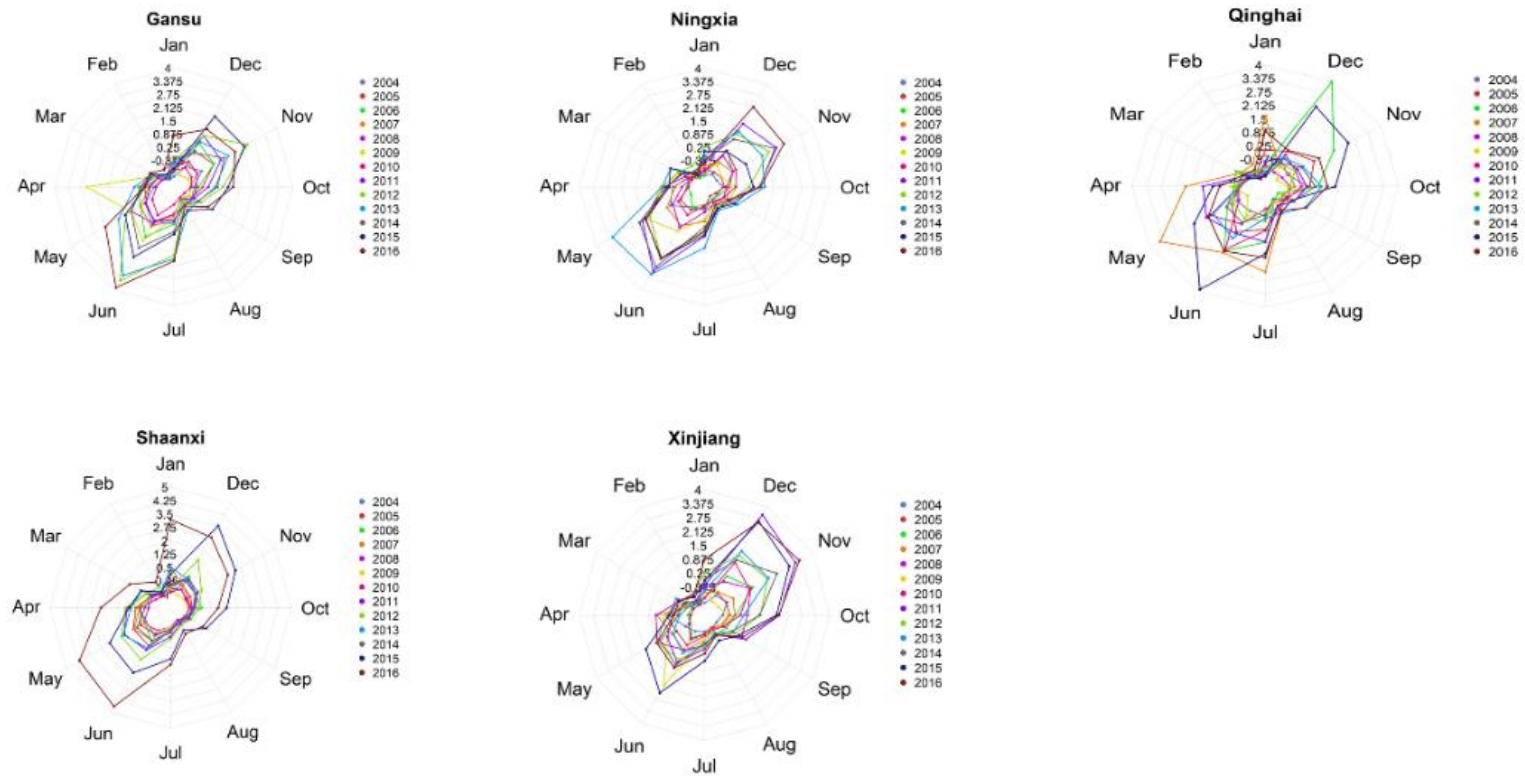
Clinical diagnosis of cases satisfying 3.3.6.

Supplement 2: Introduction for the Joinpoint regression

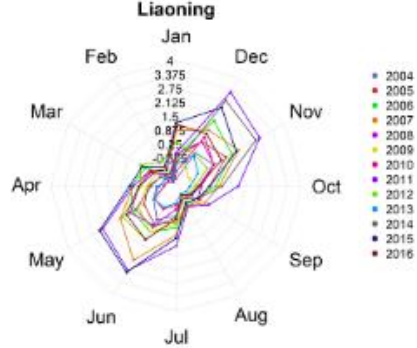
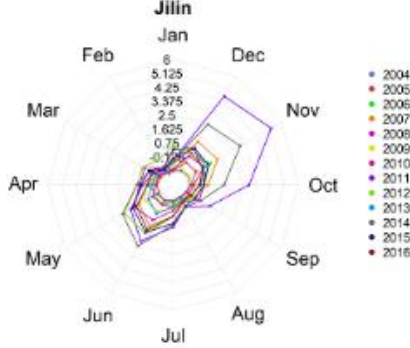
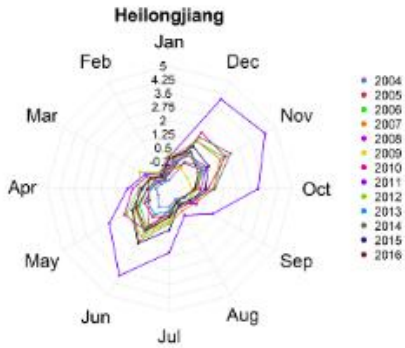
Joinpoint regression analysis is conducted with Joinpoint Regression Program version 4.5.0.1 (Statistical Research and Applications Branch, National Cancer Institute). Joinpoint regression analysis fits a series of joined linear models of the natural logarithm of annual incidence using calendar year as an independent variable [Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for Joinpoint regression with applications to cancer rates. *Stat Med* 2001; 28;20 (4):655], which is useful to describe changes in trend data. We allow a maximum of 2 joinpoints and use a permutation test to select the best-fitted model with the significance level of 0.05 and 4,499 randomly permuted data sets as suggested by the software. We report the segments with statistical significance ($p < 0.05$) in table 1. In Jiangxi and Shaanxi, there are only some years with a significant surging trend during the studied period. The p -value for a two-sided test that the true annual percentage change is zero is calculated based on a t distribution, and the parametric method is used to calculate 95% CIs.

Supplement 3: Seasonal distribution of scarlet fever cases reported in 31 provinces of China during 2004 to 2016

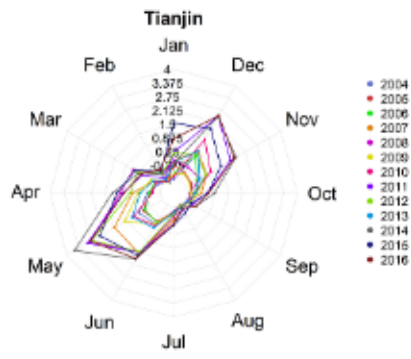
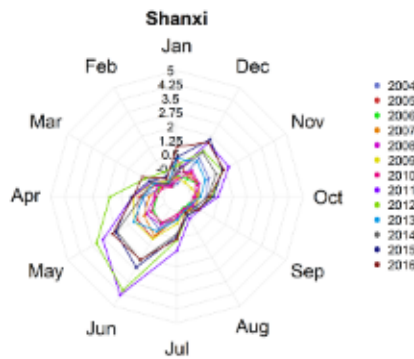
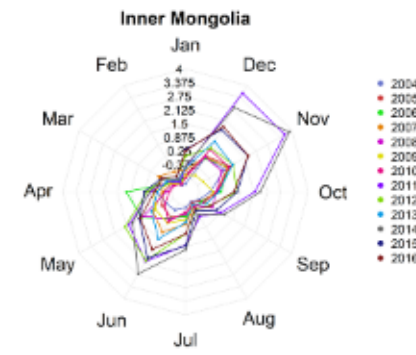
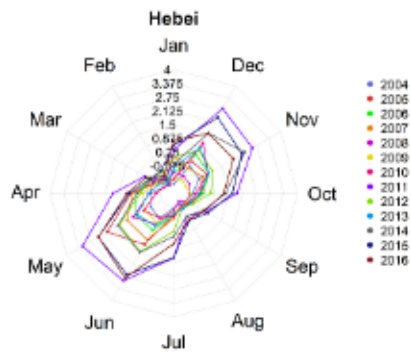
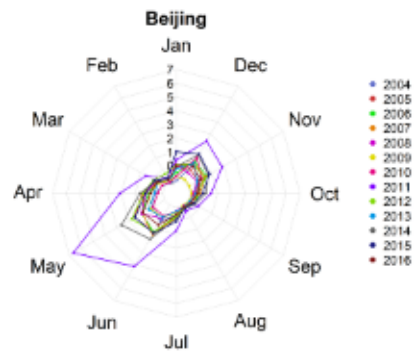
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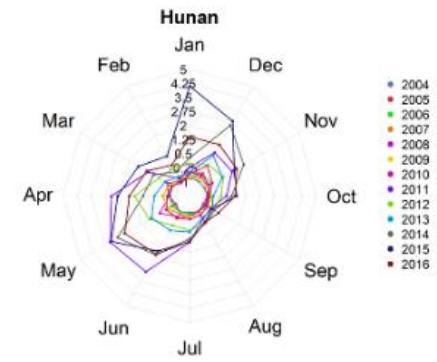
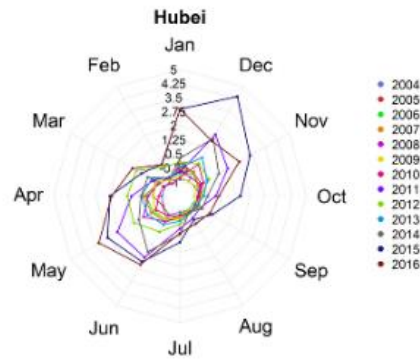
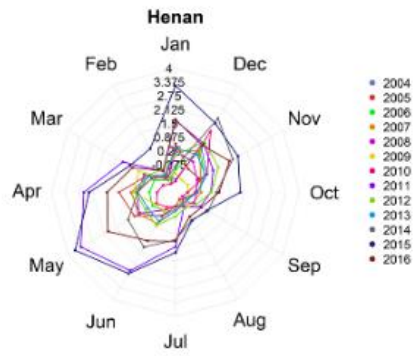
(B) Northeast China



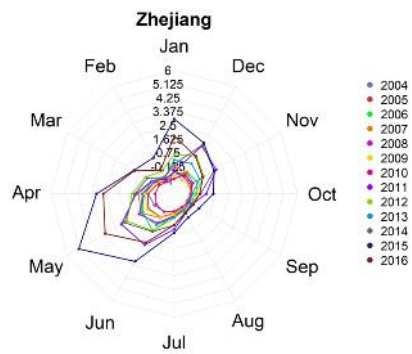
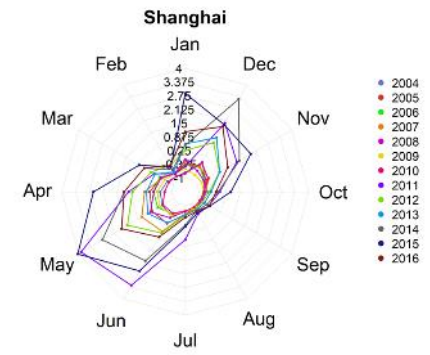
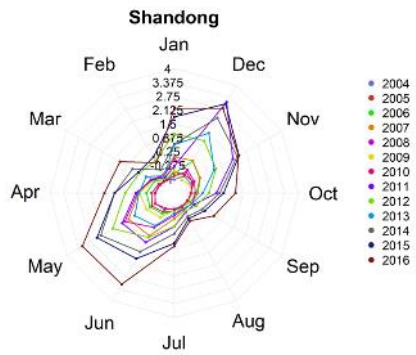
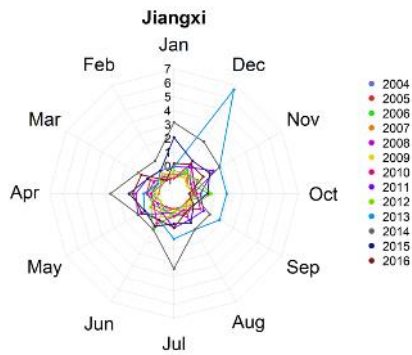
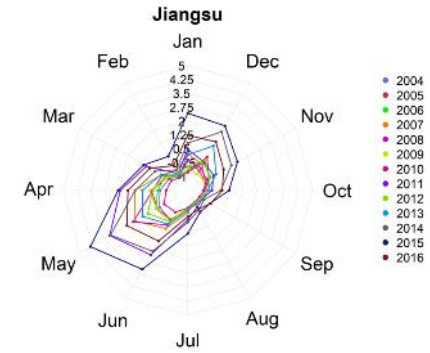
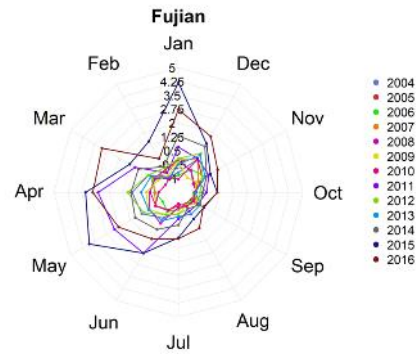
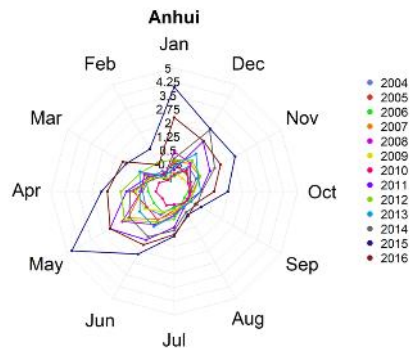
(C) North China



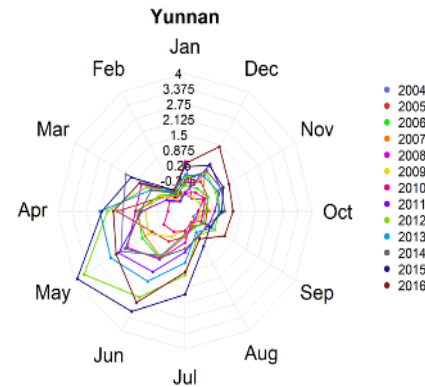
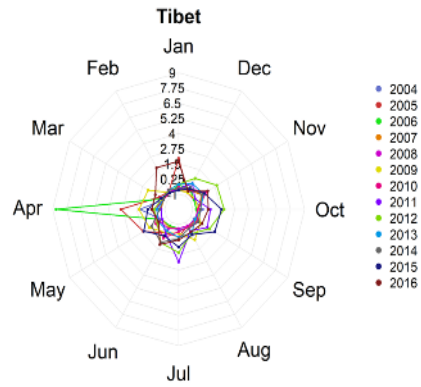
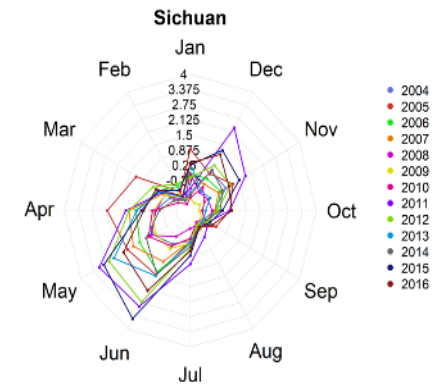
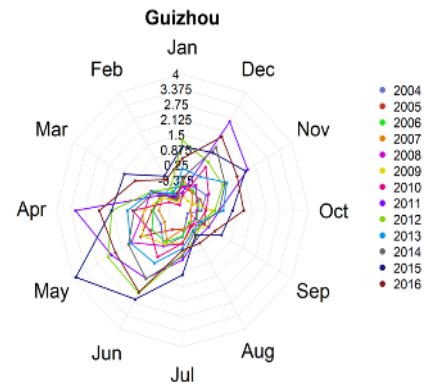
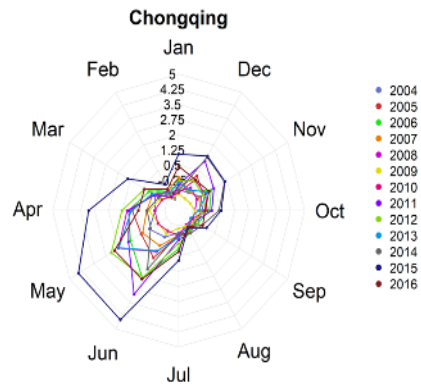
(D) Central China



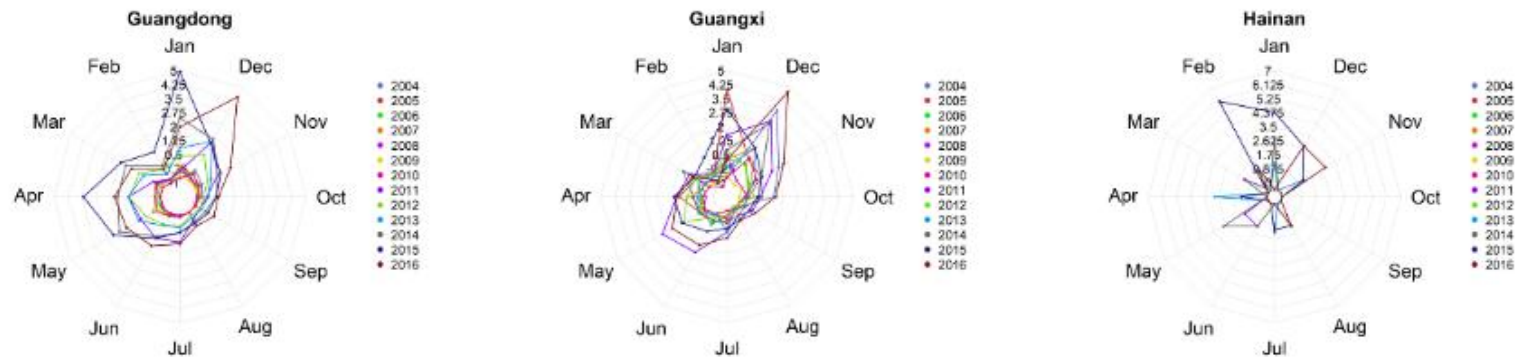
(E) East China



(F) Southwest China



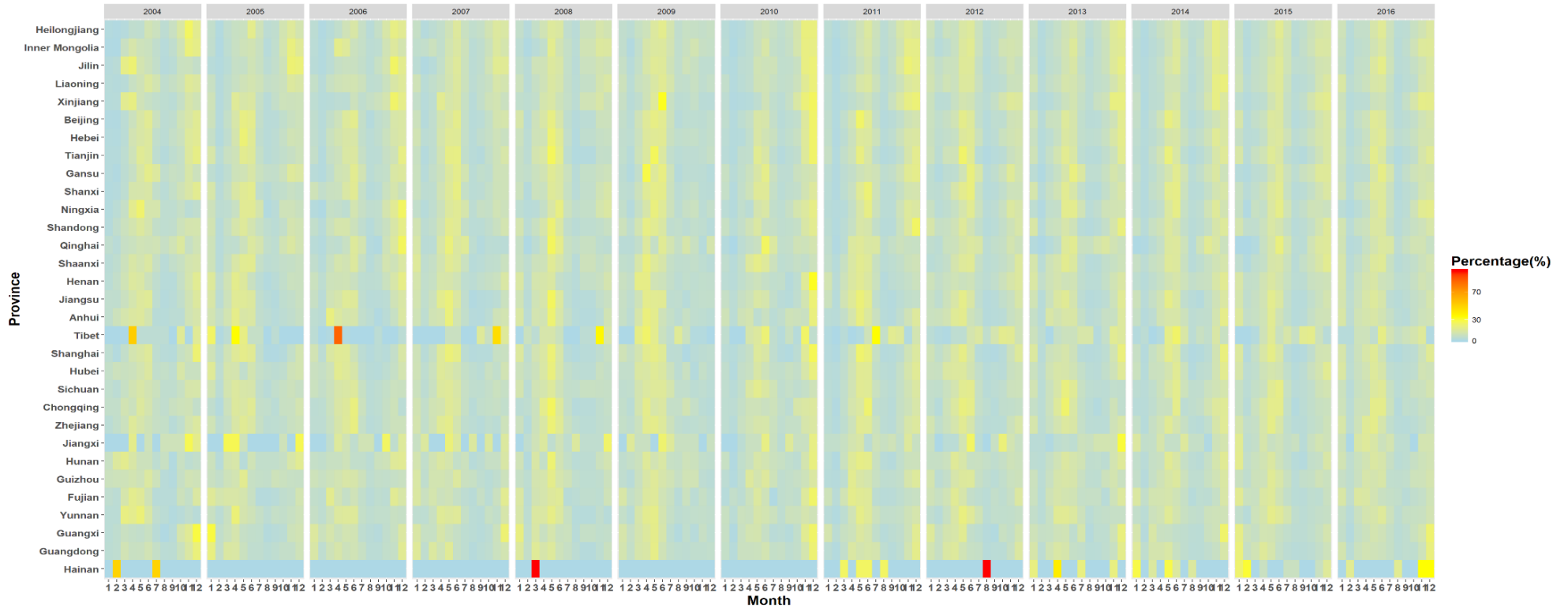
(G) South China



Notes: We standardized monthly incidences of scarlet fever for different areas, then applied a radar chart to display Z scores of incidence in each area by using R package fmsb (<https://cran.r-project.org/web/packages/fmsb/index.html>). There were 12 spikes in the radar chart representing 12 months in a year and different colors represented different years.

Supplement 4: Seasonal distribution of scarlet fever cases reported in 31 provinces of China from 2004 to 2016

(N=502,723)



Notes: The provinces were ordered by latitude from northernmost (top) to southernmost (bottom) in the heat map. Time series of cases standardized by the proportion of annual cases. A heat map created using the gplot package in R software (<https://cran.r-project.org/web/packages/gplots/index.html>).

Supplement 5: Estimated incidence rate ratios of different months before and after the 2011 upsurge of scarlet fever, China

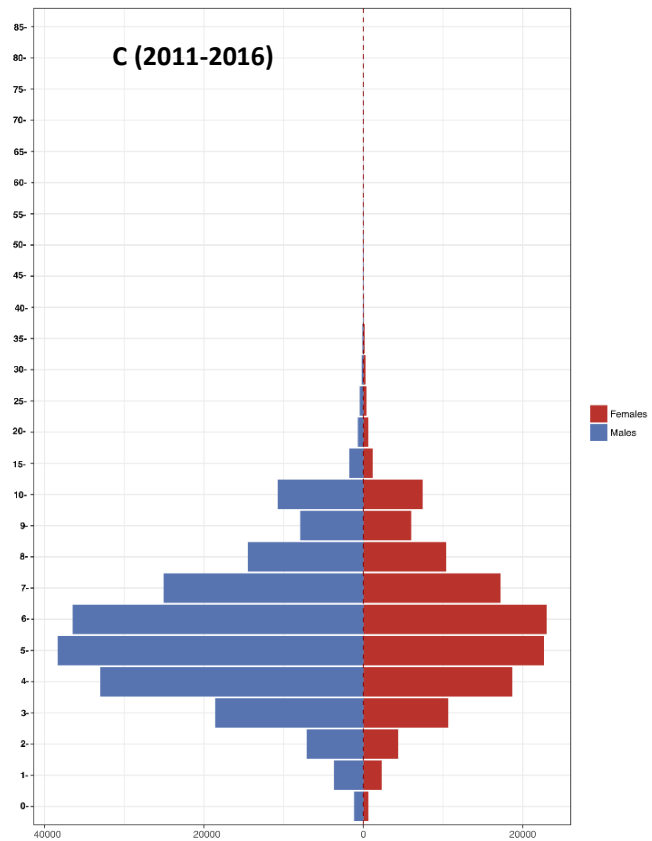
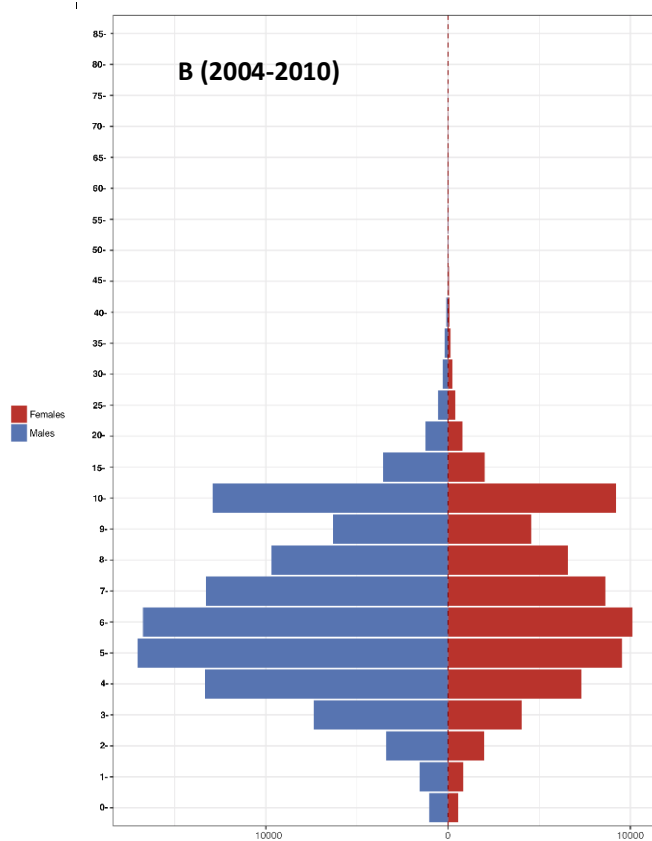
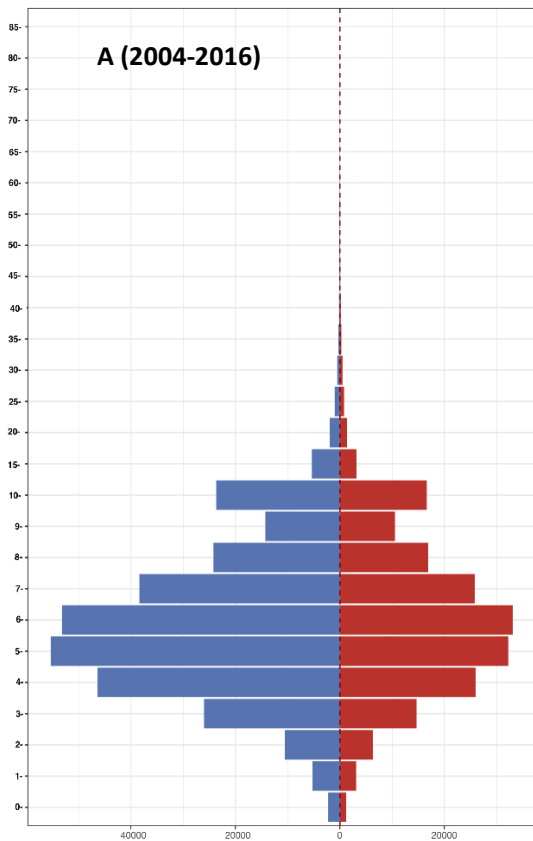
Month	No. of cases			Average annual incidence (per 100 000 population)			Incidence rate ratios (Post/pre-upsurge)
	Overall	Pre-upsurge	Post-upsurge	Overall	Pre-upsurge	Post-upsurge	
January	37789	11896	25893	0.2165	0.1293	0.3183	2.46
February	15624	5513	10111	0.0896	0.0599	0.1243	2.08
March	31423	11896	19527	0.1805	0.1293	0.2403	1.86
April	46938	18677	28261	0.2699	0.2030	0.3479	1.71
May	70330	24213	46117	0.4036	0.2629	0.5678	2.16
June	68651	23670	44981	0.3941	0.2572	0.5538	2.15
July	35028	12241	22787	0.2011	0.1330	0.2805	2.11
August	17091	6709	10382	0.0982	0.0728	0.1278	1.75
September	22744	8616	14128	0.1307	0.0936	0.1739	1.86
October	35753	12669	23084	0.2054	0.1377	0.2843	2.06
November	56388	19151	37237	0.3237	0.2082	0.4585	2.20
December	64703	20590	44113	0.3711	0.2237	0.5431	2.43

Supplement 6: Estimated incidence rate ratios of the age groups before and after the 2011 upsurge of scarlet fever, China

Age groups	No. of cases			Average annual incidence (per 100 000 population)			Incidence rate ratios (Post/pre-upsurge) [95% CI]
	Overall	Pre-upsurge	Post-upsurge	Overall	Pre-upsurge	Post-upsurge	
0-	3401	1599	1802	1.6573	1.3552	2.0098	1.48 (1.39-1.59)
1-	8344	2399	5945	4.0141	2.1748	6.1599	2.83(2.7-2.97)
2-	16817	5368	11449	8.2368	4.7366	12.3203	2.60(2.52-2.69)
3-	40671	11398	29273	20.6481	10.1193	32.9318	3.25 (3.18-3.33)
4-	72353	20658	51695	38.1961	18.7518	60.8810	3.25(3.19-3.30)
5-	87567	26570	60997	48.7749	25.2026	76.2760	3.03(2.98-3.07)
6-	86309	26840	59469	49.4675	26.4598	76.3098	2.88(2.84-2.93)
7-	64172	21892	42280	34.5623	21.8951	49.3406	2.25(2.22-2.29)
8-	41098	16239	24859	20.0628	15.5376	25.3422	1.63(1.6-1.66)
9-	24807	10860	13947	13.2772	9.4460	17.7469	1.88(1.83-1.93)
10-	40313	22123	18190	3.7532	3.1945	4.4051	1.38(1.35-1.41)
15-	8494	5555	2939	0.5921	0.6518	0.5225	0.80(0.77-0.84)
20-	3341	2039	1302	0.2261	0.2704	0.1744	0.65(0.6-0.69)
25-	1796	927	869	0.1438	0.1425	0.1453	1.02(0.93-1.12)
30-	1010	534	476	0.0785	0.0717	0.0864	1.21(1.06-1.36)
35-	614	328	286	0.0409	0.0387	0.0436	1.13(0.96-1.32)
40-	347	179	168	0.0237	0.0235	0.0240	1.02(0.83-1.26)
45-	213	89	124	0.0169	0.0153	0.0189	1.23(0.94-1.62)
50-	156	66	90	0.0144	0.0110	0.0184	1.67(1.22-2.3)

55-	117	54	63	0.0112	0.0109	0.0115	1.05 (0.73-1.52)
60-	75	41	34	0.0109	0.0122	0.0095	0.77 (0.49-1.23)
65-	60	30	30	0.0124	0.0112	0.0138	1.24 (0.74-2.04)
70-	37	20	17	0.0098	0.0094	0.0104	1.10 (0.58-2.11)
75-	24	13	11	0.0104	0.0114	0.0084	0.74 (0.33-1.64)
80-	11	5	6	0.0096	0.0103	0.0089	0.86 (0.26-2.83)
>85	5	4	1	0.0254	0.0380	0.0065	0.17 (0.02-1.53)

Supplement 7: Comparison of gender distribution in scarlet fever cases reported in pre-upsurge period (2004-2010) and post-upsurge period (2011-2016), China



Notes: Demographic pyramid by age and sex was generated by the gplot package in R software (<https://cran.r-project.org/web/packages/gplots/index.html>)

Supplement 8: Estimated incidence rate ratios of female and male population before and after the 2011 upsurge of scarlet fever, China

Age groups (Years)	Average annual incidence (per 100 000 population)								Incidence rate ratios (Post/pre-upsurge)	
	Pre-upsurge				Post-upsurge				Male	Female
	Male	Female	Sex ratio (M/F)	p value	Male	Female	Sex ratio (M/F)	p value		
Overall	2.3036	1.4967	1.54	<0.0001	4.8259	3.1873	1.51	<0.0001	2.09	2.13
0-	1.7090	0.9751	1.75	<0.0010	2.4625	1.5563	1.58	<0.0003	1.44	1.60
1-	2.6930	1.6048	1.68	<0.0001	6.7754	4.9400	1.37	<0.0001	2.52	3.08
2-	5.7194	3.6655	1.56	<0.0001	13.7167	9.8560	1.39	<0.0001	2.40	2.69
3-	12.5155	7.4954	1.67	<0.0001	37.5330	25.2274	1.49	<0.0001	3.00	3.37
4-	23.0611	13.9938	1.65	<0.0001	68.6647	45.5692	1.51	<0.0001	2.98	3.26
5-	30.4353	19.2857	1.58	<0.0001	84.0854	57.7952	1.45	<0.0001	2.76	3.00
6-	30.8195	21.4377	1.44	<0.0001	80.9738	59.1269	1.37	<0.0001	2.63	2.76
7-	24.6351	18.7010	1.32	<0.0001	51.2399	38.8757	1.32	<0.0001	2.08	2.08
8-	17.3729	13.4363	1.29	<0.0001	26.6026	20.4172	1.30	<0.0001	1.53	1.52
9-	10.2197	8.5515	1.20	<0.0179	17.0138	15.8544	1.07	<0.0635	1.66	1.85
10-	3.5102	2.8346	1.24	<0.0001	4.6062	3.7707	1.22	<0.0001	1.31	1.33
15-	0.7941	0.4954	1.60	<0.0001	0.5944	0.4158	1.43	<0.0002	0.75	0.84
20-	0.3205	0.2166	1.48	<0.0003	0.1800	0.1569	1.15	<0.3637	0.56	0.72

25-	0.1618	0.1225	1.32	<0.1094	0.1525	0.1299	1.17	<0.3913	0.94	1.06
30-	0.0785	0.0646	1.22	<0.5668	0.0821	0.0887	0.93	<0.8143	1.05	1.37
35-	0.0435	0.0338	1.29	<0.4819	0.0396	0.0433	0.91	<0.8633	0.91	1.28
40-	0.0273	0.0195	1.40	<0.4863	0.0239	0.0214	1.12	<0.9370	0.87	1.10
45-	0.0141	0.0166	0.85	<0.9703	0.0202	0.0155	1.30	<0.6972	1.43	0.93
50-	0.0105	0.0116	0.91	<1.0000	0.0222	0.0152	1.46	<0.6917	2.11	1.32
55-	0.0113	0.0107	1.06	<1.0000	0.0133	0.0109	1.22	<1.0000	1.18	1.02
60-	0.0144	0.0115	1.25	<0.7093	0.0085	0.0100	0.85	<1.0000	0.59	0.86
65-	0.0112	0.0112	1.00	<1.0000	0.0118	0.0119	0.99	<1.0000	1.05	1.06
70-	0.0149	0.0096	1.55	<0.9926	0.0130	0.0039	3.33	<0.9926	0.87	0.41
75-	0.0184	0.0097	1.90	<1.0000	0.0151	0.0079	1.91	<1.0000	0.82	0.82
80-	0.0197	0.0120	1.64	-	0.0112	0.0050	2.24	<0.9182	0.57	0.41
>85	0.0466	0.0321	1.45	-	0.0171	0.0000	-	-	0.37	0.00

Note: “-” = no data.

Supplement 9: Comparison of occupational distribution in the scarlet fever cases between the children (<15 years) and adults (≥ 15 years) during pre-upsurge period (2004-2010) and post-upsurge period (2011-2016) in China

Occupation	Percentage of childhood cases				Percentage of adult cases			
	Overall (N1=18 663)	Pre-upsurge period (n1=4 395)	Post-upsurge period (n2=14 268)	p vale	Overall period (N2=248)	Pre-upsurge period (n3=125)	Post-upsurge period (n4=123)	p vale
Kindergarten	44.33% (8274/18663)	40.14% (1764/4395)	45.63% (6510 /14268)	0.0000	-	-	-	
Students	34.76% (6487/18663)	34.63% (1522 /4395)	34.80%(4965/14268)	0.8381	25.40% (63/248)	30.40% (38/125)	20.33% (25/123)	00684
Prenursery-aged children	20.86% (3894/18663)	25.21% (1108/4395)	19.53% (2786/14268)	0.0000	-	-	-	
Workers	-	-	-		21.77% (54/248)	21.60% (27/125)	21.95% (27/123)	0.9466
Farmers	-	-	-		17.34% (43/248)	10.40% (13/125)	24.39% (30/123)	0.0036
Teachers	-	-	-		6.05% (15/248)	8.00% (10/125)	4.07% (5/123)	0.1937
Businesspeople	-	-	-		7.26% (18/248)	8.00% (10/125)	6.50% (8/123)	0.6498
Others	-	-	-		5.65% (14/248)	7.20% (9/125)	4.07% (5/123)	0.2848
Housekeepers	0.01% (1/18663)	0.02% (1/4395)	-		5.24% (13/248)	4.00% (5/125)	6.50% (8/123)	0.3763
Catering staff	-	-	-		1.61% (4/248)	3.20% (4/125)	-	
Officers	-	-	-		3.63% (9/248)	2.40% (3/125)	4.88% (6/123)	0.2968
Retirees	-	-	-		0.81% (2/248)	1.60% (2/125)	-	
Unknown	0.04% (7/18663)	-	0.05% (7/14268)		2.42% (6/248)	0.80% (1/125)	4.07% (5/123)	0.0943
Waiters	-	-	-		0.81% (2/248)	0.80% (1/125)	0.81% (1/123)	0.9909
Fishing (boat) people	-	-	-		0.40% (1/248)	0.80% (1/125)	-	
Healthcare personnel	-	-	-		1.61% (4/248)	0.80% (1/125)	2.44% (3/123)	0.3056

Notes: Prenursery-aged children refer to children aged 0-2 years who are taken care of by family members and/or a nanny at home. Kindergarten is a form of education for children 3-6 years old. Students refers to those over 7 years old studying in primary school through college. Healthcare personnel are individuals who provide preventive, curative, promotional or rehabilitative health care services in a systematic way to people, families or communities. “-” = no case.

Supplement 10: Comparison of case fatality rate (CFR) and annual mortality of scarlet fever cases reported in pre-upsurge (2004-2010) and post-upsurge periods (2011-2016) in China

Area	Pre-upsurge period				Post-upsurge period				<i>p</i> value*
	No. of cases	No. of deaths	CFR (%)	Annual mortality (per 100 000)	No. of cases	No. of deaths	CFR (%)	Annual mortality (per 100 000)	
Overall	176401	4	0.0023	0.0001	326322	6	0.0018	0.000112	0.748
Beijing	12269	0	0.0000	0	21775	0	0.0000	0	
Tianjin	3946	0	0.0000	0	8365	0	0.0000	0	
Hebei	10413	0	0.0000	0	20059	0	0.0000	0	
Shanxi	7774	0	0.0000	0	15692	0	0.0000	0	
Inner Mongolia	9272	0	0.0000	0	16701	0	0.0000	0	
Liaoning	25946	0	0.0000	0	28734	1	0.0035	0.00115	1.000
Jilin	9079	0	0.0000	0	17407	0	0.0000	0	
Heilongjiang	20182	1	0.0050	0.0013	23373	3	0.0128	0.002603	0.629
Shanghai	4152	0	0.0000	0	18458	0	0.0000	0	
Jiangsu	6488	0	0.0000	0	12413	1	0.0081	0.00065	1.000
Zhejiang	4895	0	0.0000	0	12682	0	0.0000	0	
Anhui	1776	0	0.0000	0	3780	0	0.0000	0	
Fujian	1090	0	0.0000	0	2546	0	0.0000	0	
Jiangxi	116	0	0.0000	0	395	0	0.0000	0	
Shandong	9052	1	0.0110	0.00055	28940	0	0.0000	0	0.238
Henan	4773	0	0.0000	0	8240	0	0.0000	0	

Hubei	1556	0	0.0000	0	4296	0	0.0000	0	
Hunan	856	0	0.0000	0	4009	1	0.0249	0.001516	
Guangdong	2260	0	0.0000	0	11593	0	0.0000	0	
Guangxi	1576	0	0.0000	0	2301	0	0.0000	0	
Hainan	3	0	0.0000	0	36	0	0.0000	0	
Chongqing	1868	0	0.0000	0	2945	0	0.0000	0	
Sichuan	8501	0	0.0000	0	9960	0	0.0000	0	
Guizhou	2236	0	0.0000	0	3785	0	0.0000	0	
Yunnan	5003	1	0.0200	0.00115	8608	0	0.0000	0	0.368
Tibet	324	0	0.0000	0	467	0	0.0000	0	
Shaanxi	5436	0	0.0000	0	10114	0	0.0000	0	
Gansu	4155	0	0.0000	0	6630	0	0.0000	0	
Qinghai	1567	1	0.0638	0.00925	1685	0	0.0000	0	0.482
Ningxia	2311	0	0.0000	0	5574	0	0.0000	0	
Xinjiang	7526	0	0.0000	0	14759	0	0.0000	0	

Notes: CFR=case fatality ratio; **p* values are for comparison of the CFR of scarlet fever cases reported in pre-upsurge (2004-2010) and post-upsurge periods (2011-2016), China. No significant difference was found in the annual mortality across China between pre and post upsurge period ($p=0.953$)

Supplement 11: Clinical characteristics of fatal scarlet fever cases reported in pre-upsurge (2004-2010) and post-upsurge periods (2011-2016) in China

No. of cases	Case type	Sex	Age (years)	Occupation	Onset date	Diagnosis date	Death date	Outcome
Patient 1	Clinically diagnosed case	Male	15	Farmer	2012/4/14	2012/04/17	2012/05/12	Fatal
Patient 2	Clinically diagnosed case	Female	6	Prenursery children	2012/06/30	2012/07/2	2012/07/2	Fatal
Patient 3	Clinically diagnosed case	Male	12	Student	2011/07/07	2011/07/11	2011/07/11	Fatal
Patient 4	Probable case	Male	5	Kindergarten	2009/06/12	2009/06/16	2009/06/18	Fatal
Patient 5	Clinically diagnosed case	Female	4	Prenursery children	2007/01/20	2007/01/22	2007/01/25	Fatal
Patient 6	Clinically diagnosed case	Male	6	Student	2005/06/25	2005/06/25	2005/06/25	Fatal
Patient 7	Clinically diagnosed case	Male	12	Student	2015/04/20	2015/04/24	2015/04/26	Fatal
Patient 8	Clinically diagnosed case	Female	12	Student	2005/12/09	2005/12/14	2005/12/15	Fatal
Patient 9	Clinically diagnosed case	Male	4	Prenursery children	2013/12/25	2013/12/30	2013/12/30	Fatal
Patient 10	-	-	-	-	-	-	-	Fatal

Supplement 12: Median days from onset to diagnosis and from onset to report date in pre-upsurge (2004-2010) and post-upsurge periods (2011-2016) between probable cases, clinically diagnosed and confirmed scarlet fever cases, China

Median days	Probable cases		<i>p1</i> value*	Clinically diagnosed cases			<i>p2</i> value*	Confirmed cases		<i>p3</i> value*
	Pre-upsurge (n1=114)	Post-upsurge (n2=357)		Pre-upsurge (n3=4 328)	Post-upsurge (n4=13 389)	Pre-upsurge (n5=82)		Post-upsurge (n6=647)		
From onset to diagnosis	2.0	1.5	0.013	2.0	1.5	<0.001	3.0	5.0	<0.001	
From onset to report	3.0	2.0	0.003	3.0	2.0	<0.001	4.0	3.0	0.001	
From diagnosis to report	1.0	0.5	<0.001	1.0	0.5	<0.001	1.0	-1.0	<0.001	