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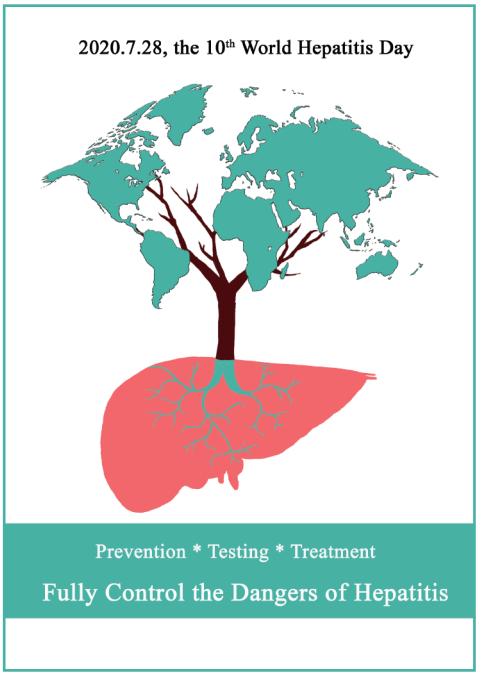

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Preplanned Studies

Burden of Acute Viral Hepatitis — China, 1990–2019

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Summary

What is already known about this topic?

The World Health Organization's (WHO) Global Health Estimates (GHE) reported that acute hepatitis caused 9,213 deaths and 307,720 person years of disability-adjusted life years (DALYs) in 2016, and acute hepatitis B accounted for 85.81% of all DALYs among acute hepatitis types A, B, C, and E in China.

What is added by this report?

In China, the percent changes in years lived with disability (YLDs) due to acute hepatitis A, B, and E in groups aged 50–69 years and 70 years or more and in all age groups for acute hepatitis C were increased from 2000 to 2019.

What are the implications for public health practices?

Effective vaccines, interventions, and treatments are key approaches to achieve the WHO's goal of reducing new hepatitis infections by 90% and deaths by 65% between 2016 and 2030.

About 1.4 million people died from viral hepatitis worldwide in 2016, and most deaths were due to cirrhosis and hepatocellular carcinoma caused by hepatitis B and C (*1*–*2*). In China, acute hepatitis caused 9,213 deaths, the number of disability-adjusted life years (DALYs) was 307,720 person years, in which acute hepatitis B accounted for 85.81% of DALYs among acute hepatitis types A, B, C, and E in 2016 (*3*). However, the nationwide incidence and prevalence of acute hepatitis were not yet reported, and the latest results were not reported. In this report, results were obtained from the latest estimates of the Global Burden of Disease Study 2019 (GBD 2019); the incidence, prevalence, deaths, and indicators of burden of acute hepatitis in 1990, 2000, and 2019 were used; and the standardized rates were calculated using the 2010 National Census as the standard population. In 2019, acute hepatitis caused 3,726 deaths, 4,501,755 cases of acute hepatitis, and 214,165 person years of DALYs; hepatitis B accounted for 66.69% of DALYs among hepatitis A, B, C, and E; percent changes of YLDs in groups aged 50–69 years and 70 years or more for acute hepatitis A, B, and E and in all age groups for acute hepatitis C were increased from 2000 to 2019. Effective vaccines and prompt action on interventions and treatments were major efforts to tackle viral hepatitis to achieve the World Health Organization's (WHO) goal of reducing new hepatitis infections by 90% and deaths by 65% between 2016 and 2030 (*4*).

Morbidity and mortality due to acute hepatitis resulting from the acute sequelae of hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis E virus (HEV) infections were estimated by the GBD 2019. With respect to morbidity, anti-HAV IgG, hepatitis B surface antigen (HBsAg), anti-HCV IgG, and anti-HEV IgG seroprevalence data were collected through published literature, grey literature, and surveys, and the meta-regression tool (DisMod-MR) utilizing age group, gender, and year was used to estimate seroprevalence and instantaneous seroconversion rates due to acute infections (*5*). The instantaneous seroconversion rate was converted to the population incidence rate (the number of infections per person in the total population) using the formula: population incidence rate = (instantaneous seroconversion rate) × (1 – seroprevalence) (*6*). HBsAg seropositivity typically existed only in chronic carriers, and the association of incidence of HBV infections that resulted in chronic carrying was modelled to estimate the incidence from HBsAg seroprevalence data (*6*).

The prevalences of acute HAV, HBV, HCV, and HEV infections were calculated as the products of the population incidence rate and estimated durations of acute infections of HAV, HBV, HCV, and HEV, which was four weeks for HAV and HEV, and six weeks for HBV and HCV (*6*). Hereby, incidence meant the number of new acute infection cases of a given hepatitis virus during a year period in a specified population; prevalence implied the proportion of the number of cases of acute viral infections found in a

population.

To calculate mortality, the vital registration, verbal autopsy, cancer registry, and mortality surveillance data were compiled, and the cause-of-death ensemble model (CODEm) was applied to estimate cause-specific mortality by age group, gender, and year for acute HAV, HBV, HCV, and HEV infections (*7*). Virus specific mortality data for acute hepatitis were too limited to direct use in the CODEm, so a two-step nested-model approach for acute hepatitis virus infections was used to estimate cause-specific mortality. First, the joint mortality from all acute hepatitis using cause-specific mortality data in the CODEm was modelled; second, a separate natural history model for each hepatitis virus infection was developed, in which mortality was estimated as the product of incidence and case fatality (*6*).

YLDs were estimated as the product of an estimate of prevalence and a disability weight for health states of each mutually exclusive sequela; years of life lost (YLLs) were expressed as the product of mortality estimates and years of life lost due to premature death; and DALYs were calculated as the sum of YLLs and YLDs.

Incidence, prevalence, deaths, and indicators of burden of acute hepatitis in 1990, 2000, and 2019 by gender were obtained, and their standardized rates were calculated using the 2010 National Census as the standard population, expressed as number and rate (1/100,000), respectively. Percent change (%) was calculated as the difference in quantities between 2019 and 2000 divided by the quantity in 2000. All statistical analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, USA).

In Table 1, standardized rates of DALYs, YLLs, and YLDs due to acute hepatitis declined when quantities in 2019 were compared to those in 2000, and YLLs had the largest percent decrease for males, females, and both genders combined, with the percent decrease for females being greater than that found in males.

From Tables 2–5, percent changes in the number of person years and standardized rate of DALYs and YLLs in all age groups due to acute hepatitis were decreased when quantities in 2019 were compared to those in 2000. Further comparisons for 2019 and 2000 showed that for acute hepatitis A (Table 2), percent changes in the number of person years and rate of YLDs were increased in groups aged 50–69 years and 70 years or more; for hepatitis B (Table 3), percent changes in the number of person years of YLDs were increased in

TABLE 1. Overall incidence, prevalence, deaths, and burden indicators of acute hepatitis for the years 1990, 2000, and 2019 in China.

Gender	Year	Incidence		Prevalence		Deaths		DALYs		YLLs		YLDs	
		N	*P'*	*N*	*P'*	*N*	*P'*	*N*	*P'*	*N*	*P'*	*N*	*P'*
Male													
	1990	38,603,733	5,455.48	3,788,134	555.26	16,651	3.51	887,637	149.59	825,936	139.38	61,700	10.21
	2000	37,113,965	5,159.80	3,701,779	523.55	9,191	1.68	456,024	73.17	388,333	63.23	67,691	9.93
	2019	27,402,638	3,880.05	2,690,260	379.58	2,661	0.33	143,697	19.11	86,490	11.00	57,207	8.11
	2019 *vs.* 2000 (%)*	−26.17	−24.80	−27.33	−27.50	−71.05	−80.61	−68.49	−73.89	−77.73	−82.61	−15.49	−18.38
Female													
	1990	28,602,658	4,141.05	2,690,025	403.99	9,511	1.91	521,406	82.99	476,669	75.48	44,737	7.51
	2000	26,765,510	3,938.87	2,567,887	383.22	3,952	0.71	216,223	34.91	167,289	27.47	48,934	7.44
	2019	19,342,044	2,974.27	1,811,496	275.44	1,065	0.12	70,468	9.91	30,543	3.82	39,925	6.09
	2019 *vs.* 2000 (%)*	−27.74	−24.49	−29.46	−28.12	−73.04	−83.25	−67.41	−71.62	−81.74	−86.09	−18.41	−18.19
Both													
	1990	67,206,390	4,818.71	6,478,159	481.98	26,162	2.72	1,409,042	117.47	1,302,605	108.56	106,437	8.91
	2000	63,879,475	4,565.51	6,269,666	455.24	13,143	1.19	672,247	54.53	555,622	45.81	116,625	8.72
	2019	46,744,682	3,433.54	4,501,755	328.24	3,726	0.22	214,165	14.53	117,032	7.42	97,133	7.11
	2019 *vs.* 2000 (%)*	−26.82	−24.79	−28.20	−27.90	−71.65	−81.57	−68.14	−73.35	−78.94	−83.80	−16.71	−18.48

Note: *N*: Number of cases for incidence, prevalence, and deaths; number of person years for disability-adjusted life years (DALYs), years of life lost (YLLs), and years lived with disability (YLDs).

P': Standardized rate calculated using the 2010 National Census as the standard population, expressed as 1/100,000.

* Percent change (%) was calculated as difference value between 2019 and 2000 divided by quantity in 2000.

TABLE 2. Incidence, prevalence, deaths, and burden indicators of acute hepatitis A for the years 1990, 2000, and 2019 in China.

Age group (years)	Year	Incidence		Prevalence		Deaths		DALYs		YLLs		YLDs	
		Number of cases	Rate (1/100,000)	Number of cases	Rate (1/100,000)	Number of cases	Rate (1/100,000)	Number of person-years	Rate (1/100,000)	Number of person-years	Rate (1/100,000)	Number of person-years	Rate (1/100,000)
<5													
	1990	12,346,148	10,699.23	949,704	823.02	3,527	3.06	312,293	270.63	310,158	268.78	2,134	1.85
	2000	7,342,017	8,719.38	564,771	670.72	597	0.71	53,774	63.86	52,465	62.31	1,309	1.55
	2019	5,889,462	7,227.14	453,036	555.93	22	0.03	2,982	3.66	1,905	2.34	1,077	1.32
	2019 *vs.* 2000 (%)*	−19.78	−17.11	−19.78	−17.11	−96.37	−96.25	−94.45	−94.27	−96.37	−96.25	−17.74	−15.01
5–14													
	1990	7,854,676	3,785.08	604,206	291.16	321	0.15	40,464	19.50	25,682	12.38	14,782	7.12
	2000	7,595,916	3,390.47	584,301	260.81	128	0.06	25,353	11.32	10,211	4.56	15,142	6.76
	2019	4,527,645	3,159.84	348,280	243.06	5	0.00	9,037	6.31	369	0.26	8,668	6.05
	2019 *vs.* 2000 (%)*	−40.39	−6.80	−40.39	−6.80	−96.39	−94.36	−64.36	−44.27	−96.38	−94.35	−42.76	−10.50
15–49													
	1990	7,576,037	1,133.35	582,772	87.18	3,818	0.57	226,470	33.88	202,265	30.26	24,205	3.62
	2000	8,538,864	1,144.40	656,836	88.03	1,533	0.21	107,072	14.35	79,636	10.67	27,435	3.68
	2019	8,105,503	1,124.63	623,500	86.51	133	0.02	32,880	4.56	6,753	0.94	26,126	3.63
	2019 *vs.* 2000 (%)*	−5.08	−1.73	−5.08	−1.73	−91.30	−90.99	−69.29	−68.21	−91.52	−91.22	−4.77	−1.41
50–69													
	1990	111,845	72.60	8,603	5.58	3,398	2.21	103,559	67.22	103,187	66.98	372	0.24
	2000	245,064	128.21	18,851	9.86	1,245	0.65	38,519	20.15	37,720	19.73	799	0.42
	2019	839,826	227.67	64,602	17.51	223	0.06	9,319	2.53	6,620	1.79	2,699	0.73
	2019 *vs.* 2000 (%)*	242.70	77.57	242.70	77.57	−82.07	−90.71	−75.81	−87.46	−82.45	−90.91	237.82	75.05
70+													
	1990	456	1.19	35	0.09	1,724	4.51	26,969	70.49	26,968	70.49	2	0.00
	2000	1,340	2.44	103	0.19	795	1.45	12,027	21.89	12,023	21.89	4	0.01
	2019	6,817	6.31	524	0.49	218	0.20	3,127	2.90	3,104	2.88	23	0.02
	2019 *vs.* 2000 (%)*	408.87	158.91	408.87	158.91	−72.61	−86.07	−74.00	−86.77	−74.18	−86.86	407.09	158.00

Abbreviations: DALYs=disability-adjusted life years; YLLs=years of life lost; YLDs=years lived with disability.

* Percent change (%) was calculated as difference value between 2019 and 2000 divided by quantity in 2000.

TABLE 3. Incidence, prevalence, deaths, and burden indicators of acute hepatitis B for the years 1990, 2000, and 2019 in China.

Age group (years)	Year	Incidence		Prevalence		Deaths		DALYs		YLLs		YLDs	
		Number of cases	Rate (1/100,000)	Number of cases	Rate (1/100,000)	Number of cases	Rate (1/100,000)	Number of person-years	Rate (1/100,000)	Number of person-years	Rate (1/100,000)	Number of person-years	Rate (1/100,000)
<5													
	1990	2,184,080	1,892.73	252,009	218.39	2,369	2.05	210,724	182.61	208,934	181.06	1,790	1.55
	2000	1,610,842	1,913.03	185,866	220.73	766	0.91	68,824	81.74	67,503	80.17	1,321	1.57
	2019	89,513	109.84	10,328	12.67	95	0.12	8,411	10.32	8,337	10.23	74	0.09
	2019 *vs.* 2000 (%)*	−94.44	−94.26	−94.44	−94.26	−87.65	−87.24	−87.78	−87.37	−87.65	−87.24	−94.40	−94.22
5–14													
	1990	4,055,400	1,954.25	467,931	225.49	146	0.07	14,950	7.20	11,596	5.59	3,354	1.62
	2000	4,296,507	1,917.76	495,751	221.28	101	0.04	11,499	5.13	7,952	3.55	3,547	1.58
	2019	185,281	129.31	21,379	14.92	10	0.01	960	0.67	806	0.56	154	0.11
	2019 *vs.* 2000 (%)*	−95.69	−93.26	−95.69	−93.26	−89.90	−84.21	−91.65	−86.95	−89.87	−84.16	−95.65	−93.21
15–49													
	1990	22,618,450	3,383.66	2,609,821	390.42	3,671	0.55	229,312	34.30	190,162	28.45	39,150	5.86
	2000	23,854,779	3,197.08	2,752,475	368.89	2,775	0.37	186,460	24.99	141,158	18.92	45,301	6.07
	2019	15,666,424	2,173.70	1,807,664	250.81	658	0.09	64,995	9.02	32,367	4.49	32,628	4.53
	2019 *vs.* 2000 (%)*	−34.33	−32.01	−34.33	−32.01	−76.29	−75.45	−65.14	−63.91	−77.07	−76.26	−27.98	−25.44
50–69													
	1990	3,654,647	2,372.34	421,690	273.73	3,535	2.29	116,089	75.36	106,488	69.12	9,601	6.23
	2000	4,229,083	2,212.55	487,971	255.29	2,537	1.33	87,336	45.69	76,167	39.85	11,169	5.84
	2019	5,914,098	1,603.25	682,396	184.99	1,217	0.33	51,939	14.08	36,258	9.83	15,681	4.25
	2019 *vs.* 2000 (%)*	39.84	−27.54	39.84	−27.54	−52.04	−75.15	−40.53	−69.18	−52.40	−75.33	40.40	−27.25
70+													
	1990	642,722	1,679.96	74,160	193.84	1,753	4.58	29,339	76.69	27,729	72.48	1,610	4.21
	2000	860,264	1,566.06	99,261	180.70	1,481	2.70	25,095	45.68	22,938	41.76	2,157	3.93
	2019	1,239,558	1,148.11	143,026	132.47	908	0.84	16,521	15.30	13,358	12.37	3,163	2.93
	2019 *vs.* 2000 (%)*	44.09	−26.69	44.09	−26.69	−38.65	−68.79	−34.17	−66.50	−41.76	−70.37	46.61	−25.40

Abbreviations: DALYs=disability-adjusted life years; YLLs=years of life lost; YLDs=years lived with disability.

* Percent change (%) was calculated as difference value between 2019 and 2000 divided by quantity in 2000.

TABLE 4. Incidence, prevalence, deaths, and burden indicators of acute hepatitis C for the years 1990, 2000, and 2019 in China.

Age group (years)	Year	Incidence		Prevalence		Deaths		DALYs		YLLs		YLDs	
		Number of cases	Rate (1/100,000)	Number of cases	Rate (1/100,000)	Number of cases	Rate (1/100,000)	Number of person-years	Rate (1/100,000)	Number of person-years	Rate (1/100,000)	Number of person-years	Rate (1/100,000)
<5													
	1990	511,319	443.11	58,998	51.13	198	0.17	18,198	15.77	17,375	15.06	823	0.71
	2000	174,481	207.21	20,132	23.91	55	0.07	5,148	6.11	4,865	5.78	283	0.34
	2019	200,678	246.26	23,155	28.41	2	0.00	505	0.62	180	0.22	325	0.40
	2019 *vs.* 2000 (%)*	15.01	18.84	15.01	18.84	−96.31	−96.18	−90.19	−89.86	−96.31	−96.18	14.90	18.73
5–14													
	1990	204,102	98.35	23,550	11.35	21	0.01	1,981	0.95	1,650	0.79	331	0.16
	2000	82,535	36.84	9,523	4.25	13	0.01	1,152	0.51	1,018	0.45	134	0.06
	2019	79,956	55.80	9,226	6.44	0	0.00	165	0.12	35	0.02	130	0.09
	2019 *vs.* 2000 (%)*	−3.12	51.47	−3.12	51.47	−96.54	−94.58	−85.68	−77.61	−96.53	−94.58	−3.21	51.34
15–49													
	1990	137,739	20.61	15,893	2.38	327	0.05	17,282	2.59	17,059	2.55	223	0.03
	2000	88,878	11.91	10,255	1.37	209	0.03	10,844	1.45	10,700	1.43	144	0.02
	2019	92,990	12.90	10,730	1.49	22	0.00	1,211	0.17	1,061	0.15	150	0.02
	2019 *vs.* 2000 (%)*	4.63	8.32	4.63	8.32	−89.71	−89.35	−88.83	−88.44	−90.09	−89.74	4.59	8.28
50–69													
	1990	25,966	16.86	2,996	1.94	332	0.22	10,023	6.51	9,981	6.48	42	0.03
	2000	41,332	21.62	4,769	2.50	189	0.10	5,717	2.99	5,650	2.96	67	0.04
	2019	62,256	16.88	7,183	1.95	37	0.01	1,217	0.33	1,116	0.30	101	0.03
	2019 *vs.* 2000 (%)*	50.62	−21.95	50.62	−21.95	−80.20	−89.74	−78.72	−88.97	−80.26	−89.77	50.58	−21.98
70+													
	1990	12,493	32.65	1,441	3.77	169	0.44	2,697	7.05	2,677	7.00	20	0.05
	2000	32,793	59.70	3,784	6.89	116	0.21	1,849	3.37	1,796	3.27	53	0.10
	2019	42,243	39.13	4,874	4.51	29	0.03	483	0.45	414	0.38	69	0.06
	2019 *vs.* 2000 (%)*	28.82	−34.46	28.82	−34.46	−75.46	−87.51	−73.91	−86.72	−76.96	−88.28	28.91	−34.41

Abbreviations: DALYs=disability-adjusted life years; YLLs=years of life lost; YLDs=years lived with disability.
* Percent change (%) was calculated as difference value between 2019 and 2000 divided by quantity in 2000.

TABLE 5. Incidence, prevalence, deaths, and burden indicators of acute hepatitis E for the years 1990, 2000, and 2019 in China.

Age group (years)	Year	Incidence		Prevalence		Deaths		DALYs		YLLs		YLDs	
		Number of cases	Rate (1/100,000)	Number of cases	Rate (1/100,000)	Number of cases	Rate (1/100,000)	Number of person-years	Rate (1/100,000)	Number of person-years	Rate (1/100,000)	Number of person-years	Rate (1/100,000)
<5													
	1990	1,049,414	909.43	79,664	69.04	213	0.18	18,910	16.39	18,782	16.28	128	0.11
	2000	790,917	939.29	60,104	71.38	72	0.09	6,411	7.61	6,314	7.50	97	0.12
	2019	744,117	913.13	56,597	69.45	5	0.01	493	0.61	402	0.49	92	0.11
	2019 *vs.* 2000 (%)*	−5.92	−2.79	−5.84	−2.70	−93.64	−93.42	−92.30	−92.05	−93.64	−93.43	−5.89	−2.76
5–14													
	1990	1,813,271	873.79	139,482	67.21	7	0.003	2,851	1.37	577	0.28	2,274	1.10
	2000	1,901,308	848.66	146,254	65.28	5	0.002	2,927	1.31	429	0.19	2,499	1.12
	2019	1,143,697	798.19	87,977	61.40	0	0.000	1,438	1.00	31	0.02	1,407	0.98
	2019 *vs.* 2000 (%)*	−39.85	−5.95	−39.85	−5.95	−92.81	−88.75	−50.89	−23.21	−92.79	−88.72	−43.70	−11.97
15–49													
	1990	2,246,961	336.14	172,843	25.86	190	0.03	15,084	2.26	9,883	1.48	5,201	0.78
	2000	1,984,400	265.95	152,646	20.46	155	0.02	12,499	1.68	7,848	1.05	4,651	0.62
	2019	1,499,585	208.07	115,353	16.01	23	0.00	4,706	0.65	1,157	0.16	3,549	0.49
	2019 *vs.* 2000 (%)*	−24.43	−21.77	−24.43	−21.77	−84.96	−84.42	−62.35	−61.02	−85.26	−84.74	−23.68	−20.99
50–69													
	1990	118,008	76.60	9,078	5.89	302	0.20	9,437	6.13	9,147	5.94	290	0.19
	2000	145,119	75.92	11,163	5.84	232	0.12	7,358	3.85	7,001	3.66	357	0.19
	2019	281,470	76.30	21,652	5.87	66	0.02	2,647	0.72	1,955	0.53	692	0.19
	2019 *vs.* 2000 (%)*	93.96	0.50	93.96	0.50	−71.65	−85.31	−64.02	−81.36	−72.08	−85.53	94.06	0.56
70+													
	1990	42,656	111.50	3,281	8.58	142	0.37	2,410	6.30	2,306	6.03	104	0.27
	2000	63,037	114.76	4,849	8.83	139	0.25	2,382	4.34	2,227	4.06	154	0.28
	2019	133,562	123.71	10,274	9.52	54	0.05	1,129	1.05	805	0.75	324	0.30
	2019 *vs.* 2000 (%)*	111.88	7.80	111.88	7.80	−61.42	−80.37	−52.58	−75.87	−63.86	−81.61	110.54	7.12

Abbreviations: DALYs=disability-adjusted life years; YLLs=years of life lost; YLDs=years lived with disability.

* Percent change (%) was calculated as difference value between 2019 and 2000 divided by quantity in 2000.

groups aged 50–69 years and 70 years or more; for acute hepatitis C (Table 4), percent changes in the number of person years of YLDs in groups aged <5 years, 15–49 years, 50–69 years, and 70 years or more were increased, and the standardized rate of YLDs in groups aged <5 years, 5–14 years, and 15–49 years were increased; and for acute hepatitis E (Table 5), percent changes of YLDs in groups aged 50–69 years and 70 years or more were increased.

DISCUSSION

In China, the latest results showed that DALY standardized rates of acute hepatitis declined from 1990 to 2019 for males, females, and both genders combined. The decrease of DALYs primarily came from the decline of YLLs, and this was in line with the previous study (*8*). In 2019, acute hepatitis A, B, C, and E caused 3,726 deaths, 4,501,755 cases, and 214,165 person years of DALYs. Although DALYs decreased over 60% from 2000 to 2019, a high burden of acute hepatitis remains, and viral hepatitis remains a major public health challenge that requires an urgent response.

China implemented the nationwide use of a hepatitis A vaccine beginning in 1992, and the high burden of hepatitis A rapidly declined. The cause of the aforementioned percent changes in YLDs requires further investigation but were likely contributed to by factors such as unsafe water or food, poor sanitation, and poor personal hygiene and high-risk groups such as men who have gender with men, travelers to countries with high levels of infection, and persons who inject drugs (*9*). People aged 50 years or above in high-risk groups should get vaccinated as this is a safe and effective way available to prevent HAV infection.

Globally, in 2015, an estimated 257 million people were living with chronic HBV infection with 27 million people aware of their infection as of 2016 and 4.5 million of diagnosed people being on treatment (*9*). This report found that acute hepatitis B caused 2,888 deaths in 2019, accounting for 77.51% (2,888/3,726) of mortality of all acute hepatitis. Of those 2,888 deaths, people aged 50 years or above were responsible for the most deaths at 73.58% (2,125/2,888) of the total. Acute hepatitis B had the highest burden among all types of acute hepatitis, especially in the groups aged 15–49 years and 50–69 years. Prevention and control strategies for HBV infection prioritize vaccinations as the safe and effective vaccine provides over a 98% protection against HBV infection.

The regions with the highest prevalence of hepatitis C were the Eastern Mediterranean Region and the European Region with estimated prevalences in 2015 of 2.3% and 1.5%, respectively (*9*). China had a relatively low prevalence of HCV infection, and the burden of acute hepatitis C was lower than that of acute hepatitis A or acute hepatitis E from our findings. Though no effective vaccine against HCV infection currently exists, antiviral medicine is effective for curing persons with HCV infection.

Hepatitis E was most common in East and South Asia, and HEV is transmitted by the fecal-oral route, primarily via contaminated water (*9*). In our report, acute hepatitis E caused 148 deaths, which outnumbered deaths due to acute hepatitis C in 2019 (90 deaths). The number of DALYs was 10,413 person years, which was greater than that of acute hepatitis C (3,581 person years). The hepatitis E vaccine has been developed and is licensed in China (*4*), and it should be used to control hepatitis E.

This study was subject to some limitations. First, large-scale seroprevalence data used for the estimation of morbidity of acute infections of hepatitis virus was limited, where data were sparse or no data, estimates were based on regional extrapolations and covariates by statistical models, which may lower spatial differences across regions and might deviate from the true value. Second, this report only presented results of incidence, prevalence, deaths, and burden indicators of acute hepatitis by gender for all acute hepatitis, and by age group for acute hepatitis A, B, C, and E at the national level; however, burdens of acute hepatitis A, B, C, and E at the provincial level and municipal level by gender and age group are necessary to make well-directed policy for the prevention and control of viral hepatitis.

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Preplanned Studies

Supervised Analysis of Hepatitis C Virus RNA-Positive Case Reporting in County-Level Hospitals — China, 2013–2018

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Summary

What is already known on this topic?

To understand the status of the diagnosis and reporting of hepatitis C and standardize the reporting of hepatitis C cases in county-level hospitals, we conducted the first supervised analysis of hepatitis C cases in county-level hospitals in China from 2013 to 2018, covering all provincial-level administrative divisions (PLADs) except Tibet.

What is added by this report?

Through 6 years of supervision, we have obtained key data such as the nucleic acid detection rate and positive rate of hepatitis C virus (HCV) antibody positive cases in our county-level hospitals, the report rate and accuracy of HCV RNA positive cases, and standardized and improved the hepatitis C case reporting in county-level hospitals to improve data quality and provide data support for the judgment and estimation of hepatitis C in China.

What are the implications for public health practice?

By strengthening the management and supervision of hepatitis C case reporting, the reporting rate and accuracy of HCV RNA positive cases in county-level hospitals in China had been greatly improved. By combining the number of HCV antibody tests and the number of viral nucleic acid tests in medical institutions around the country, it was possible to effectively assess the current status of hepatitis C in China and to provide a scientific basis for the development of hepatitis C prevention and treatment measures.

Hepatitis C is an infectious disease that results in liver disease caused by hepatitis C virus (HCV), including acute and chronic hepatitis, liver cirrhosis, and even liver cancer. The transmission route is mainly through blood transmission, input of contaminated blood, or blood products, organ transplantation, sharing of needles by drug users, etc., and the efficiency of direct body fluid transmission and sexually transmitted infection is low (*1*–*2*). From data from China's Infectious Disease Report Information Management System, the number of HCV cases showed rapid growth from 2004 to 2011 with an average annual increase of 48.79% (*3*). Due to the emergence of drugs that can completely cure hepatitis C, including those based on long-acting interferons and small molecule oral drugs, the National Health Commission of China has strengthened the prevention and treatment of hepatitis C including infectious disease case reports and clinical treatment. At the end of 2012, a department dedicated to the prevention and treatment of hepatitis C was established at the National Center for STD/AIDS Prevention and Control of China CDC. Due to the implementation of 'special disease management' for the prevention and treatment of hepatitis C, the standardized diagnostic and reporting standards for hepatitis C, and the effectively reducing excessive and repeated reporting, the number of reports from 2012–2016 was clearly flat and stable and the growth rate was 0.65% from 2012–2016 (*4*). According to the "Hepatitis C Diagnostic Criteria (WS 213-2018)", nucleic acid (HCV RNA) positive results can be diagnosed as a confirmed case and must be reported (*5*). According to the Law on the Prevention and Control of Infectious Diseases of the People's Republic of China, China's infectious disease case reporting adopts the first clinician or hospital's responsibility system. The clinician or hospital receiving the first visit is the first clinician and the first consulting hospital, and the first clinician or hospital is responsible for the diagnosis and reporting of infectious diseases of patients. Most township and community hospitals do not have the ability to diagnose infectious diseases. Therefore, the majority of county-level hospitals have become the main force of infectious disease reports in China. This study selected county-level hospitals with nucleic acid detection capabilities as survey and analysis objects. From 2013–2018, we continuously carried out verification of HCV RNA positive case reports in county-level hospitals, conducted research, and improved work

through routine supervision and improved work quality.

A county-level hospital with HCV RNA detection capability was selected as a survey object, and research work was conducted in the form of work supervision. In 2013, 7 county-level hospitals in 5 provincial-level administrative divisions (PLADs) including Hebei, Henan, Hubei, Guangdong, and Yunnan were inspected; in 2014, 217 county-level hospitals in 27 PLADs (excluding Guangdong, Yunnan, Hainan, and Tibet) were inspected; in 2015, 13 county-level hospitals in 6 PLADs including Shanxi, Inner Mongolia, Anhui, Hainan, Guizhou, and Gansu were inspected; in 2016, 25 county-level hospitals in 10 PLADs of Hebei, Jilin, Heilongjiang, Shandong, Henan, Hunan, Guangxi, Guizhou, Yunnan, and Gansu were inspected; in 2017, 30 county-level hospitals in 9 PLADs of Liaoning, Shanghai, Zhejiang, Henan, Hubei, Hunan, Guangxi, Sichuan, and Qinghai were inspected; in 2018, 19 county-level hospitals in 5 PLADs of Shandong, Yunnan, Fujian, Sichuan, and Henan were inspected. The 2013–2018 inspection covered 30 PLADs except Tibet. See Table 1 for details.

In 2013 to verify hospital laboratories, we checked the RNA detection status of HCV antibody positive cases, including RNA detection rates (RNA detection number/antibody positive number) and positive rates (RNA positive number/RNA detection number). From 2013 to 2018, the laboratory of the hospital was inspected to check the HCV RNA positive list detected in the first quarter of the year. All verification was carried out when the quantity was small, and when the quantity was large, the sample was sampled by simple random sampling. The hospitals were examined on whether it had reported in the past five years from the day of the verification to the Infectious Disease Report Information Management System, and the HCV RNA positive case report rate (HCV RNA positive report number/HCV RNA positive number) was calculated. Finally, the reported cases were checked for accurately reporting confirmed cases and the accuracy of HCV RNA positive cases (HCV RNA positive report accurate number/HCV RNA positive report number) was calculated.

The examination results in 2013 showed that 585 of the 1,856 cases of HCV antibody-positive cases were tested for HCV RNA (RNA detection rate was 31.52%), and 536 were RNA-positive (RNA positive rate was 91.62%). See Table 1 for details.

From 2013 to 2018, a total of 11,946 cases that were HCV RNA positive in 30 PLADs (excluding Tibet) and 311 county hospitals were examined. The reported rates for each year from 2013–2018 were 46.83%, 52.09%, 65.59%, 53.06%, 82.10%, and 94.81%, respectively. The reported rate of HCV RNA positive cases in the 6-year average was 60.32%, which increased year by year. The accuracy rates of reports in 2013–2018 were 52.59%, 65.79%, 70.09%, 74.87%, 86.26%, and 96.12%, respectively. The accuracy rate of the 6-year average HCV RNA positive cases was 73.42%, which increased year by year. See Table 2 for details.

DISCUSSION

Scientific research and investigations have found that about 10% to 15% of people infected with HCV can spontaneously eliminate the virus. Healthy people under 40 years old and women infected with HCV have higher spontaneous clearance rates, but they still tested positive for HCV antibodies (*6*–*7*). In practice, however, many clinicians do not have this knowledge and consider HCV-antibody-positive test results to indicate HCV infection, so there is an over-reporting of HCV antibody-positive cases. Simultaneously, according to the "Hepatitis C Diagnostic Criteria (WS 213-2018)", being HCV antibody positive and fulfilling epidemiological or clinical criteria can be reported. Epidemiological criteria include patients' reported contact with any blood, blood products, or human tissue; history of any invasive medical procedures, hemodialysis, organ transplants, or unsafe injections (including that of illicit drugs); or history of commercial blood donation, sexual contact with an HCV-infected person, and being a child born to an

TABLE 1. HCV -RNA testing of antibody positive cases in 7 inspected country hospitals in China in 2013.

Case type	Antibody positive number	RNA detection number	RNA detection rate(%)	RNA positive number	RNA positive rate(%)
Hospitalized cases	1,008	356	35.32	327	91.85
Outpatient cases	848	229	27.00	209	91.27
Total	1,856	585	31.52	536	91.62

TABLE 2. Report on HCV-RNA positive cases of hepatitis C in inspected county hospitals in China, 2013–2018.

Year	Number of PLADs*	Number of county hospitals	HCV-RNA positive number	HCV-RNA positive reported number	HCV-RNA positive reported rate (%)	HCV-RNA positive report accurate number	HCV-RNA positive report accurate rate (%)
2013	5	7	536	251	46.83	132	52.59
2014	27	217	7,946	4,139	52.09	2,723	65.79
2015	6	13	247	117	47.37	82	70.09
2016	10	25	360	191	53.06	143	74.87
2017	9	30	1,933	1,587	82.10	1,369	86.26
2018	5	19	924	876	94.81	842	96.12
Total	30	311	11,946	7,206	60.32	5,291	73.42

* Provincial-level administrative divisions including provinces, autonomous regions, and municipalities.

HCV-infected mothers. Clinical criteria include the clinical symptoms of liver disease; elevated liver enzymes (serum aspartate aminotransferase, alanine aminotransferase, or bilirubin); B-mode ultrasounds, CT scans, or MRI imaging indicative of splenomegaly and hepatomegaly; damage to the liver parenchyma; or widening of the portal vein. Therefore, being HCV-antibody positive alone could not confirm the diagnosis of hepatitis C, and only HCV-RNA positive could be the basis for the diagnosis of an HCV infection.

Based on the above principles, this study only investigated the infectious disease reporting rate and reporting accuracy rate of HCV RNA positive cases in county-level hospitals, and the results obtained were more accurate and more convincing. The verification results showed that the HCV antibody-positive cases had a low RNA detection rate, which may be due to two main reasons. First, this phenomenon may be caused by a lack of nucleic acid detection capabilities in the hospital, and the nucleic acid detection capabilities should be prioritized in county hospitals in the future. Second, professional may fail to understand the causes of hepatitis C or not pursue further RNA testing due to cost. In the future, the cost of hepatitis C RNA testing and treatment should be included in the scope of medical insurance to reduce the financial burden of patients.

Since 2013, the National Center for STD/AIDS Prevention and Control of China CDC has strengthened training on hepatitis C case reporting for provincial-level CDCs, and provincial-level CDCs have organized secondary training in their regions. The training target was mainly county-level hospitals, which greatly improved the ability of hepatitis C diagnosis and reporting in county-level hospitals (*8*). At the same time, we conducted annual spot checks and verification for county-level hospitals and used work guidance to further improve case reporting rates and report quality. The verification of the national team played a leading role. Through national supervision, the provincial-level and municipal CDCs carried out a wider range of verification and gradually improved the quality of data. By strengthening the management of hepatitis C case reports, the reporting rate of infectious diseases of hepatitis C HCV RNA positive cases in county-level hospitals in China had increased significantly from 46.83% in 2013 to 94.81% in 2018, and the accuracy rate of reports increased from 52.59% in 2013 to 96.12% in 2018.

This study was subject to some limitations. First, only county-level hospitals with nucleic acid testing capabilities were tested. Second, selection of PLADs and county-level hospitals for investigation was also arranged according to work plans rather than random sampling. Third, using work supervision to collect data and provide onsite guidance was due to convenience and might unintentionally affect the data. However, this study provided a preliminary understanding of the infectious disease reporting rate and accuracy of HCV-RNA positive cases in county-level hospitals with nucleic acid detection capabilities in China, and this data was extremely important for understanding the overall situation of hepatitis C in China and for providing a scientific basis for developing prevention strategies.

Assessing the prevalence of local hepatitis C outbreaks depends on the detection rate and positive rate of HCV antibody-positive cases, the reporting rate and the accuracy of the reports, and the number of antibody and RNA detections in medical institutions. These can effectively fill gaps in the infectious disease report data and can be used to correct reported data. In the future, all regions should strengthen the RNA detection of HCV antibody-positive cases, further improve the reporting rate and accuracy of RNA-

positive cases, and provide real epidemic data support for the prevention and treatment of hepatitis C.

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Recollection

Progress Towards Hepatitis A Control and Prevention Through 2019: the National Immunization Program of China

Xiaojin Sun[1]; Fuzhen Wang[1]; Guomin Zhang[1]; Hui Zheng[1]; Ning Miao[1]; Zundong Yin[1]; Zhijie An[1,#]

Hepatitis A is an infectious liver disease caused by hepatitis A virus (HAV) that results in mild to severe illness. HAV is spread to immunologically naïve persons who ingest food or water contaminated with feces from HAV-infected individuals (*1*). Hepatitis A is often seen in sporadic cases, but is also seen in large outbreaks, such as the 1988 outbreak in Shanghai that caused over 300,000 cases and huge economic losses (*2*). In the pre-vaccine 1970s, China was highly endemic for HAV with a seroprevalence due to infection of 85%–95% in children aged 10–15 years. With China's socioeconomic development and improvements in standard of living through the 1990s, HAV exposure and hepatitis A incidence shifted from a younger population to an older population (*3*). Following hepatitis A (HepA) vaccine development, licensure, and widespread introduction, China made great progress in hepatitis A control and prevention. In this report, we describe and interpret a comprehensive analysis of progress towards hepatitis A control and prevention through 2019 from the perspective of China's National Immunization Program.

ACHIEVING HIGH HEPA VACCINE COVERAGE

Domestically-developed live-attenuated and inactivated HepA vaccines were licensed in China in 1992 and 2002. Annual production of HepA vaccines increased steadily; between 1992 and 2007, 156 million doses of HepA were distributed, mainly for vaccinating school-aged children (*4*). Before 2008, all HepA vaccines were non-program vaccines, paid for out-of-pocket by families. Vaccination coverage was relatively low and varied geographically. Coverage was around 16% to 21% among those born before 2000 but was growing fast, reaching 53.8% in western provincial-level administrative divisions (PLADs) and 80.2% in eastern PLADs among the 2000–2007 birth cohorts.

In 2008, live and inactivated HepA vaccines were both integrated into the Expanded Program on Immunization (EPI). PLADs could select which vaccine to use, and most chose the live-attenuated HepA vaccine with its one-dose schedule at 18 months. A few PLADs selected the inactivated HepA vaccine with its two-dose schedule at 18 and 24 months. Nationally, coverage increased rapidly, reaching 88.1%–94.9% in all 3 regions of China among the 2008–2012 birth cohorts (Figure 1)(*5*).

Successful immunization programs ensure uniformly high HepA vaccine coverage, regardless of regional socioeconomic development. High coverage following HepA introduction into EPI was seen in other countries such as the United States and Israel (*6*–*7*).

POPULATION IMMUNITY FROM VACCINATION

In a 2006 serological survey, anti-HAV seroprevalence was shown to be increasing with age and was relatively low among children (*8*). Seroprevalence among children aged 2–14 years was significantly higher in the more developed eastern PLADs than in the developing central and western PLADs, which was consistent with varying vaccine coverage by regions (*8*–*9*).

In 2014, after HepA vaccines had been included in the national program in all 3 regions for 6 years, a serological survey showed that anti-HAV seroprevalence among children aged 2–4 years was much higher and had little regional variation (Figure 2). However, seroprevalence was lower among individuals aged 15–19 years than other age groups, indicating an immunity gap among individuals aged 15–19 years. This immunity gap has been described in two other studies (*10*–*11*) and is a result of a rapid decrease in hepatitis A incidence following national HepA vaccine introduction causing a decrease in HAV exposure to those born prior to HepA vaccine introduction. Many in this age group, thus, escaped natural infection due to decreased circulation of HAV

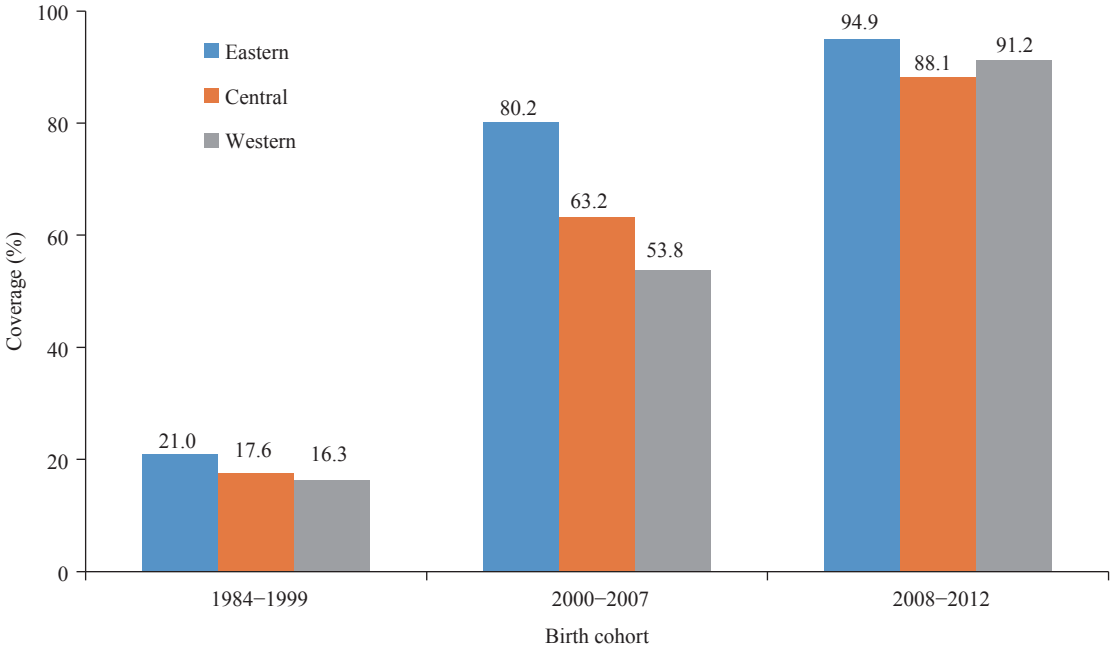

FIGURE 1. Coverage of HepA vaccine by birth cohort and region, China (data from a national serological survey conducted in 2014).

but also had not been immunized by HepA vaccine, which had low coverage before inclusion into EPI.

CONTINUOUS DECREASES IN THE INCIDENCE OF HEPATITIS A

Hepatitis A incidence is closely related to both sanitation and vaccination. In China and abroad, declines in the incidence of hepatitis A have been well documented among vaccine-targeted populations, but incidence has also been shown to decline among non-vaccine-targeted populations due to indirect protection, e.g. through herd immunity (*6*–*7*,*9*). With better sanitation and widespread use of HepA vaccines in China, HAV-infection-induced immunity has been replaced by vaccine-induced immunity (*8*). Comparing 2004–2007 (pre-EPI) with 2008–2011, hepatitis A incidence decreased in all age groups and decreased further from 2012–2019. Incidence declines were seen in all PLADs, irrespective of region. In the pre-EPI era, hepatitis A incidence peaked at 5–9 years of age, but the peak was nearly eliminated after nationwide HepA vaccine introduction. Incidence declined in all age groups and in all three phases of EPI, and geographic disparities were greatly narrowed (*9*). (Figure 3).

However, the hepatitis A incidence was high in the western PLADs, up to 4.28/100,000 among children under 5 years, although there were decreases in incidence. Possible factors for the higher incidence include lower EPI performance, less on-time vaccination, failure to vaccinate, and perhaps weaker sanitation in the western PLADs (*12*).

DISCUSSION AND CONCLUSION

Study strengths were that the vaccination status of children aged under 15 years was obtained from official vaccination records; there has been long-term, consistent hepatitis A surveillance; and seroprevalence was determined by nationwide serological surveys with national-level laboratory testing. Limitations were that the vaccination status of individuals aged 15–29 years was based on recall; the passive hepatitis A surveillance system underreports mild cases or infections among individuals who did not seek medical attention; and that laboratory tests cannot distinguish between immunity from disease and immunity from vaccination.

The nationwide introduction of the HepA vaccination has eliminated most age and geographic disparities of hepatitis A disease. HepA vaccine introduction into the EPI system reduced disparities in coverage and seroprevalence in all three regions of China.

An immunity gap among older children and young adults indicated a potential risk of outbreaks among individuals who were born in the years immediately

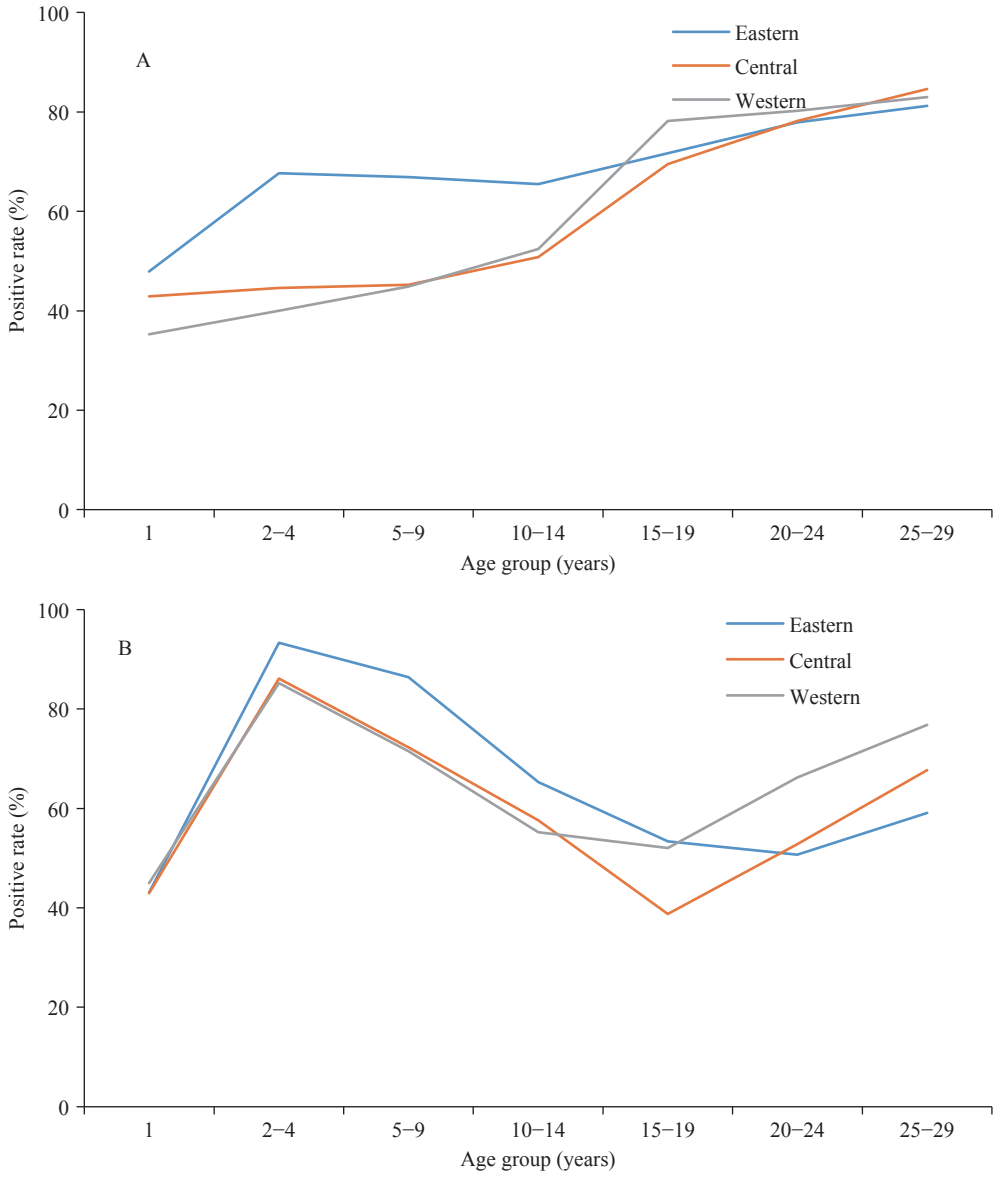

FIGURE 2. Anti-HAV seroprevalence by age and region in 2006 (A) and 2014 (B).

prior to nationwide HepA vaccine introduction. A catch-up vaccination effort could close this immunity gap and should be given serious consideration. An unexpectedly high hepatitis A incidence among children aged 0–4 years in the western PLADs should be closely monitored. Careful evaluation of the western PLADs' immunization programs should be conducted to identify weakness in program performance and means to strengthen the programs.

Maintaining high vaccination coverage among children and strengthening western provincial-level programs will help ensure long-term progress towards elimination of hepatitis A in China.

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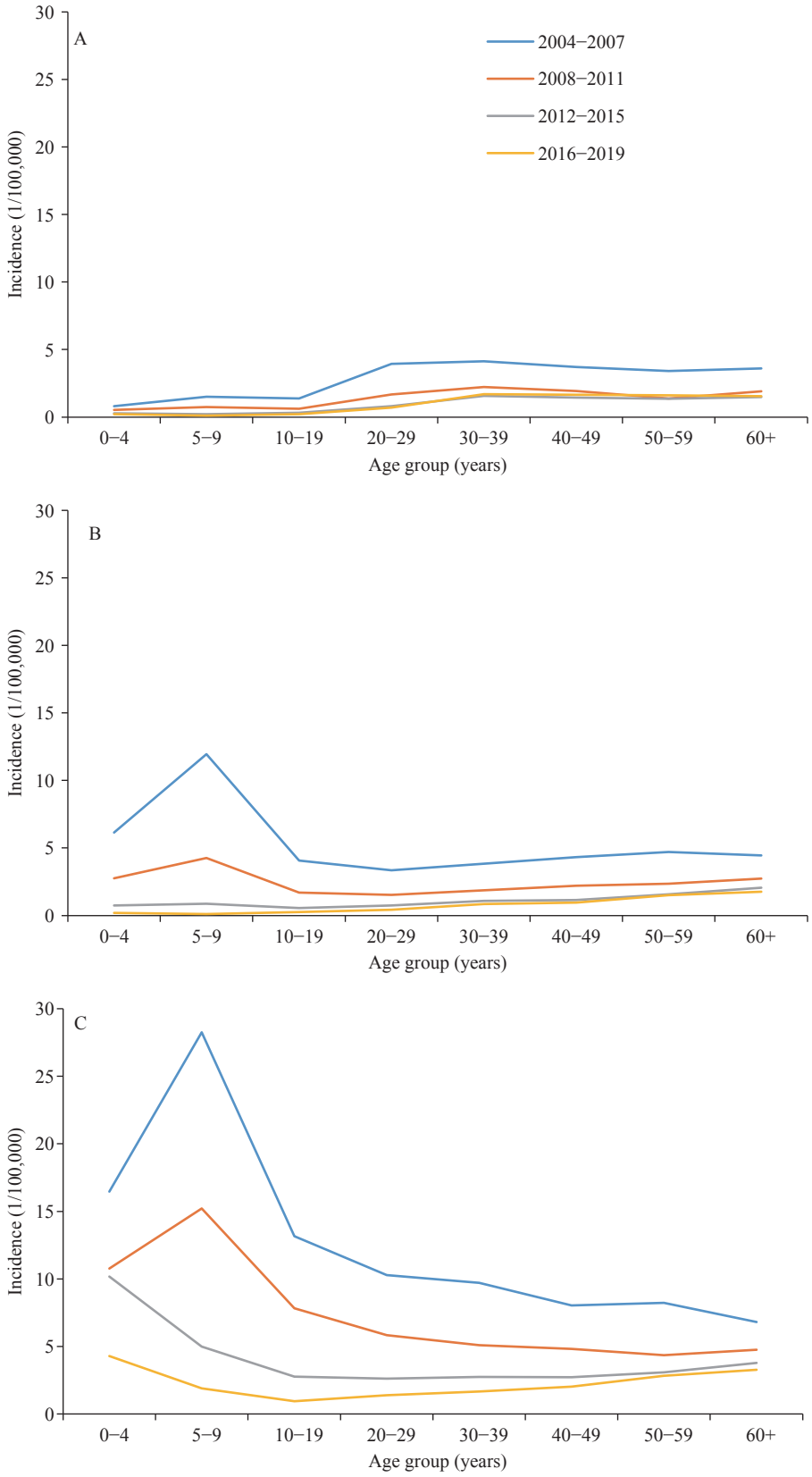

FIGURE 3. Incidence of hepatitis A in three regions in different phases of the expanded program on immunization (EPI). (A) eastern region; (B) central region; (C) western region.

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Recollection

Control of Chronic Hepatitis B in China: Perspective of Diagnosis and Treatment

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In the last three decades, China has made extraordinary effort and achieved great progress in the control of hepatitis B. Thanks to the adoption of universal administering of HBV vaccinations for newborns since 1992, the prevalence of hepatitis B surface antigen (HBsAg) in the population born after 1992 decreased significantly resulting in a decline in the general population from 9.75% to about 6% (*1*). In the last 10 years, under the support of national major scientific research grants, many multicenter, randomized controlled trials (RCTs) have been conducted, generating more and more clinical evidence for antiviral therapy for chronic hepatitis B (CHB) (*2*). From 2005 to 2019, 4 editions of "Guidelines on the Prevention and Treatment of Chronic Hepatitis B" were jointly issued by 2 sister branches of the Chinese Medical Association including the Chinese Society of Hepatology and Chinese Society of Infectious Diseases (*3*–*6*). Sustained effort on continued medical education based in the clinical guidelines have raised the knowledge base of specialists and internists and improved the standard of care for CHB (*7*). Recently, the National Healthcare Secrurity Adminstration has conducted government negotiations to massively reduce the price of antiviral medicine. The improvement of the reimbursement policy together with increased patient accessibility and affordability for antiviral therapy have increased the uptake of antiviral therapy and improved the clinical outcomes (*8*). As a result, considerable progress has been made in diagnosis and treatment, making it possible to control hepatitis B in China.

IMPROVEMENTS IN DIAGNOSTIC MODALITY

In recent years, new serological markers, transient elastography (TE), and novel pathological criteria in the diagnosis of CHB have been extensively investiaged and increasingly used in China. Conventional HBV serological markers have been widely used in patients with CHB to establish the phases of HBV infection and guide antiviral therapy. Recently, the clinical utility of some novel markers have been investigated in patients with HBV infection. Quantitative HBsAg (qHBsAg) levels are correlated with intra-hepatic covalently closed circular DNA (cccDNA) and can predict treatment response (*9*). Baseline anti-HBc quantification (qAnti-HBc) may serve as a useful marker indicating ongoing host-immune activity against HBV, with high levels of anti-HBc being used to predict the loss of hepatitis B envelope antigen (HBeAg) (*10*–*12*), the efficacy of antiviral therapy (*13*–*14*), and the absence of HBV relapse after treatment cession (*15*). HBV core-related antigen (HBcrAg) is a novel serum marker measuring composite viral protein and considered to be a surrogate marker of intrahepatic HBV cccDNA. A decrease in HBcrAg is related to the loss of HBeAg and HBsAg and the safe discontinuation of antivirus treatment. HBcrAg may also be helpful for predicting hepato cellular carcinoma (HCC) development. Serum pre-genomic RNA (pgRNA) transcribed from HBV cccDNA has a strong correlation with intrahepatic cccDNA and is considered to be an indirect marker of reservoir size (*16*–*17*). These novel serum markers provide useful tools for better monitoring of disease progression and evaluation of the efficacy of antiviral therapy.

TE is a noninvasive tool with ease of operation, good repeatability, and reasonable accuracy for identifying liver fibrosis or early cirrhosis. A multicenter study validated the diagnostic performace of TE measured by FibroScan to stage liver fibrosis in a cohort of 469 Chinese patients with CHB (*18*). Another device for TE measurement (FibroTouch) has also comfirmed its clinical utility in a single-center prospective study including 435 chronic liver disease paitents including 237 CHB paitents (*19*).

To quantitatively measure the degree of liver fibrosis in CHB patients, an automatic digital technique qFbrosis has been investigated and shown promising results (*20*). In complementary to Ishak modified histology activity index (HAI) and Ishak fibrosis score, a new classification (Beijing Classification) has been

proposed by Chinese investigators that further divides fibrosis beyond stage 3 into predominantly progressive, indeterminate, and predominately regressive (P-I-R score) to assess the dynamic changes in fibrosis pre- and post-antiviral therapy (*21*). Recently, one study using the Beijing classification found that liver fibrosis progression was associated with low serum HBV DNA level (20–200 IU/mL) at week 78 of nucleoside (nucleotide) analogue (NA) therapy, indicating that switching to or adding a more potent antiviral agent would benefit these patients (*22*).

IMPROVEMENT IN CLINICAL STUDIES OF ANTIVIRAL THERAPY

In the last decade, both the number and quality of clinical studies on treatment of HBV has dramatically improved (*2*). A large number of studies conducted by Chinese hepatologists showed that NA treatment can strongly suppress virus replication, improve liver histology, reduce the risk of complications and HCC progression, and reduce liver related all-cause mortality (*23–27*). An observational study showed that entecavir (ETV) monotherapy is associated with less virological breakthroughs and potentially higher HBV-DNA suppression than de novo combinationof lamivudine (LAM) and adefovirdipivoxil (ADV) during 3 years of treatment for naïve HBV-related compensated liver cirrhosis (*28*). Another real world study also demonstrated that ETV was efficacious and well tolerated through 48 weeks of treatment in a heterogeneous Chinese CHB population (*29*). A nationwide observational study showed that more than 50% of patients with CHB in Tier-2 city hospitals in China initially received ETV therapy, which not surprisingly was more effective than LAM-based treatments and associated with lower rate of treatment modification (*30*).

Effective viral suppression is necessary to reduce HCC development in cirrhotic patients (*31*). Tenofovir disoproxil fumarate (TDF) and ETV are first-line therapies, and in recent years, controversy exists on which one is superior to reduce the risk of HCC development. A meta-analysis was performed by Chinese researchers to clarify this issue with critical clinical and methodological considerations, showing that disparities in follow-up duration may be a key factor to influence the results (*32*).

Combination or sequential strategies based on the potent antiviral effect of NA and immune modulation of interferons (IFN) have been estenstively explored in China. Based on evidence from the "Optimising HBeAg Seroconversion in HBeAg-positive CHB Patients with Combination and Sequential Treatment of PegIFN alfa-2a and ETV" (OSST) study, "Switching to PegIFN a-2a in NUC treated CHB patients " (NEW SWITCH) study, Endeavor Study, and Anchor study, Chinese researchers proposed a roadmap for NA-Peg-IFN sequential therapy. In particular, in patients who achieved undectable HBV, the loss of HBeAg, and a low level of HBsAg (<1,500 IU/mL) under NA therapy, adding or swiching to Peg-IFN could yield a relatively higher rate of HBsAg loss ((and a low level of HBsAg (<1,500 IU/mL) under NA therapy, adding or swiching to Peg-IFN could yield a relatively higher rate of HBsAg loss (*33–39*). Furthermore, a prospective cohort study from China showed that Peg-IFN α -2a-based therapy could reach high rates of HBsAg clearance (29.8% and 44.7% at week 48 and 96, respectively) and seroconversion (20.2% and 38.3% at week 48 and 96, respectively) in patients diagnosed as inactive HBsAg carrier status (*40*).

UPDATE OF GUIDELINES AND OF EDUCATION ACTIVITY

The guidelines on the Prevention and Treatment for Chronic Hepatitis B were first jointly published by the Chinese Society of Hepatology and Chinese Society of Infectious Diseases in 2005, and updated in 2010, 2015, and 2019. The 2019 version of the guidelines has two important changes (*3*). First, antiviral therapy is recommended if aminotransferase (ALT) is higher than 1 times instead of 2 times of the upper limit of normal levels (ULN, 40 IU/L for both men and women) for those with evidence of cirrhosis, intermediate degree of necroinflammation/fibrosis on non-invasive modality or on liver histology, older than 30 years, or family history of HCC/cirrhosis. This expansion of treatment indications will convey the benefit to antiviral therapy for larger populations, thereby reducing the risk of disease progression. Secondly, ETV, TDF, tenofoviralafenamide (TAF), and Peg-IFN α are recommended as the first-line choice for treatment of naïve patients, which is in line with recommendations from the World Health Organization (WHO), American Association for the Study of Liver Diseases (AASLD), Asian Pacific Association for the Study of the Liver (APASL) and European Association for the Study of the Liver (EASL); however, LAM, telbivudine (LdT), and ADV are not recommended.

With the update of the guidelines, educational activities, and training programs were conducted to improve the standard of care (SOC) for CHB in China, especially in health resource limited areas. A 3-year initiative titled "China Grassroots Hepatitis B Prevention & Treatment Training Program" was implemented by the Chinese Society of Hepatology and Chinese Society of Infectious Diseases from 2015 to 2017. Totally, 58 training sessions of 1-day courses covered nearly 10,000 primary care physicians from 31 provincial-level administrative divisions (PLADs). In 2018, the China Health Promotion Foundation launched the another 3-year hepatitis training program: "Poverty Alleviation and Health Preservation-Hepatitis Prevention and Treatment". In this program, the hepatologists and infectious disease doctors went to the remote and small cities in the 12 PLADs of western China to give the public education and clinical training to local doctors. In parallel, over 300 local physicians from the western part of China came to the 8 designated centers of excellence in Beijing, Shanghai, Guangzhou, and Chengdu for 3-months of onsite clinical training.

REIMBURSEMENT POLICY AND MASSIVE PRICE REDUCTIONS FOR ANTIVIRALS

With economic and social development, the pricing and reimbursement policies have been steadily improved. Data from Beijing indicated that coverage of antiviral therapy by basic medical insurance since 2011 has reduced the risk of developing liver-related death for patients with CHB (*8*). The selection of a potent NA with high barrier to resistance as a first-line therapy, especially in areas with limited healthcare resources, may provide the best chance of achieving treatment goals (*41*). Until 3 years earlier, NA with high barrier to resistance like ETV and TDF had been much more expensive, so they were not widely used. To make a change, the government sectors, medical community, civil societies, and manufacturers have made joint efforts. Through government negotiation, the prices of TDF and TAF have reduced by >50% and have been included in the basic medical insurance in the mainland of China. In 2019, the price of generic ETV and TDF has reduced to less than10 yuan RMB per month in 11 PLADs. Indeed, data from the China Registry of Hepatitis B (CR-HepB) showed that among all CHB patients who received NA therapy, the proportion of those who received ETV and TDF had increased from 13.5% in 2003 to 79.7% in 2016 (*42*), and the proportions in cirrhotic paitents increased from 41.9% in 2010 to 92.8% in 2019 (*43*).

PERSPECTIVE ON THE MASSIVE TEST-AND-TREAT STRATEGY

Although the number of people with new HBV infections will become smaller, there are still an estimated 80 million people that are positive for HBsAg (*44*). According to the POLARIS modeling study, in the mainland of China, only around 20% of those chronically infected with HBV were actually diagnosed and and 10% of those who were eligible to be treated received treatment (*45*). Investment case modeling studies suggested that if we only treat the few millions of CHB who are already on the treatment, the HBV-related cirrhosis/HCC mortality will still be increasing over the next two decades; on the other hand, if we scale up test-and-treatment strategies and treat most or even all persons who need the treatment, the HBV-associated mortality will dramatically decline, which is cost-effective or even cost-saving (*46*). For example, if the treatment coverage increased from current practice (12.5%) to 100% from 2018, the numbers of chronic HBV infections, new HBV infections, and HBV-related deaths in 2035 would be reduced by 26.60%, 24.88%, and 26.55%, respectively, and in 2050, it would be reduced by 44.93%, 43.29%, and 43.67%, respectively (*47*). Therefore, we can conclude that implementations of HBV vaccination and increasing the test-and-treat coverage strategies are the most important and effective in controlling CHB in China.

SUMMARY

There is no doubt that China has made great achievements in the prevention and treatment of CHB. Predictably, in the future, the prevalence of HBsAg in the general population and HBV-related morbidity and mortality will further decline if we continue the current prevention measures and adopt massive test-and-treat strategies. Finally, development of novel therapies aiming to clear HBsAg is under way. Therefore, we are confident that China will succeed in achieving the goal of eliminating hepatitis as a public health threat by 2030.

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Profiles

Qiyong Liu, China CDC's Chief Expert of Vector Control

Peter Hao[1,&]; Yu Chen[2,&]; Zhenjun Li[1]; Jingjing Xi[1,#]; Feng Tan[1,#]

Qiyong Liu is a leading expert and scientist for vector surveillance and control and leads national research on health and climate change in China. Qiyong Liu heads the World Health Organization (WHO) Collaborating Centre for Vector Surveillance and Management (WHOCCVSM) and has been awarded over 20 national and international prestigious grants including the following: National Basic Research Program of China (973 Program), the National Natural Science Foundation of China (NSFC), National Programs for Science and Technology Development, Australian Agency for International Development (AusAID), China Prosperity Strategic Programme Fund (SPF), and Wellcome Trust. His ability to build collaborations between influential multidisciplinary partners has yielded strong results and has led to his recognition with the Australia China Alumni of the Year Award 2019.

Qiyong Liu completed his undergraduate study at the Department of Biology of Shandong University in 1985, one of China's top universities, before continuing to Beijing to start work at the Department of Vector Biology and Control (DVBC), Institute of Epidemiology and Microbiology (IEM), Chinese Academy of Preventive Medicine (CAPM). Following the establishment of China CDC in 2002, this institution was renamed the National Institute for Communicable Disease Control and Prevention of China CDC. During this time, Qiyong Liu went abroad to Griffith University in Australia where he obtained a Master of Sciences in Public Health from 2004–2006 and a PhD from 2013 to 2014 in climate change and mosquito-borne disease. Combined, Qiyong Liu has more than 35 years of experience in public health and research.

With expertise in zoology, ecology, epidemiology, microbiology, and immunology, Qiyong Liu has dedicated himself to public health research with a focus on the control of disease vectors and vector-borne diseases and assessing climate-change-related health risks and adaptation. He has already become a renowned influential public health leader of global significance through his important roles and appointments in various international affairs and projects such as the 8th Communication for Leadership and Management Program, WHO Western Pacific Regional Office (WPRO; 2001–2002) in the Philippines, and the WHO consultant for vector control — responsible for risk assessment and control planning of vector borne disease in tsunami-affected area in Sri Lanka (2005) — a Medical Officer (STP) of the Communicable Disease Surveillance and Response, WHO WPRO (2007–2008), a Member of the Global Vector Control Standing Committee (GVCS) of the WHO, a Trustee of Innovative Vector Control Consortium (IVCC), and the Executive Chair of International Forum for Sustainable Vector Management (IFSVM) since 2006.

Prof. Cordia Chu, Director of the Centre for Environment and Population Health at Griffith University, supervised Qiyong Liu's Master and PhD research programs. Prof. Chu has highly recognized Liu's scientific achievements, especially his great efforts in the response to public health threats due to rapid changes in the transmission patterns and trends of vector-borne diseases (e.g., dengue, Zika, Chikungunya, Yellow fever) under the climate change scenarios. She described that "*His innovative, comprehensive, and ecological approach has greatly facilitated the sustainable management of vector-borne diseases, from effective surveillance for early warnings, to risk assessments, development of appropriate response strategies, community education, and mobilizing community participation. His expertise and contributions in public health-related policy making are far-reaching, and his research has provided important evidence to national and local governments in the development and improvement of public health systems and the prevention and control of vector-borne disease outbreaks, particularly during and after natural disasters.*"

Given that vector surveillance is the key basis of vector-borne diseases control, Qiyong Liu has worked hard to promote the development of China's vector surveillance system from the manual recording and printing of reports to the current national surveillance systems that use the internet and big data. The manual paper-based system in 1985 was based on 4 pests nationwide, and recognizing the challenges and gaps that arrived with the 21st century,

Qiyong Liu developed the current system and put forward a sustainable vector management (SVM) strategy in 2004. The SVM innovations lie in the strategic transition from outbreak response to outbreak risk reduction for dengue in China. However, vector control for disease prevention requires broad international collaboration, and Qiyong Liu saw this need and established the IFSVM in 2006 to facilitate international communication and exchange. To lead and coordinate the global community and collaborative efforts, Qiyong Liu was then designated the head of the WHOCCVSM in October 2012. Since then, he has continued to develop constructive policies, guidelines, and innovative inventions to prevent and control vectors and vector-borne diseases. These works have been continuously referenced and recirculated by the WHO headquarters and the WHO WPRO.

Filling gaps in knowledge for the prevention and control of vectors and vector-borne diseases requires not only sophisticated quantitative modeling, precise scientific laboratory testing and assessments, and fieldwork in challenging conditions. To address these issues, Qiyong Liu has conducted research in hazardous and extreme environmental conditions and locations to collect and study disease-carrying vectors such as mosquitoes, ticks, and rodents. His research work in Southeast Asia, parts of Africa, and North America exposed him to multiple infectious agents, and his continued risk-taking reflects his commitment and passion to the field.

Qiyong Liu has frequently been deployed by the Chinese national government to provide expert advice to guide local governments, healthcare practitioners, and epidemiologists in the aftermath of natural disasters within in China and also as a WHO consultant to help countries to respond to emergencies or outbreaks to develop prevention strategies and control measures. So far, Qiyong Liu has helped over 40 countries in their responses including vector control and infectious disease prevention in tsunami-affected areas in Sri Lanka, dengue and Zika control in Southeast Asia and South America, infectious disease prevention after the Sichuan Province Earthquake, malaria reductions in Sierra Leone, and Chikungunya fever in Mauritius.

Qiyong Liu's pioneering and persistent work has been repeatedly recognized throughout the world. His integrative, innovative model for SVM, for instance, has been known in the international research community as "the Chinese Model" for control strategies for *Plasmodium vivax* malaria and dengue in varying scenarios. Qiyong Liu continues to work on improving existing strategies and developing new strategies as the chief expert in vector surveillance and control at China CDC.

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Notifiable Infectious Diseases Reports

Reported Cases and Deaths of National Notifiable Infectious Diseases — China, June, 2020

Diseases	Cases	Deaths
Plague	0	0
Cholera	0	0
SARS-CoV	0	0
Acquired immune deficiency syndrome	6,915	1,811
Hepatitis	123,474	50
Hepatitis A	1,249	1
Hepatitis B	99,319	36
Hepatitis C	20,367	11
Hepatitis D	16	0
Hepatitis E	1,708	1
Other hepatitis	815	1
Poliomyelitis	0	0
Human infection with H5N1 virus	0	0
Measles	91	0
Epidemic hemorrhagic fever	826	6
Rabies	17	10
Japanese encephalitis	6	0
Dengue	4	0
Anthrax	18	0
Dysentery	7,775	0
Tuberculosis	84,952	134
Typhoid fever and paratyphoid fever	832	0
Meningococcal meningitis	3	0
Pertussis	159	1
Diphtheria	0	0
Neonatal tetanus	1	0
Scarlet fever	677	0
Brucellosis	6,193	0
Gonorrhea	9,292	0
Syphilis	46,538	5
Leptospirosis	12	0
Schistosomiasis	6	0
Malaria	74	0
Human infection with H7N9 virus	0	0
COVID-19*	517	0
Influenza	15,640	0
Mumps	11,995	0

Continued

Diseases	Cases	Deaths
Rubella	114	0
Acute hemorrhagic conjunctivitis	2,788	0
Leprosy	41	0
Typhus	113	0
Kala azar	26	0
Echinococcosis	264	0
Filariasis	0	0
Infectious diarrhea[†]	114,085	2
Hand, foot and mouth disease	6260	0
Total	439,708	2,019

[*] The data were from the website of the National Health Commission of the People's Republic of China.

[†] Infectious diarrhea excludes cholera, dysentery, typhoid fever and paratyphoid fever.

The number of cases and cause-specific deaths refer to data recorded in National Notifiable Disease Reporting System in China, which includes both clinically-diagnosed cases and laboratory-confirmed cases. Only reported cases of the 31 provincial-level administrative divisions in the mainland of China are included in the table, whereas data of Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan are not included. Monthly statistics are calculated without annual verification, which were usually conducted in February of the next year for de-duplication and verification of reported cases in annual statistics. Therefore, 12-month cases could not be added together directly to calculate the cumulative cases because the individual information might be verified via National Notifiable Disease Reporting System according to information verification or field investigations by local CDCs.

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