

Supplementary material

Rising burden of herpes zoster among general adults and increased-risk groups in eastern China, 2015–2021: a population-based cohort study

Zhenwei Li MS^{1*}, Shenjia Gu MS^{1*}, Jiajun Li MS^{1*}, Guomin Zhang MS^{1*}, Zheng Wu MPH^{1*}, Hongbo Lin MPH², Kan Chen MPH^{1,3}, Zhexin Xu MPH^{1,3}, Chuanxi Fu PhD^{1,3}

From the ¹ Zhejiang Chinese Medical University, No. 548, Binwen Rd., Hangzhou China 310053

² Yinzhou District Center for Disease Control and Prevention, No. 1221, Xueshi Rd., Ningbo, China 315100

³ Center for Vaccine Impact Assessment, Key Laboratory for Quality Monitoring and Evaluation of Vaccines and Biological Products, National Medical Products Administration, No.74, Zhongshan 2nd Rd, Guangzhou, 510080, China

Corresponding to: Dr Chuanxi Fu, Institute of Infectious Disease and Vaccine, School of Public Health, Zhejiang Chinese Medical University, E-mail address: fuchuanxi@zcmu.edu.cn.

*These authors contribute to the article equally.

Table S1 Diagnosis codes for at increased risk conditions

At increased risk conditions	ICD-10-Codes
Rheumatoid arthritis (RA)	M05.9, M06.0, M06.8
Systemic lupus erythematosus (SLE)	M32
Psoriasis (PSOR)	L40
Hematologic Malignancy (HM)	C81-C96
Human immunodeficiency virus disease (HIV)	
-Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases	B20
-Human immunodeficiency virus [HIV] disease resulting in malignant neoplasia	B21
-Human immunodeficiency virus [HIV] disease resulting in other specified diseases	B22
-Human immunodeficiency virus [HIV] disease resulting in other conditions	B23
-Unspecified human immunodeficiency virus [HIV] disease	B24
Solid Tumor (ST)	
Malignant neoplasms of lip, oral cavity and pharynx	C00-C14
Malignant neoplasms of digestive organs	C15-C26
Malignant neoplasms of respiratory and intrathoracic organs	C30-C39
Malignant neoplasms, bone and articular cartilage	C40-C41
Melanoma and other malignant neoplasms of skin	C43-C44
Malignant neoplasms of mesothelial and soft tissue	C45-C49
Malignant neoplasm of breast	C50
Malignant neoplasms of female genital organs	C51-C58
Malignant neoplasms of male genital organs	C60-C63
Malignant neoplasms of urinary tract	C64-C68
Malignant neoplasms of thyroid and other endocrine glands	C73-C75
Malignant neoplasms of ill-defined, secondary, and unspecified sites	C76-C80
Solid Organ Transplant (SOT)	
-Kidney transplant status	Z94.0
-Heart transplant status	Z94.1
-Lung transplant status	Z94.2
-Heart and lungs transplant status	Z94.3
-Liver transplant status	Z94.4
-Skin transplant status	Z94.5
-Bone transplant status	Z94.6
-Corneal transplant status	Z94.7
Hematological Stem Cell Transplant (HSCT)	Z94.84
Psoriatic arthritis	L40.5
Multiple sclerosis (MS)	G35
Inflammatory Bowel Disease (IBD)	
-Crohn's disease (CD)	K50
-Ulcerative colitis (UC)	K51

Table S2 Herpes zoster-related clinical diagnostic coding

ICD-10	Definition	Complication Category
B02.900	Zoster without complications	
B02.901	Herpes Zoster	
TCD code: BWP020 Snake herpes (Traditional Chinese Medicine)		
B02.0	Zoster encephalitis	Encephalitis
B02.1	Zoster meningitis	Meningitis
B02.2	Zoster with other nervous system involvement	Neurological
B02.201	Postherpetic geniculate ganglionitis	Neurological
B02.202	Postherpetic trigeminal neuralgia	Neurological
B02.203	Postherpetic polyneuropathy	Neurological
B02.204	Postherpetic myelitis	Neurological
B02.206	Neuralgia after herpes zoster	Neurological
B02.3	Zoster ocular disease	Ocular
B02.30	Unspecified	Ocular
B02.301	Zoster conjunctivitis	Ocular
B02.302	Zoster iridocyclitis	Ocular
B02.303	Zoster keratitis	Ocular
B02.304	Zoster scleritis	Ocular
B02.309	Other herpes zoster eye disease	Ocular
B02.7	Disseminated zoster	Cutaneous
B02.8	Zoster with other complications	Other

Table S3 Distribution of increased risk subjects by age

Health status	Age, No. (%)						
	18-29	30-39	40-49	50-59	60-69	70-79	80-
IC	378(2.16)	1230(7.02)	2330(13.30)	4110(23.46)	5185(29.59)	3211(18.33)	1078(6.15)
HSCT	3(25.00)	3(25.00)	2(16.67)	3(25.00)	1(8.33)	/	/
HM	30(2.91)	101(9.80)	125(12.12)	229(22.21)	282(27.35)	196(19.01)	68(6.60)
HIV	16(18.39)	29(33.33)	20(22.99)	10(11.49)	9(10.34)	3(3.45)	/
ST	313(1.97)	1014(6.37)	2057(12.92)	3730(23.43)	4819(30.27)	2984(18.74)	1004(6.31)
SOT	16(3.40)	83(17.62)	126(26.75)	138(29.30)	74(15.71)	28(5.94)	6(1.27)
AID	864(10.22)	1516(17.92)	1653(19.54)	1803(21.32)	1587(18.76)	769(9.09)	266(3.14)
RA	90(2.72)	247(7.47)	500(15.11)	882(26.66)	911(27.54)	494(14.93)	184(5.56)
SLE	42(21.65)	47(24.23)	51(26.29)	29(14.95)	19(9.79)	5(2.58)	1(0.52)
Psoriasis	636(16.83)	997(26.39)	823(21.78)	655(17.34)	448(11.86)	172(4.55)	47(1.24)
Psoriatic arthritis	/	4(28.57)	3(21.43)	3(21.43)	4(28.57)	/	/
MS	1(3.57)	8(28.57)	3(10.71)	6(21.43)	7(25.00)	2(7.14)	1(3.57)
IBD	95(8.36)	213(18.75)	273(24.03)	228(20.70)	198(17.43)	96(8.45)	33(2.90)
-CD	11(13.58)	18(22.22)	17(20.99)	14(17.28)	16(19.75)	2(2.47)	3(3.70)
-UC	84(7.96)	195(18.48)	256(24.27)	214(20.28)	182(17.25)	94(8.91)	30(2.84)

IC immunocompromising, *HSCT* hematopoietic stem cell transplant, *HM* hematologic malignancies, *HIV* human immunodeficiency virus disease, *ST* solid tumors, *SOT* solid-organ transplant, *AID* autoimmune disease, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *MS* multiple sclerosis, *IBD* inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis.

Table S4 Incidence (/1000 PY) of herpes zoster by health status

Health Status	No. of Cases	Person years	Incidence	95% <i>CI</i>	Incidence Rate Ratio (95% <i>CI</i>)	χ^2	<i>P</i> value
Non-IC/ AID	24623	5242497.53	4.70	4.64-4.76	1.00		
IC	769	47558.28	16.17	15.05-17.35	3.44(3.20,3.70)	1139.70	<0.001
HSCT	1	33.56	29.79	0.75-166.00*	6.34(0.89,45.04)	3.41	0.065
HM	93	2790.88	33.32	26.90-40.82	7.09(5.79,8.70)	355.69	<0.001
HIV	5	188.00	26.60	8.64-62.07*	5.66(2.36,13.61)	15.03	0.001
ST	637	42761.84	14.90	13.76-16.10	3.17(2.93,3.43)	827.26	<0.001
SOT	33	1783.99	18.50	12.73-25.98	3.94(2.80,5.54)	61.92	<0.001
AID	463	28804.54	16.07	14.64-17.61	3.42(3.12,3.75)	687.89	<0.001
RA	247	10891.76	22.68	19.94-25.69	4.83(4.26,5.47)	606.24	<0.001
SLE	11	707.77	15.54	7.76-27.81	3.31(1.83,5.98)	15.74	<0.001
Psoriasis	143	12908.91	11.08	9.34-13.05	2.36(2.00,2.78)	104.67	<0.001
Psoriatic arthritis	1	39.45	25.35	0.64-141.22*	5.40(0.76,38.31)	2.84	0.092
MS	2	70.77	28.26	3.42-102.09*	6.02(1.50,24.06)	6.44	0.011
IBD	59	4185.88	14.09	10.73-18.18	3.00(2.32,3.87)	71.08	<0.001

PY person-years, *CI* confidence interval, *AID* autoimmune disease, *IC* immunocompromising, *HSCT* hematopoietic stem cell transplant, *HM* hematologic malignancies, *HIV* human immunodeficiency virus, *ST* solid tumors, *SOT* solid-organ transplant, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *MS* multiple sclerosis, *IBD* irritable bowel disease

* Rare strata with wide *Cis*, interpret cautiously

Table S5 Incidence of PHN by group, age and sex (/1000 PY)

	General Adults		Group with Increased Risk	
	N (%)	IR (95%CI)	N (%)	IR (95% CI)
Overall	2317(8.96)	0.43(0.41, 0.45)	134(10.88)	1.75(1.47, 2.08)
Age				
18-49	1067(8.46)	0.26(0.24, 0.27)	27(9.96)	1.04(0.69, 1.51)
≥50	1250(9.44)	0.97(0.91, 1.02)	107(11.13)	2.12(1.74, 2.57)
18-29	340(10.87)	0.20(0.18, 0.22)	5(29.41)	1.15(0.37, 2.67)
30-39	305(7.85)	0.24(0.21, 0.27)	8(12.121)	0.93(0.40, 1.84)
40-49	422(7.53)	0.37(0.34, 0.41)	14(7.45)	1.08(0.59, 1.80)
50-59	512(8.41)	0.73(0.67, 0.79)	36(11.39)	2.04(1.43, 2.83)
60-69	481(9.55)	1.16(1.06, 1.27)	45(10.82)	2.27(1.66, 3.04)
70-79	201(11.89)	1.51(1.30, 1.73)	18(9.94)	1.80(1.07, 2.84)
80-	56(13.27)	1.28(0.97, 1.66)	8(16.67)	2.70(1.16, 5.31)
Sex				
Male	1067(8.71)	0.41(0.38, 0.43)	64(11.09)	1.65(1.27, 2.11)
Female	1250(9.19)	0.45(0.42, 0.47)	70(10.69)	1.86(1.45, 2.35)

PHN Postherpetic neuralgia, IR incidence rate, CI confidence interval, PY person-years.

95% CIs were calculated using exact Poisson limits.

Table S6 Incidence (IR, /1000 PY) of PHN by health status

Health Condition	N (%)	IR (95% <i>CI</i>)	<i>P</i> value vs. non-IC/non-AID
Non-IC/AID	2183(8.87)	0.42(0.40,0.43)	Reference
IC	91(11.83)	1.91(1.54,2.35)	<0.001
HSCT	0(0.00)	/	1.000
HM	15(16.13)	5.37(3.01,8.86)	<0.001
HIV	1(20.00)	5.32(0.13,29.64)	0.220
ST	72(11.30)	1.68(1.32,2.12)	<0.001
SOT	3(9.09)	1.68(0.35,4.91)	0.153
AID	43(9.29)	1.49(1.08,2.01)	<0.001
RA	19(7.69)	1.74(1.05,2.72)	0.002
SLE	2(18.18)	2.83(0.34,10.21)	0.107
Psoriasis	14(9.79)	1.08(0.59,1.82)	0.329
Psoriatic arthritis	0(0.00)	/	1.000
MS	0(0.00)	/	1.000
IBD	8(13.56)	1.67(0.67,3.45)	0.018
-CD	0(0.00)	/	1.000
-UC	8(14.29)	2.03(0.87,3.99)	0.012

IR incidence rate, *PY* person-years, *PHN* Postherpetic neuralgia, *CI* confidence interval, *IC* immunocompromising, *HSCT* hematopoietic stem cell transplant, *HM* hematologic malignancies, *HIV* human immunodeficiency virus disease, *ST* solid tumors, *SOT* solid-organ transplant, *AID* autoimmune disease, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *MS* multiple sclerosis, *IBD* inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis.

Supplementary Table S7 Crude incidence rate and standardized incidence rate (/1000 person-year) of herpes zoster among adults from 2015 to 2021

Group	Year	Cases	Person-years	Crude rate(95%CI)	Standardized incidence rate (95%CI) *
Male	2015	1202	381794	3.15(2.97-3.33)	4.30(4.05-4.55)
	2016	1406	380529	3.69(3.50-3.89)	4.98(4.69-5.27)
	2017	1666	377212	4.42(4.21-4.63)	5.70(5.41-5.99)
	2018	1851	375017	4.94(4.71-5.17)	6.24(5.93-6.55)
	2019	2065	372856	5.54(5.30-5.78)	7.01(6.68-7.34)
	2020	1999	371755	5.38(5.14-5.62)	6.90(6.57-7.23)
	2021	2065	368458	5.60(5.37-5.85)	7.06(6.71-7.41)
Female	2015	1368	403369	3.39(3.21-3.58)	5.04(4.75-5.33)
	2016	1490	402182	3.70(3.52-3.90)	5.61(5.30-5.92)
	2017	1844	398784	4.62(4.42-4.84)	6.53(6.20-6.86)
	2018	2048	396526	5.16(4.94-5.39)	7.38(7.01-7.75)
	2019	2268	394238	5.75(5.52-5.99)	7.95(7.58-8.32)
	2020	2300	392892	5.85(5.62-6.10)	8.04(7.67-8.41)
	2021	2283	389434	5.86(5.62-6.11)	7.97(7.60-8.34)
Overall	2015	2570	785163	3.27(3.15-3.40)	4.67(4.52-4.82)
	2016	2896	782711	3.70(3.57-3.84)	5.29(5.13-5.45)
	2017	3510	775996	4.52(4.37-4.68)	6.11(5.94-6.28)
	2018	3899	771543	5.05(4.90-5.21)	6.81(6.62-6.99)
	2019	4333	767094	5.65(5.48-5.82)	7.48(7.28-7.67)
	2020	4299	764557	5.62(5.46-5.79)	7.47(7.28-7.66)
	2021	4348	757892	5.74(5.57-5.91)	7.51(7.31-7.70)

CI confidence interval.

* The incidence rates for males and females were age-standardized, whereas the overall population rate was standardized for both age and sex using the direct method, with reference to China's population distribution data from 2020.

Table S8 Annual percentage change (APC) in herpes zoster from 2015 to 2021

Group	Year	Crude incidence			Standardized incidence		
		APC	95%CI	<i>P</i>	APC	95%CI	<i>P</i> value
Male	2015~2019	14.60	12.52-21.42	<0.001	12.44	8.05-17.00	0.006
	2019~2021	-0.58	-7.07-6.25	0.875	-0.20	-10.57-11.38	0.946
	2015~2021	9.30	7.40-12.00	<0.001	8.06	5.86-10.31	<0.001
Female	2015~2019	14.75	12.90-18.24	<0.001	12.48	9.83-15.20	0.002
	2019~2021	0.07	-3.73-5.24	0.931	-0.95	-7.26-5.80	0.598
	2015~2021	9.63	8.39-11.32	<0.001	7.82	6.49-9.16	<0.001
Overall	2015~2019	14.68	12.83-19.12	<0.001	12.47	10.41-14.58	0.002
	2019~2021	-0.24	-5.28-5.77	0.903	-0.58	-6.18-5.36	0.708
	2015~2021	9.48	7.98-11.52	<0.001	7.94	6.78-9.12	<0.001

CI confidence interval.

Table S9 The Direct economic expenditure of new herpes zoster patients by age and sex

	Outpatient			<i>P</i> value	Inpatient			<i>P</i> value
	NO. of cases	Mean cost (¥)	SD		NO. of cases	Mean cost (¥)	SD	
Age group				<0.001				0.212
18-29	3086	372.54	606.58		10	5461.24	3345.14	
30-39	3846	466.08	900.15		9	8550.95	8614.78	
40-49	5550	590.69	1738.35		26	6673.82	6214.37	
50-59	6039	677.77	1270.16		32	8202.59	7585.78	
60-69	4986	799.39	1700.29		46	9914.46	12747.58	
70-79	1670	837.53	1484.93		37	10470.13	14335.35	
80-	412	748.57	1169.02		11	9364.18	4941.03	
Sex				0.034				0.119
Male	12126	607.54	1202.08		82	8959.60	9744.58	
Female	13463	641.71	1552.24		89	8756.76	11235.89	

SD standard deviation.

Table S10 Healthcare resource utilization and costs of herpes zoster patients by complications

	NO.	Frequency of visits		<i>P</i> value	Costs (¥)		<i>P</i> value
		Mean	SD		Mean	SD	
Outpatient				<0.001			<0.001
No Complication	22649	2.79	3.02		566.67*	1068.38	
Complication	2940	4.52	5.04		1419.51**	2847.62	
PHN	2288	4.58	5.01		1456.79***	2232.22	
Inpatient				0.230			0.357
No Complication	76	1.09	0.33		10153.64 [#]	12946.19	
Complication	95	1.02	0.14		7814.34 ^{##}	7990.35	
PHN	60	1.03	0.18		8970.77 ^{###}	9384.62	

SD standard deviation, *PHN* postherpetic neuralgia.

The converted USD values are provided for reference:

* No complication outpatient episodes: \$85.47;

** Complication outpatient episodes: \$214.10;

*** PHN outpatient episodes: \$219.73;

[#] No complication inpatient episodes: \$1531.47;

^{##} Complication inpatient episodes: \$1178.63;

^{###} PHN inpatient episodes: \$1353.06.