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Cover Photo: A child receiving a vaccination based on the Childhood Immunization Schedule (photo taken by Qingmin Xi, China CDC).

Recommendations

Childhood Immunization Schedule for National Immunization Program Vaccines — China (Version 2021)

National Health Commission of the People's Republic of China

GENERAL PRINCIPLES

Vaccination Age

The age of administration in the immunization schedule refers to the minimum age for giving a vaccine dose. Vaccines should be administered at the recommended age or as soon as possible after the recommended age. Specific timings and ages for administering certain vaccine doses are shown below and detailed in the second section, "Instructions for Use of Vaccines."

1. The first dose of hepatitis B (HepB) vaccine is to be given within 24 hours of birth.

2. Bacille Calmette-Guérin (BCG) vaccine is given <3 months of age.

3. The third dose of HepB vaccine, the third dose of poliovirus vaccine, the third dose of Diphtheria, tetanus, and pertussis (DTaP), the first dose of Measles, mumps, and rubella (MMR), and the first dose of Japanese encephalitis vaccine, live (JE-L) or the second dose of Japanese encephalitis vaccine, inactivated (JE-I) are all to be administered before 12 months of age (during infancy, before the first birthday).

4. The second dose of Group A meningococcal polysaccharide vaccine (MPSV-A) is given <18 months.

5. The second MMR dose, the first hepatitis A vaccine, live (HepA-L) or hepatitis A vaccine, inactivated (HepA-I) dose, and the fourth DTaP are all to be given <24 months of age (during the second year of life).

6. The second dose of HepA-I, and the second dose of JE-L or the third dose of JE-I are to be given <3 years of age (before the third birthday).

7. The first dose of Group A and Group C meningococcal polysaccharide vaccine (MPSV-AC) is to be given <4 years of age.

8. The fourth dose of poliovirus vaccine is to be given <5 years of age.

9. Diphtheria-Tetanus vaccine (DT), the second dose of MPSV-AC, and the fourth dose of JE-I are to be given <7 years of age.

Children who are not vaccinated on time according to the routine schedule shown above should be vaccinated in accordance with the catch-up vaccination principles, described below and given in detail in the second section, "Instructions for Use of Vaccines."

Vaccination Routes

Vaccines are given in one of several routes that are specific to each vaccine — oral, intramuscular injection (IM), subcutaneous injection (SubQ), or intradermal injection (ID). Refer to "Instructions for Use of Vaccines" for details. The injection sites are normally the deltoid muscle in the lateral aspect of the upper arm or the vastus lateralis muscle in the anterior and lateral aspect of the thigh. When multiple vaccines are given by injection at the same visit (IM, SubQ, or ID), injections may be on the left and right upper arms and the left and right thighs, sequentially. BCG should only be given via the ID route in the upper arm.

Simultaneous Vaccination and Minimum Intervals

1. When giving more than one injectable vaccine simultaneously, injections should be at different sites. Mixing vaccines in the same syringe prior to injection is strictly forbidden.

2. All National Immunization Program (NIP) vaccines may be given simultaneously according to the immunization schedule and catch-up vaccination principles.

3. It is important to pay attention to the interval between administration of different vaccines. For two or more live vaccines that are not given simultaneously by injection, a minimum interval of 28 days between injections is required. There is no minimum interval between inactivated vaccines or orally administered attenuated live vaccines that are not given simultaneously with other types of inactivated, and

TABLE 1. Childhood Immunization Schedule for National Immunization Program Vaccines (2021 Version).

Vaccine-Preventable disease	Vaccine	Route of administration	Dose	Abbreviation	Minimum age														
					Birth	1 Month	2 Months	3 Months	4 Months	5 Months	6 Months	8 Months	9 Months	18 Months	2 Years	3 Years	4 Years	5 Years	6 Years
Hepatitis B	Hepatitis B vaccine	IM	10/20 μg	HepB	1	2					3								
Tuberculosis*	Bacille Calmette-Guérin vaccine	ID	0.1 mL	BCG	1														
Poliomyelitis	Inactivated Polio vaccine	IM	0.5 mL	IPV			1	2											
	Bivalent Oral Polio vaccine	Oral	1 pill or 2 drops	bOPV					3								4		
Pertussis, diphtheria, and tetanus	Diphtheria, tetanus, and pertussis combination vaccine	IM	0.5 mL	DTaP				1	2	3				4					
	Diphtheria-Tetanus vaccine	IM	0.5 mL	DT															5
Measles, mumps and rubella	Measles, mumps, and rubella vaccine	SubQ	0.5 mL	MMR								1		2					
Japanese encephalitis†	Japanese encephalitis vaccine, live	SubQ	0.5 mL	JE-L								1			2				
	Japanese encephalitis vaccine, inactivated	IM	0.5 mL	JE-I								1, 2			3				4
Meningococcal disease	Group A meningococcal polysaccharide vaccine	SubQ	0.5 mL	MPSV-A							1		2						
	Group A and Group C meningococcal polysaccharide vaccine	SubQ	0.5 mL	MPSV-AC												3			4
Hepatitis A§	Hepatitis A vaccine, live	SubQ	0.5/1.0 mL	HepA-L										1					
	Hepatitis A vaccine, inactivated	IM	0.5 mL	HepA-I										1	2				

Note: The numbers represent the dose number of vaccines given in multi-dose series.

Abbreviations: IM=intramuscular injection; ID=intradermal injection; SubQ=subcutaneous injection.

* Tubercular meningitis and miliary tuberculosis.

† JE-L is given in a 2-dose series. JE-I is given in a 4-dose series with an interval between dose 1 and dose 2 of 7 to 10 days.

§ HepA-L is given as a single dose. HepA-I is given in a 2-dose series.

attenuated vaccines (injected or oral administration).

Catch-up Vaccination Principles

Children below 18 years of age who have not completed their NIP vaccination series by the recommended ages should be caught up based on the following principles.

1. Catch-up vaccination should be accomplished as early as possible to enable children not fully vaccinated to complete the entire vaccine series and be protected at the youngest age possible.

2. It is never necessary to restart a vaccination series; only the remaining doses need to be given.

3. If, when completing a vaccination series, the same vaccine from the same manufacturer is unavailable, the same type of vaccine from a different manufacturer may be used.

4. Additional details are in the next section, "Instructions for Use of Vaccines."

Vaccination During Epidemic Peak Seasons

NIP vaccines may be given routinely throughout the year, including during the epidemic season, according to the routine immunization schedule, catch-up vaccination principles, requirements of the immunization program, and as required by outbreak response immunization plans.

INSTRUCTIONS FOR USE OF VACCINES

Recombinant Hepatitis B Vaccine

1. Schedule

HepB vaccine is given in a 3-dose series at 0, 1, 6 months, with the first dose administered within the first 24 hours following birth, the second dose given at 1 month of age, and the third dose given at 6 months of age. HepB is administered by IM injection.

The dose to be administered varies by vaccine type. Recombinant (yeast) HepB is given only in 10 μg doses. Newborn infants are given 10 μg of HepB in a single injection, regardless of their mother's hepatitis B surface antigen (HBsAg) status (positive or negative). Recombinant (CHO cells) HepB is given in two different dose amounts, 10 μg or 20 μg. Babies born to HBsAg-negative mothers are given 10 μg of CHO HepB in a single injection, and babies born to HBsAg-positive mothers are given 20 μg of CHO HepB in a single injection.

2. Notes

Babies delivered in hospitals should be given the first dose of HepB in the hospital, with the birthing hospital responsible for ensuring vaccine administration. Subsequent doses of HepB are given by the responsible vaccination service center. Newborns not delivered in hospitals are to be given all three HepB doses by the district vaccination service center.

If the mother is HBsAg-positive, 100 units of Hepatitis B hyper-immune globulin (HBIG) are to be administered via intramuscular injection as prescribed by the doctor. HBIG is given with the first dose of HepB vaccine, injected simultaneously in a different limb. HepB, HBIG, and BCG vaccine may be administered simultaneously (at different injection sites).

If the mother is HBsAg-positive or has unknown HBsAg status, the first dose of HepB should be given as early as possible, within 12 hours of birth. Infants whose birth weight is <2,000 grams should receive the first dose of HepB as soon as possible after birth; they should be given an additional 3 doses of HepB (4 doses total) beginning at 1 month of age, with the third and fourth doses given at 2 months and 7 months of age.

Newborn infants who are critically ill, have very low birth weights of less than 1,500 grams, have severe birth defects, suffer from severe asphyxia, or have respiratory distress syndrome should be given the first dose of HepB as soon as possible, once vital signs have stabilized.

For infants born to HBsAg positive mothers who receive post-vaccination serologic testing (PVST) for HBsAg and anti-HBs 1–2 months after the last dose of HepB, if the HBsAg test is negative, and the anti-HBs test is negative or less than 10 mIU/mL, 3 additional doses of HepB can be given at no charge to the family, in accordance with the catch-up schedule.

3. Catch-up vaccination

Infants not vaccinated within 24 hours of birth should be vaccinated as soon as possible. Infants who have not received their vaccinations on time should complete the remaining doses as soon as feasible, paying attention to minimum intervals. The minimum interval between dose 1 and dose 2 is 28 days; between dose 2 and dose 3, 60 days; between dose 1 and dose 3 is 4 months.

BCG Vaccine

1. Schedule

BCG vaccine is recommended for 1 dose, given at

birth through ID. The dose is 0.1 mL.

2. Notes

Subcutaneous or intramuscular injection is strictly prohibited.

Preterm infants born at gestational age >31 weeks and who are in stable condition according to medical evaluation may receive BCG vaccine. Preterm infants born at gestational age ≤31 weeks may be vaccinated before hospital discharge when their condition is stable according to medical evaluation.

There are no special restrictions on the interval between immunoglobulin administration and BCG vaccination.

3. Catch-up vaccination

Infants below 3 months of age may be vaccinated with BCG vaccine.

Children 3 months to 3 years of age whose tuberculin pure protein derivative (TB-PPD)- or Bacilli Calmette Guérin pure protein derivative (BCG-PPD) test is negative and who have not been vaccinated should be provided with catch-up vaccination.

Children 4 years of age and older cannot receive BCG catch-up vaccination.

Children who have been vaccinated with BCG cannot receive BCG catch-up vaccination, even in the absence of a BCG scar.

Poliovirus Vaccines (IPV and bOPV)

1. Schedule

Poliovirus vaccination is administered in a 4-dose series — inactivated poliovirus vaccine (IPV) is given at 2 months and 3 months of age followed by bivalent oral poliovirus vaccine (bOPV) given at 4 months and 4 years of age (a 4-dose IPV-IPV-bOPV-bOPV schedule).

IPV is given by IM injection with a dose amount of 0.5 mL; bOPV is given orally as 1 dragée candy or 2 drops of liquid bOPV (approximately 0.1 mL).

2. Notes

A child who receives a 4-dose-series of IPV or a 4-dose-series of an IPV-containing combination vaccine given in a schedule consistent with the vaccine package insert is considered fully vaccinated against poliovirus. It is not necessary to give bOPV to children at 4 years of age if they have completed a 4-dose series of IPV-containing vaccine.

Some children are recommended to receive only IPV. These children include those with a primary immunodeficiency, who have thymic disease, are living with HIV, have malignant tumors and are undergoing chemotherapy, are currently undergoing hematopoietic stem cell transplantation, are using immunosuppressive or immunomodulating drugs (e.g., high-dose systemic corticosteroids, alkylating agents, anti-metabolic drugs, TNF-α inhibitors, IL-1 blockers, or other immune cell-targeted monoclonal antibodies), or are receiving or have received immune cell-targeted radiation therapy.

3. Catch-up vaccination

Children less than 4 years of age who have not received 3 doses of poliovirus vaccine (including catch-up vaccination) should complete the 3-dose series. Children 4 years and older who have not received 4 doses of poliovirus vaccine (including catch-up vaccination) should complete the 4-dose series. For catch-up vaccination, IPV takes precedence over bOPV. The minimum interval between any 2 doses is 28 days. Children who have received 4 doses of polio vaccine after catch-up vaccination should be considered to have completed their full course of polio vaccination.

Children with delayed or missed polio vaccinations but with a vaccination history of trivalent OPV (tOPV), regardless of the number of doses, may be vaccinated with bOPV instead of IPV. For children with no tOPV vaccination history, if they were born before October 1, 2019 (a date when the 2-dose IPV immunization schedule was implemented, and which may vary by PLAD), they should be given 1 dose of IPV; if they were born after October 1, 2019, they should be given 2 doses of IPV.

DTaP and DT Vaccines

1. Schedule

DTaP and DT are given in a 5-dose series: DTaP at 3 months, 4 months, 5 months, and 18 months of age, and DT at 6 years of age. DTaP and DT are given by IM injection with doses of 0.5 mL.

2. Notes

Children who have been vaccinated with a DTaP-containing combination vaccine according to the vaccine package insert may be considered as to have completed the corresponding dose of DTaP vaccines.

The vaccine type (DTaP or DT) should be selected based on the age of administration: DTaP is for children aged 3 months to 5 years; child-type DT is appropriate for children aged 6 to 11 years old.

3. Catch-up vaccination

Children who did not receive the recommended number of DTaP vaccine doses and who are 3 months

to 5 years of age should receive the remaining DTaP doses through catch-up vaccination. The minimum interval between any of the first 3 doses is 28 days; the minimum interval between the third and fourth doses is 6 months.

Catch-up vaccination of children 6 years and older is subject to the following principles. Children who received fewer than 3 doses of DTaP/DT should receive a cumulative total of 3 doses of DT. Acceptable intervals are 1 to 2 months between the first and second doses, and 6 to 12 months between the second and third doses.

Children who have received 3 or more doses of DTaP/DT cumulatively should be caught up with the following principles. If the child has received at least 1 dose of DT, there is no need for catch-up vaccination. If the child has received only 3 doses of DTaP, he or she should receive 1 dose of DT, with a minimum interval of 6 months between the third dose of DTaP and the DT dose. If the child has received 4 doses of DTaP but no DT vaccine by 7 years of age, he or she should be given 1 dose of DT, with a minimum interval of 12 months between the fourth dose of DTaP and the DT dose.

MMR Vaccine

1. Schedule

Children should receive 2 doses of MMR vaccine — the first dose at 8 months and a second dose at 18 months. MMR vaccine is given by subcutaneous injection (SubQ) with a dose amount of 0.5 mL.

2. Notes

If a child is in need of MMR and other vaccines, but it is not possible to give all of the vaccines at the same visit, MMR should be the priority vaccine to be administered, and the other vaccines should be given later.

There is a minimum interval of 3 months between administration of immunoglobulin and subsequent administration of MMR vaccine. No immunoglobulin should be given during the 2 weeks after MMR vaccination.

If emergency measles vaccination is necessary according to an epidemiological situation such as an outbreak of measles, children 6 to 7 months of age at risk of measles may receive a single dose of MMR vaccine. This dose is considered a supplemental dose and is not counted as part of routine immunization.

3. Catch-up vaccination

From June 1, 2020, children who have not received 2 doses of MMR vaccine and were born on or after October 1, 2019 should be given MMR to complete the vaccination series.

Children born between 2007 (when MMR vaccine was included in the Expanded Program on Immunization [EPI]) and September 30, 2019, should receive at least 2 doses of measles-containing vaccine, 1 dose of rubella-containing vaccine, and 1 dose of mumps-containing vaccine. MMR should be used to complete the vaccination series if any of the above doses have not been fully received.

Children born before the 2007 inclusion of MMR into EPI, who are under 18 years of age, and have not received 2 doses of measles-containing vaccine, should be given MMR to complete their measles-containing vaccination series.

The minimum interval between MMR doses is 28 days.

JE-L Vaccine

1. Schedule

JE-L is given as a 2-dose series: the first dose at 8 months and a second dose at 2 years. JE-L is given by subcutaneous injection (SubQ) with a dose amount of 0.5 mL.

2. Notes

People living in Qinghai, Xinjiang, or Tibet who have never received JE vaccination are recommended to receive 1 dose of JE-L prior to travelling to other provincial-level administrative divisions (PLADs) during the JE epidemic season, or prior to moving to settle down in another PLAD.

There should be a 3-month interval between receiving immunoglobulin and being vaccinated with JE-L vaccine.

3. Catch-up vaccination

Age-eligible children born after 2007, when JE-L vaccine was included into EPI, who have not received JE-L should be given 2 doses of JE-L (if JE-L vaccination is chosen) with a minimum interval of 12 months between doses.

JE-I Vaccine

1. Schedule

JE-I is administered in a 4-dose series, with 2 doses give at 8 months with an interval of 7 to 10 days, 1 dose given at 2 years, and 1 dose given at 6 years. JE-I is given by IM in a dose amount of 0.5 mL.

2. Notes

There is a 1-month minimum interval between

receipt of immunoglobulin and vaccination with JE-I.

3. Catch-up vaccination

Age-eligible children who were born after JE-I vaccine was included into EPI (2007) and have not received JE-I vaccine should be given 4 doses of JE-I (if JE-I vaccine is chosen) with a 7-to-10-day interval between the first dose and the second dose, a 1–12-month interval between the second dose and the third dose, and minimum 3-year interval between the third dose and the fourth dose.

MPSV-A and MPSV-AC Vaccines

1. Schedule

MPSV-A and MPSV-AC vaccines are given in a 4-dose series: 2 doses of MPSV-A (a dose at 6 months and another dose at 9 months) followed by 2 doses of MPSV-AC (a dose at 3 years and another dose at 6 years). MPSV-A and MPSV-AC are given by subcutaneous injection with dose amounts of 0.5 mL.

2. Notes

A minimum interval of 3 months is recommended between any 2 doses of MPSV-A. A minimum interval of 12 months is recommended between the second dose of MPSV-A and the first dose of MPSV-AC.

An interval of at least 3 years is recommended between any 2 doses of MPSV-AC. Repeat vaccination should be avoided for 3 years.

If emergency vaccination against meningitis is necessary, an appropriate meningococcal vaccine should be chosen based on epidemiological characteristics and bacteria serogroup caused the epidemic.

Children less than 24 months old are considered to have completed the recommended schedule of MPSV-A vaccine if they received valid doses of meningococcal polysaccharide conjugate vaccine (MPCV-AC) according to the vaccine package insert.

Children are considered to have completed the recommended schedule of MPSV-AC vaccine if have received meningococcal vaccines containing serogroups A and C by 3 years and 6 years.

3. Catch-up vaccination

Children who were born after MPSV vaccine was included into EPI (2007) and have not received MPSV or completed the prescribed vaccine series should be given an appropriate type of MPSV based on their age. Children less than 24 months old should be given the missed doses of MPSV-A. Children 24 months or above should be given 2 doses of MPSV-AC, and MPSV-A is not necessary. Children 24 months or above who have not received MPSV-A should be given MPSV-AC as soon as possible before 3 years of age; if the child received 1 dose of MPSV-A, he or she should be given MPSV-AC as soon as possible, after a minimum interval of 3 months. Intervals for catch-up doses should comply with the requirements under "notes" above.

HepA-L Vaccine

1. Schedule

HepA-L is given at 18 months of age via SubQ (subcutaneous) injection with a dose amount of either 0.5 mL or 1.0 mL, depending on the vaccine package insert.

2. Notes

Children who have received 2 or more doses of HepA-I-containing vaccine are considered to have completed the HepA vaccine series and do not need HepA-L vaccine.

There is a 3-month minimum interval between administration of immunoglobulin and vaccination with HepA-L vaccine.

3. Catch-up vaccination

Age-eligible children should be given 1 dose of HepA-L (if HepA-L vaccine is chosen) if they were born after HepA vaccine was included into EPI (2007) and have not received HepA.

HepA-I Vaccine

1. Schedule

HepA-I is given as a 2-dose series: the first dose at 18 months and the second dose at 24 months. HepA-I is given by IM (intramuscular) injection in a dose amount of 0.5 mL.

2. Notes

Children should be considered as to have completed the HepA-I vaccination series if they have received 2 or more doses of a HepA-I-containing combination vaccine.

3. Catch-up vaccination

Age-eligible children born after HepA vaccine was included into EPI (2007) and have not received HepA should be given 2 doses of HepA-I (if HepA-I vaccine is chosen) with a minimum interval of 6 months between doses.

If the second dose of HepA-I vaccine is not available, children who received a single dose of HepA-I vaccine may complete their HepA vaccination series by administration of 1 dose of HepA-L after a minimum interval of 6 months following HepA-I

administration.

VACCINATIONS FOR CHILDREN WITH MEDICAL CONDITIONS

Prematurely Born and Low Birthweight Infants

Preterm (delivery before 37 weeks of gestation) and/or low birthweight (less than 2,500 grams at birth) infants should be vaccinated at their calendar age if they are assessed to be medically stable and are continuously improving medically (i.e., without requiring ongoing treatment of severe infection, metabolic diseases, acute kidney disease, liver disease, cardiovascular disease, neurological, or respiratory diseases). For BCG vaccination, see BCG vaccine notes, above.

Allergy

An "allergic constitution" is not a contraindication to vaccination. Children who have a severe allergy to any vaccine ingredient or have previously had throat swelling, anaphylactic shock, or any other severe systemic allergic reaction to a vaccine component are not permitted to receive the same type of vaccine.

Children Born to Mothers Living with HIV

For purposes of immunization, children are in 1 of 3 human immunodeficiency virus (HIV) infection statuses after being born to an HIV-infected mother: (1) HIV-infected children; (2) children with unknown HIV status; and (3) non-HIV-infected children. Medical institutions make a diagnosis of whether a child is HIV-infected or has any symptom or sign of immunosuppression. Children younger than 18 months who were born to an HIV-infected mother do not need to be screened for HIV prior to vaccination, but should be managed as having unknown HIV status, as described in the table below, until their HIV status is determined.

Children born to an HIV-infected mothers should not be vaccinated with BCG vaccine immediately after birth. BCG should be offered only if the infant is confirmed to be not HIV-infected.

Children born to HIV-infected mothers who have been diagnosed with AIDS-related symptoms or who have symptoms or signs of immune deficiency according to medical institutions should not be vaccinated with any measles-containing vaccine; measles-containing vaccines can be given to children without AIDS-related symptoms.

Children born to HIV-infected mothers can be

TABLE 2. Recommended national immunization program vaccines for children born to HIV-infected mothers.

Vaccine	HIV-infected children		Children with unknown HIV status		Non-HIV-infected children
	With symptoms or immunosuppression	Without symptoms or immunosuppression	With symptoms or immunosuppression	Without symptoms	
HepB	√	√	√	√	√
BCG	×	×	Delay vaccination	Delay vaccination	√
IPV	√	√	√	√	√
bOPV	×	×	×	×	√
DTaP	√	√	√	√	√
DT	√	√	√	√	√
MMR	×	√	×	√	√
JE-I	√	√	√	√	√
JE-L	×	×	×	×	√
MPSV-A	√	√	√	√	√
MPSV-AC	√	√	√	√	√
HepA-L	×	×	×	×	√
HepA-I	√	√	√	√	√

Note: Delay vaccination: Supplemental vaccination should be offered to children if HIV antibody has been confirmed negative, and should not be given to children whose HIV antibody is confirmed positive. "√" means "no special contraindications", and "×" means "no vaccination." HepB=Hepatitis B vaccine; BCG=Bacillus Calmette-Guerin vaccine; IPV=Inactivated Polio vaccine; bOPV=Bivalent Oral Polio vaccine; DTaP=Diphtheria, tetanus, and pertussis combination vaccine; DT=Diphtheria-Tetanus vaccine; MMR=Measles, mumps, and rubella vaccine; JE-I=Japanese encephalitis vaccine, inactivated; JE-L=Japanese encephalitis vaccine, live; MPSV-A=Group A meningococcal polysaccharide vaccine; MPSV-AC=Group A and Group C meningococcal polysaccharide vaccine; HepA-L=Hepatitis A vaccine, live; HepA-I=Hepatitis A vaccine, inactivated.

vaccinated with HepB, DTaP, MPSV-A, MPSV-AC, and DT according to the immunization schedule.

Children born to HIV-infected mothers should not be vaccinated with JE-L, HepA-L, or bOPV unless they are clearly not HIV infected. The inactivated versions of these three vaccines JE-I, HepA-I, and IPV can be given according to the immunization schedule.

Children born to non-HIV-infected mothers do not need routine HIV screening before vaccination. If a child has exposure risk and is diagnosed with HIV infection, follow-up vaccination should follow the vaccination recommendations for HIV-infected children in the attached table.

Please refer to the table below for recommendations of NIP vaccines for children according to HIV status.

Immune Function Abnormalities

Children with immunodeficiencies or who are undergoing systemic immunosuppressive therapy, excluding HIV-infected children as per above, as a principle, should receive inactivated vaccines rather than live vaccines. This principle does not apply to patients with complement deficiency.

Other Medical Conditions

The following conditions are not contraindications to vaccination: physiological jaundice, breast-milk jaundice, history of simple febrile convulsions, epilepsy controlled by medication, static neurologic disorders, liver disease, common congenital diseases (e.g., congenital hypothyroidism, phenylketonuria, Down syndrome, congenital heart disease), and congenital infections (e.g., syphilis, cytomegalovirus, and rubella).

Children with other medical conditions can be vaccinated according to the immunization schedule, in principle, if there is no clear evidence that vaccination poses safety risks.

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Outbreak Reports

Human Plague Case Diagnosed in Ningxia Tracked to Animal Reservoirs — Inner Mongolia Autonomous Region, China, 2021

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Summary

What is already known about this topic?

There were a total of 4 and 3 human plague cases that occurred in the Inner Mongolia Autonomous Region in 2019 and 2020, respectively, with 1 and 2 deaths in 2019 and 2020 respectively, which indicated that plague still poses a significant threat to human health especially for farmers, shepherds, or residents living in native plague foci.

What is added by this report?

On August 14, 2021, 1 patient from the Otog Qi (County) in the Inner Mongolia sought treatment in Yinchuan City (the capital of Ningxia Hui Autonomous Region), where the patient was diagnosed with bubonic plague and secondary septicemic plague. The genetic source tracking of associated *Yersinia pestis* strains indicated that human plague cases were infected from animal reservoirs in Inner Mongolia.

What are the implications for public health practice?

Major threats of plague to residents living in native plague foci are the infection by bites of bacterium-bearing fleas or direct contact with diseased or dead plague-infected animals. And the ability of early diagnostic is very critical for county-level hospital in native plague foci.

On August 20, 2021, a human plague case (55-year-old woman) suffered bubonic plague with secondary septicemic plague was reported from General Hospital of Ningxia Medical University (GHNMU) in Ningxia Hui Autonomous Region (Ningxia), China. Effective patient's treatment, together with enhanced rodents plague surveillance and control, was performed in Ningxia and Inner Mongolia Autonomous Region (Inner Mongolia). The genome-wide single nucleotide polymorphism (SNP) analysis was used in source tracing based on phylogenetic relationship of *Yersinia pestis* (*Y. pestis*) strains in this event. The *Y. pestis* strain isolated from the patient in Ningxia and the strain from local *Meriones unguiculatus* (*M. unguiculatus*) that were found near the patients' residences were clustered into the same lineage (2.MED3q). Such observations indicated that human plague cases originated from local reservoirs.

INVESTIGATION AND RESULTS

On August 20, 2021, a human plague case suffering from bubonic plague with secondary septicemic plague was reported from GHNMU in Ningxia. The patient was a 55-year-old female herdsman who lived in Wulan Village, Otog Qi (County), Erdos City in Inner Mongolia. On August 14 and 15, 2021, the patient presented with the onset of nausea and vomiting with low blood pressure and sought treatment in a village clinic but the patient's condition deteriorated further. On August 16, 2021, the patient was admitted to the local county hospital in Pingluo County of Ningxia for high fever (40 °C) with weakness and vomiting. Subsequently, on August 17 later, the patient was transferred to GHNMU in Yinchuan City and was admitted to the intensive care unit (ICU) for septic shock symptoms with left inguinal lymphadenitis. During this period, no coughing, chest pain, or breathlessness was observed. Thereafter, the blood of patient was conducted a bacteria culture and examined through biochemical analyzer in GHNMU, and the results of biochemical analyzer reported that bacteria in the patient's blood was *Yersina* genus. Such results led the clinical doctors in GHNMU began to suspect the patient might suffer from plague and reported to the Ningxia CDC on August 20.

This human plague case was confirmed via polymerase chain reaction (PCR) positive results in lymph node aspirates and blood by the Ningxia CDC within four hours, targeting the *caf*1, *pla*, and

YPO0392 genes of *Y. pestis* (*1*), as well as the positive results of the colloidal gold-immunochromatography assay and reverse indirect hemagglutination assay (RIHA) test targeting the F1 antigen in lymph node aspirates and blood. The titer of RIHA for the lymph node aspirates and blood were 1∶64 and 1∶128, respectively. In addition, the bacteria isolated from blood were identified as *Y. pestis* by Gram staining, microscopy, and a phage lysis test. While, the PCR assays for the patient were negative in the sputum and throat specimens of the patient.

Based on clinical manifestations and laboratory test results, the patient was diagnosed with bubonic plague with secondary septicemic plague and she was treated with antibiotics (streptomycin and ciprofloxacin) and recovered on September 6, 2021.

One *Y. pestis* (Ningxia 2021) isolated from the 55-year-old patient was sequenced by Ningxia CDC. Meanwhile, one strain (Neimeng 2021) isolated from *M. unguiculatus* eighty meters away from the house of the patient was isolated and sequenced by Inner Mongolia CDC. Under the source tracing mechanism of the Chinese Pathogen Identification Net (CPIN), the patient-related (Ningxia 2021), the strain from *M. unguiculatus* in Inner Mongolia (Neimeng 2021), *Y. pestis* strains isolated from Inner Mongolia in 2019, together with *Y. pestis* genomes in CPIN were compared by the genome-wide SNPs (*2*). As shown in Figure 1A, the strain isolated from the patient and the strain isolated from *M.unguiculatus* 80 meters away from the houses of patient were clustered as 2.MED3q lineage, a lineage inherently belonging to the *Y. pestis* in the Erdos Plateaus *M. unguiculatus* plague focus in Inner Mongolia in 2019 (*2*).

In this *Y. pestis* infection event, the patient was a shepherd, and the family of the patient lived in a comparatively independent house that was located on the Ordos Plateaus *M. unguiculatus* plague focus in Inner Mongolia. There were a total of six families together with the patient's family within a three-kilometer radius away from the house of the patient. According to reports from local residents, in the past two months, several dead *M. unguiculatus* had been found in the region before the case of human plague occurred. Because there were a total of four and three human plague cases occurred in the Inner Mongolia in 2019 and 2020, respectively, with 1 and 2 deaths in 2019 and 2020, respectively, and there were 2 *Y. pestis* strains isolated from *M. unguiculatus* plague focus in Otog Qi in 2019, thus regulations were performing in Inner Mongolia that the local residents should be alerted to dead reservoirs and were required to report to local CDCs once the affected areas were found. The family of patient just had moved from Ningxia and been employed by a local inhabitant for only one year, so they did not know of the regulations and neglected to report dead rat phenomenon. Other five families' residents reported the abnormal dead rats phenomenon, and local professional staff conducted rodenticides in residential surrounding areas, but nothing less than the areas patient lived in was left.

After the human plague was confirmed, an enhanced rodent surveillance campaign was performed. A total of 2 recently dead *M. unguiculatus* were found, and the *Y. pestis* strain was isolated from each dead rat, with one just 80 meters away from the house of patient; in addition, over 70 fleas were found on the rat. In addition, there were a large number of fleas inhabiting those reported reservoirs. Such an observation indicated that serious *M. unguiculatus* plague epizootics with plenty of fleas existed in the patient's living areas and that the patient might have been infected from a flea bite.

PUBLIC HEALTH RESPONSE

First, before the 55-year-old patient was diagnosed as having plague, she sought treatment in 4 clinics or hospitals in Inner Mongolia and Ningxia. Therefore, it is critical to strengthen professional training for local clinicians in order to recognize and identify the disease earlier and be alerting to various forms of plague. In addition, the patient suffered from bubonic plague with secondary septicemic plague; unlike the pneumonic plague, the bubonic and the septicemic plague has limited the ability of person-to-person transmission (*3*). Therefore, more reasonable public health measures should be recommended in affected areas.

Secondly, since the human plague cases occurred in 2019 and 2020, the local CDCs had offered the local farmers or shepherds a Health Box [which included insect repellent (DEET), thermometer and report card et al.]. Corresponding educational efforts should be enhanced to promote behaviors such as wearing long pants and applying DEET to anyone engaged in outdoor activities in plague focus area; reporting rodent die-offs; avoiding direct contact with sick or dead wild animals (e.g., foxes or rabbits); using insecticides and rodenticides to eliminate the fleas and the host animals simultaneously, or insecticide be priority to animal plague control.

Thirdly, the Ordos Plateaus *M. unguiculatus* plague focus in Inner Mongolia is also adjacent to Ningxia

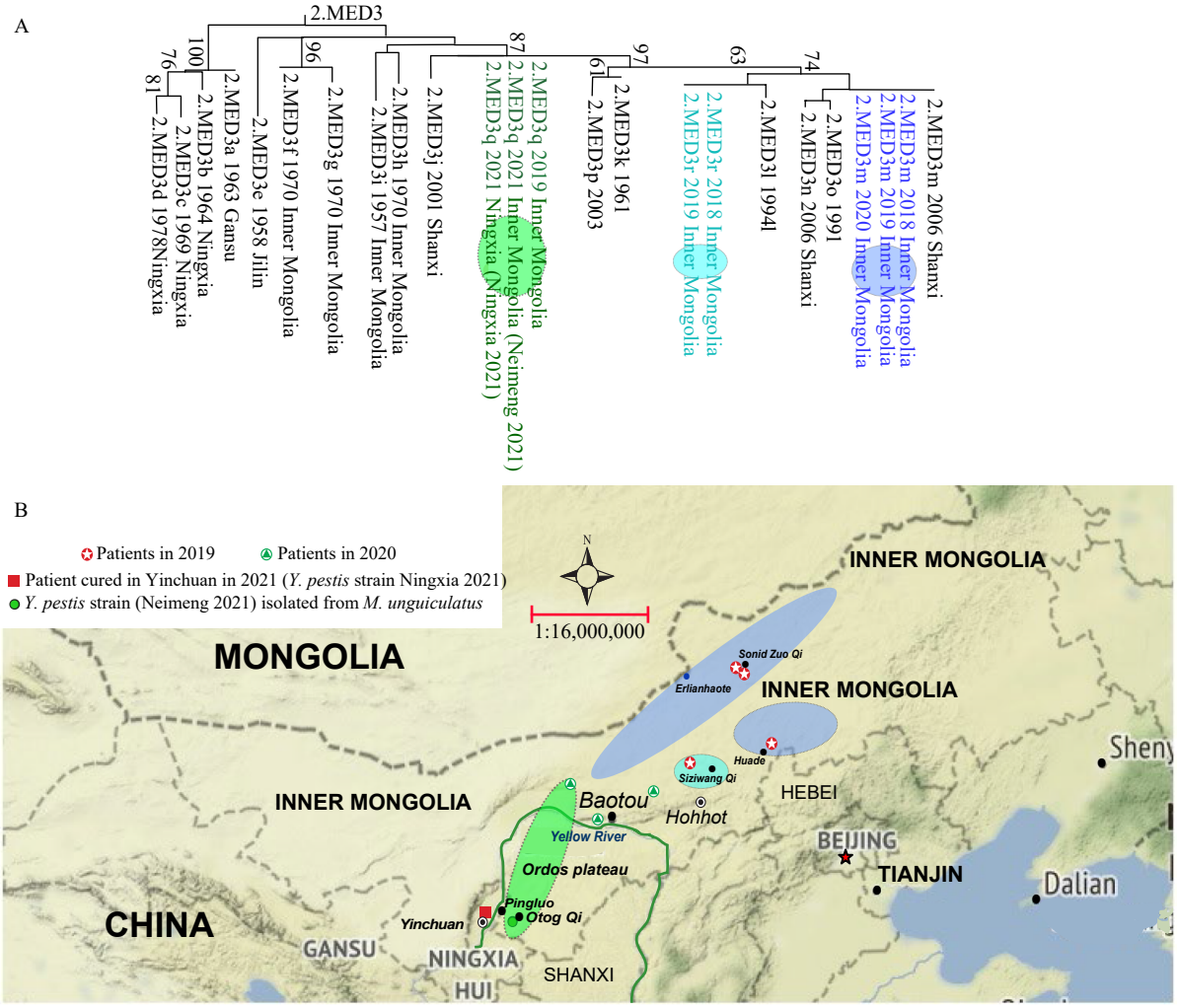

FIGURE 1. Geographical distribution and phylogenetic relationship of patients and various epizootics in Inner Mongolia and Ningxia. (A) Phylogenetic relationship based on whole genomic SNPs in *Y. pestis* 2. MED3 population. (B) Geographical distribution of phylogenetic lineages in Inner Mongolia.
Note: The maximum likelihood tree in Figure 1A was constructed by the concatenated SNP using MEGA (Molecular Evolutionary Genetics Analysis Version 6.0. Tamura K, Stecher G, Peterson D, Filipski A, and Kumar S, 2013). Strains in colored circle on evolutionary trees isolated from the sites with same color on the map.

and Shanxi provincial-level administrative divisions (PLADs) in China (Figure 1B). There are no obvious geographic barriers between the *M. unguiculatus* plague focus in Inner Mongolia and its counterpart area in adjacent PLADs, so the joint prevention and control, including early joint warning and risk communication are necessary.

In addition, in the process of responding to the human plague events in China, the clinics commonly responsible for finding and treating patients, while the various level CDCs confirmed the diagnosis according to evidence based on laboratory assays. In this event, the biochemical analyzer in GHNMU reported that bacteria in the patient's blood were of the *Yersinia* genus, even though it did not definitively that the sample was *Y. pestis* (due to lacking a corresponding database of bacteria), the clinicians began to suspect that the patient might have plague. It was the second time that such situation had occurred in China as the first occurred in Yunnan Province in 2016 (*1*). In fact, with the gains in technical competence in hospitals, there are many techniques such as the genome sequencing, biochemical analyzers, and mass-spectrometric techniques, that can firstly give the clinicians the clues to plague.

DISCUSSION

The *M. unguiculatus* plague focus in Inner Mongolia

can be divided into two parts: the Ordos Plateaus and the desert steppe of the Ulanqab plateaus. Previous studies provided insight into the relationship between plague intensity and the level of precipitation in the semi-arid grasslands of Inner Mongolia (*4*). i.e., Plague epizootics depend on changes in the density and distribution of local *M. unguiculatus* (*3*), while elevated rainfall facilitates increasing population levels of *M. unguiculatus* (*4*). A great increase in the local rodent population was an obvious feature in Inner Mongolia *M. unguiculatus* plague focus in 2019 (*2*). In 2019, a comparatively higher density (3.1/hm^2) of the major host in this focus than the historical average level (2/hm^2) on the Inner Mongolia Plateau (*5*) was observed. In 2021, drought was the main feature in Ordos Plateaus. The density of the main host reached to 4.46/hm^2, and high flea density is a major feature of Otog Qi in August, such as the percentage of host infested flea was 52.63% with host-flea index was 3.93 in Otog Qi in August 2021. Similar situations could be observed in the adjacent Pingluo county, the percentage index and host-flea index were 59.26% and 2.15, respectively, in August (local plague surveillance data). Such ecological factors, i.e., higher flea density, also aroused a more potent animal plague epidemic with more risk of human infection.

EPIZOOTICS OF PLAGUE IN 2018 TO 2021 IN INNER MONGOLIA

Plague is primarily a disease of wild rodents. Animal-to-animal transmission is mediated by flea bites, while human infection is often an accidental event, including being infected by the bites of escaped bacterium-bearing fleas. Continuous animal plague had occurred in previous years (in 2018, 2019, and 2020) in the *M. unguiculatus* Plague Focus in Inner Mongolia, and corresponding surveillance results indicated that animal plague epizootics were still active in the *M. unguiculatus* Plague Focus in Inner Mongolia (National Plague Surveillance report).

The *Y. pestis* strains inhabiting Inner Mongolia belong to 2.MED3 population. While *Y. pestis* strains in 2.MED3 population were further divided into various lineages (2.MED3a–p) in Inner Mongolia or adjacent PLADs such as Shanxi, Hebei, and Ningxia in China (*6*) (Figure 1). The *Y. pestis* strains isolated in 2018 and 2019 in Inner Mongolia could be divided into 3 lineages (2.MED3m, 2.MED3q, 2.MED3r) (*2*). Previous research found lineage 2.MED3m was a major lineage generally and affected most of the geographical area in Inner Mongolia *M. unguiculatus* plague focus in 2018 and 2019 (*2*). However, the patient-related stain was 2.MED3q lineage, which was mainly located in the Ordos Plateaus *M. unguiculatus* Plague Focus in Inner Mongolia (*2*).

Conflicts of interest: No conflicts of interest.

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Preplanned Studies

Incidence Tendency Analysis on Type 2 Diabetes in 4 Asian Countries — China, Malaysia, Singapore, and Thailand, 1990–2019

Wenhui Shi[1]; Qiqi Wang[2]; Jiaojiao Zhang[3]; Jingwen Zhang[4]; Feng Tan[5,#]; Shicheng Yu[2,#]

Summary

What is already known about this topic?

Roughly 80% of the global disease burden caused by diabetes comes from low-and-middle income countries, and 60% of diabetics are located in Asia; 6 of the top 10 countries with the highest prevalence of diabetes are in Asia.

What is added by this report?

Compared with 1990, the growth rate of the standardized incidence rate of type 2 diabetes in 2019 in China was significantly lower than that of the entire world, while Malaysia, Singapore, and Thailand all had a negative growth rate in incidence. A great difference was found by the 5-year growth of the standardized incidence rate of type 2 diabetes from 1990 to 2019 in the 4 selected countries.

What are the implications for public health practices?

Compared with the measures taken for comprehensive prevention and control of risk factors in Singapore, there is still a lot of work that needs to be done in China, Malaysia, and Thailand.

The International Diabetes Federation (IDF) has pointed out that 60% of diabetics are from Asia (*1*). Moreover, 6 of the top 10 countries with the highest prevalence of diabetes are also in Asia. The 30 years results of Daqing's diabetes prevention and control program in China showed that a healthy lifestyle has a long-term effect on diabetes prevention (*2*). In this article, 4 Asian countries were selected (China, Malaysia, Singapore, and Thailand) that have taken measures to prevent and control diabetes at the national level and also have the largest ethnically Chinese populations in Asia.

All data used in this article, i.e., the incidence of type 2 diabetes, were fetched from Global Burden of Disease (GBD) 2019 (*3–4*), and *the standardized incidence rates* (*IRs*, /100,000) was calculated based on *the World Standard Population in 2019* provided by GBD 2019 (*3*). The growth rate, 5-year growth, and annual speed of increase between 1990 to 2019 were adopted as a metric to represent and evaluate the tendency of the standardized incidence rate along with time. Based on the results and analyses, evidence and guidance are provided for implementing and evaluating diabetes prevention and control.

Table 1 showed that there was a huge difference in the changes of the standardized incidence, e.g., growth rate and annual speed of increase, from 1990 to 2019 between the 4 Asian countries and the entire world. The global standardized incidence rate has increased by more than 40%. The increase of the incidence in China, with a growth rate of 6.26%, was significantly lower than that of the world overall. Although differing in the specific values, Malaysia, Singapore, and Thailand all have had a negative growth rate in incidence; particularly, the incidence growth rates were –50.02%, –86.88%, and –26.75%, respectively.

As shown in Table 2, like the former observation, the 5-year growth of the standardized incidence from 1990 to 2019 differed greatly among the 4 Asian countries. Specifically, China has an overall increasing trend, and its growth rate fluctuates greatly. A negative growth period could be observed in 1990–1995 and 2005–2015, during which its overall growth rate gradually slowed down, and there was no incremental change from 2015 to 2019. The annual speed of increase of Malaysia showed a rapid decrease on average, but it rebounded from 2015 to 2019 with an annual speed of increase of 3.69%. The annual speed of increase of Singapore was also continuously decreasing, where a rapid decline could be seen during 2005–2015, with a decreasing rate of 15% approximately. However, the speed of decline in Singapore was reduced to 0.82% during 2015–2019. In general, the decreasing rate of Singapore was quite higher than that of Malaysia from 1990 to 2019. The annual speed of increase of Thailand presented an

TABLE 1. The standardized incidence rate of type 2 diabetes and its changes worldwide, 1990–2019.

Nations	Standardized incidence rate (/100,000)		Changes of 2019 relative to 1990		
	1990	2019	Increment (/100,000)	Growth rate (%)	Annual speed of increase (%)
Worldwide	184.55	259.94	75.39	40.85	1.82
China	8.63	9.17	0.54	6.26	0.32
Malaysia	26.57	13.28	–13.29	–50.02	–3.58
Singapore	18.22	2.39	–15.83	–86.88	–10.14
Thailand	24.90	18.24	–6.66	–26.75	–1.62

TABLE 2. The 5-year growth of the standardized incidence rate in China, Singapore, Malaysia, and Thailand, 1990–2019.

Year	China			Malaysia			Singapore			Thailand		
	IRs	*ΔIRs*	*ASI*	*IRs*	*ΔIRs*	*ASI*	*IRs*	*ΔIRs*	*ASI*	*IRs*	*ΔIRs*	*ASI*
1990	8.63	–	–	26.57	–	–	18.22	–	–	24.90	–	–
1995	8.43	–0.20	–0.47	25.44	–1.13	–0.87	12.82	–5.40	–6.79	26.73	1.83	1.43
2000	9.40	0.97	2.20	24.85	–0.59	–0.47	12.60	–0.22	–0.35	24.58	–2.15	–1.66
2005	10.65	1.25	2.53	20.98	–3.87	–3.33	11.59	–1.01	–1.66	18.64	–5.94	–5.38
2010	9.54	–1.11	–2.18	13.77	–7.21	–8.08	5.39	–6.20	–14.20	16.59	–2.05	–2.30
2015	9.17	–0.37	–0.79	11.49	–2.28	–3.56	2.47	–2.92	–14.45	17.51	0.92	1.09
2019*	9.17	0.00	0.00	13.28	1.79	3.69	2.39	–0.08	–0.82	18.24	0.73	1.03

Note: – means the growth and the annual speed of increase in 1990 cannot to be calculated.
Abbreviations: *IRs*=standardized incidence rate (1/100,000); *ΔIRs*=5-year growth of the standardized incidence (1/100,000); *ASI*=annual speed of increase over the last 5 years of the standardized incidence (%).
* The growth and the annual speed of increase in 2019 were computed based on the 4-year change with respect to 2015.

overall downward tendency but with a non-negligible fluctuation: it maintained its decline from 1995 to 2010, but it rebounded during 2010–2015, with an annual speed of increase of 1.09%, and then maintained the annual speed of 1.03% from 2015 to 2019.

Figure 1A, 1B, and 1C showed that the standardized incidence rate of different age groups in the 4 Asian countries differed. The country that had the lowest standardized incidence rate for all 3 age groups (i.e., 15–44, 45–59, and above 60 years old) in 1990 was China, but Singapore had the lowest incidence in 2019. In summary, the age group of 15–44 years had the lowest standardized incidence rate of type 2 diabetes (<0.5/100,000), while the age group of above 60 years old had the highest one (<20/100,000).

According to the change from 1990 to 2019, for the age group of 15–44 years, Malaysia had the largest decline in the standardized incidence rate, with a decrease of 0.61/100,000, followed by Singapore, with a decrease of 0.58/100,000. China only had a decrease of 0.02/100,000, and Thailand even increased 0.17/100,000. For the age group of 45–59 years, Malaysia and Singapore attained the largest decline in the standardized incidence rate, with a decrease of 16.10/100,000 and 16.01/100,000, respectively, followed by Thailand, with a decrease of 10.58/100,000. China had the smallest decrease, i.e., 2.79/100,000; For the age group of above 60 years old, Singapore made the largest decline, followed by Malaysia and Thailand, with a decrease of 99.76/100,000, 81.11/100,000, and 35.01/100,000, respectively. China had a decline that was much lower than the above three countries, only a decrease of 7.47/100,000.

Therefore, this article conducted an analysis of the tendency of incidence with respect to different age groups. In terms of the age group of 45–59 years, as plotted in Figure 1B, the standardized incidence rate of type 2 diabetes in the 4 Asian countries showed overall decreases. Among the 4 countries, Singapore had an always-decreasing curve and had the most significant decline, but its downward tendency was relieved after the low point in 2013. Malaysia and Thailand both had a relatively large decline, which was always higher than that of China, but with fluctuations. The incidence for China remained relatively stable, just having a slight decline.

However, of the age group above 60 years old, as shown in Figure 1C, only Singapore showed an

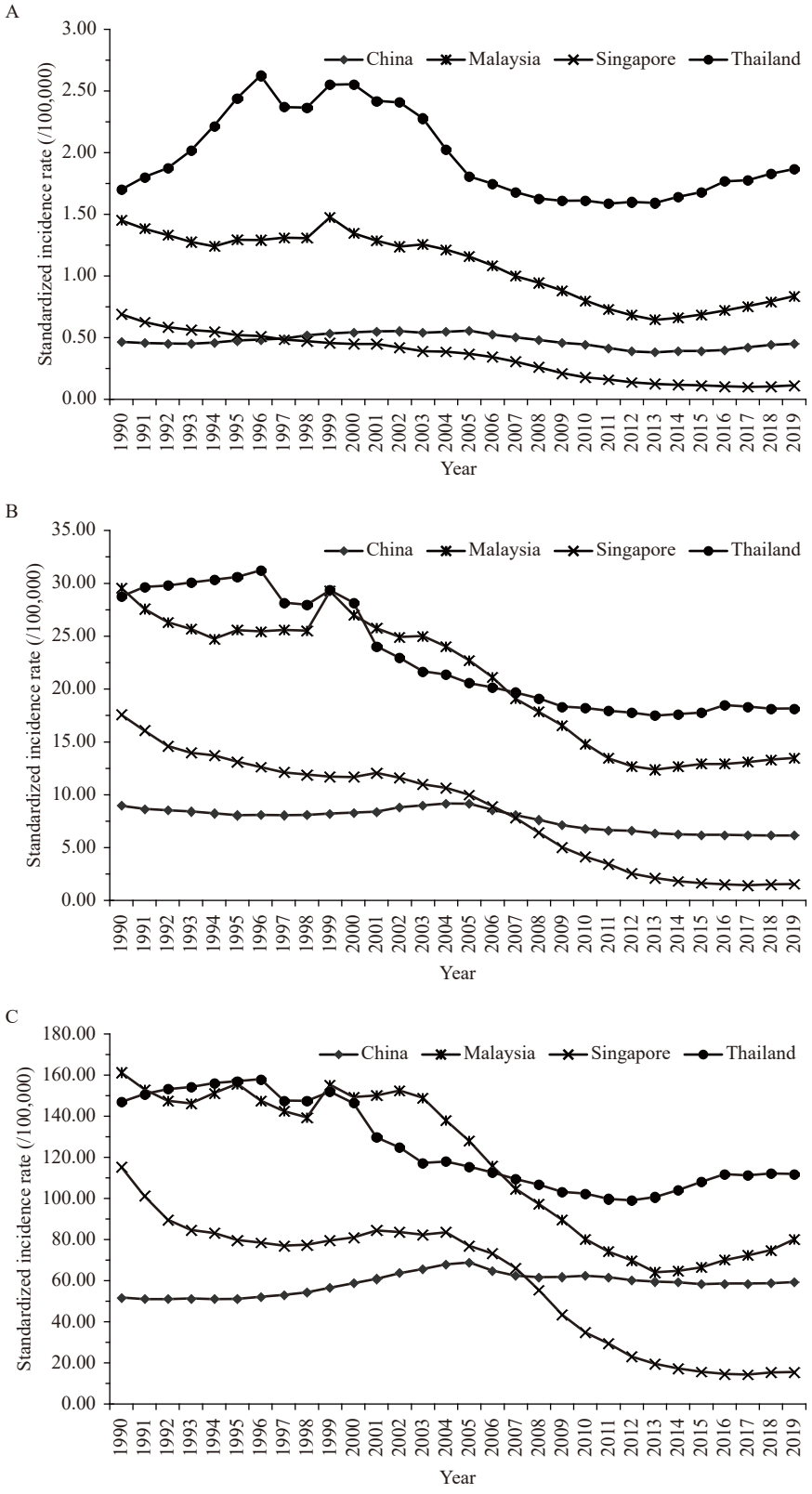

FIGURE 1. The standardized incidence rate of type 2 diabetes in different age groups in the 4 countries, 1990–2019. (A) 15–44 years; (B) 45–59 years; (C) 60 years.

Note: There are 4 countries shown in Figure 1C; however, in order to highlight the main findings, only the lowest standardized incidence rate of type 2 diabetes in the age group of 60 years old and above in 1990 and 2019 (China and Singapore, respectively) were described in the corresponding text. Malaysia and Thailand were described in other parts.

obvious downward trend. Malaysia had a significant rebound since 2013 after a decrease with fluctuation. After an early-stage reduction, the incidence rate of Thailand started to fluctuate and increase slightly in the high incidence rate range, i.e., roughly from 110/100,000 to 130/100,000. The incidence rate in China was lower than in Malaysia and Thailand, but the overall trend showed a slow rise.

DISCUSSIONS

The incidence of diabetes from 1990 to 2019 in 4 Asian countries decreased according to the GBD 2019 in 4 Asian countries. The difference in the incidence of diabetes from 1990 to 2019 in the 4 Asian countries provides evidence and guidance for the implementation and evaluation of diabetes prevention and control measurements. However, the continuous decreases in the past 30 years in Singapore showed a successful example of diabetes control at the national level, which can be described as a comprehensive strategy and is worth consideration in other countries, including risk factor control, guarantee of funding, laws, National Healthy Lifestyle Project (*5*) in the whole society, and the consistent adoption of comprehensive measures.

Although healthy lifestyle strategies for the prevention and control of diabetes were undertaken in the 4 countries (*6*), the specifics were different. The measures taken in Thailand included the practice of prohibiting smoking (*7*) since 1953, the "Alcohol Control Law" promulgated since 2008, and advocating reducing salt and sodium intake and encouraging people to increase exercise. Malaysia in the 1970s had implemented schools' nutrition programs for students since the 1970s (*8*), and smoking was prohibited in public places and religious sites. In China, such measures as tobacco control, "China Healthy Lifestyle for All"(*9*), "National Nutrition Plan (2017–2030)," and Healthy China were continuously carried out from a national perspective.

The incidence tendency of type 2 diabetes in different groups meant different measures should be taken according to the characteristics of different groups. At present, China is the only country whose incidence rate is on the rise, and the incidence of diabetes in the 60 years and over group was much higher than that in 18–44 years group, which means that China still has the most diabetes patients of the 4 countries. China is also facing population aging, which may cause more diabetes and a higher burden, more measures should be learned from Singapore immediately. Meanwhile, although this study found that the elderly were a key group for diabetes prevention and control, young people should not be ignored, and early interventions for young people may achieve more benefits.

This study was subject to some limitations. First, this study used GBD 2019 data to ensure comparability of the four countries, but the actual circumstances may differ from the actual incidence due to limitations in GBD methodology, e.g., data source and calculation methods. If real data could be obtained from an intelligent crowd monitoring system in the future, the results and analyses derived from this article can be further verified and refined. Second, the sampling, diagnosis, and statistical analysis of diabetes have an important influence on the estimation of diabetes incidence; because of the difference in healthcare services between the elderly and adolescents, elderly patients are more likely to be diagnosed, and the incidence of diabetes in adolescents is more likely to be underestimated. More research and proactive surveillance are needed to help us learn the current circumstances and trends of the burden of type 2 diabetes in adolescents.

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Methods and Applications

The Incidence of Lymphoma in Beijing: Comparing Results from MIS-CASS (2019) and Beijing Cancer Registry (2017)

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ABSTRACT

Introduction: This study aimed to evaluate the performance of the Medical-Insurance-System-based Cancer Surveillance System (MIS-CASS) in estimating cancer incidence by comparing the results with the Beijing Cancer Registry (BCR), which is one of the highest-quality population-based cancer registries in China.

Methods: Using lymphoma as an example, we extracted relevant claims data from the administrative systems of medical insurance in Beijing (2012–2020) and estimated the most current lymphoma incidence in Beijing (2019) using a standard data processing procedure. The absolute number of new cases, crude incidence rate, and age-standardized incidence rate of lymphoma were compared with the latest data reported by the BCR (2017).

Results: Both lymphoma incidence rates and age distribution of new cases estimated based on MIS-CASS were similar to the BCR data (crude incidence rate: 9.8/100,000 *vs*. 10.6/100,000). However, because MIS-CASS included more designated hospitals and covered a larger local stationary population irrespective of household registration (*hukou*), the absolute number of incident lymphoma cases identified by MIS-CASS was 39.1% higher than that reported by the BCR (2,002 *vs*. 1,439).

Conclusions: The MIS-CASS approach reflected the actual cancer burden in a more complete and timely manner as compared with the current BCR, providing new insights for improving cancer surveillance strategies in China.

INTRODUCTION

Continuous cancer surveillance is fundamental for cancer prevention and control as well as for allocation of medical resources. Population-based cancer registration is recognized as the gold standard for reporting cancer incidence in a defined population (*1*). In China, the establishment of cancer registration dates back to the late 1950s, and currently, cancer registries cover approximately 43% of the population in the country (*2*). In the past 60 years, cancer registration in China has played a crucial role in the measurement of the cancer burden, allocation of medical resources, and promotion of cancer research. However, due to the vast territory, huge population, and limited resources of China, it is still difficult to establish a real nationwide population-based cancer registry (PBCR), and the quality of available cancer data showed significant variation across geographic areas (*2*). In addition, since the collection and ascertainment of incident cancer cases is labour intensive and time consuming under the current surveillance approach, the delay in reporting annual national cancer incidence statistics is often as long as 3 to 5 years (*3*).

The basic medical insurance system, including the Urban Employee Basic Medical Insurance (UEBMI), the New Rural Co-operative Medical Care Scheme (NCMS), and the Urban Residents Basic Medical Insurance (URBMI), is administrated by local governments, and in recent years has covered 95% of the population in China (*4*). For each discharged patient, diagnosis-related information is automatically submitted to the medical insurance system in real time once reimbursement is complete. We have previously conducted 2 studies to evaluate the accuracy of NCMS claims data in capturing cancer cases in a rural area of China, observing high sensitivity and specificity of the approach (*5*–*6*). Based on these results, we established the Medical-Insurance-System-based Cancer Surveillance System (MIS-CASS) and reported the latest cancer incidence in 2 regions (over 6 million residents altogether) not covered by PBCRs (*7*). The study demonstrated that the MIS-CASS efficiently and accurately reflected local cancer burden with a lag time of only 6 months. But the real-world performance of MIS-CASS in cancer incidence surveillance still needs to be further explored and validated based on evidence

from direct comparison with high-quality PBCR data.

The Beijing Cancer Registry (BCR) was established in 1976 and has covered all the 6 urban and 10 rural districts in Beijing since 1998 (*8*). This registry is one of the highest-quality PBCRs in China (*9*). Generally, registrars of all the BCR-designated hospitals (168 in the year of 2017) collect and submit data of new cancer cases through a special health information system (*10*). The entire household registered population in Beijing (13 million in 2017) are used for calculating cancer incidence rates (*8*).

Using lymphoma as an example neoplasm, this study aimed to estimate the latest incidence of lymphoma in Beijing based on medical insurance claims data and to evaluate the performance of MIS-CASS by comparing with the BCR.

METHODS

Data Collection and Data Processing

The medical insurance system of Beijing covers individuals who continuously worked or resided in the administrative area of Beijing, irrespective of place of household registration. In this study, we obtained data of the insured population in 2019 (covering about 20 million permanent residents and local employees) from the medical insurance administrative systems and extracted all the lymphoma-related medical claims records from January 1, 2012 to December 31, 2020, using both the International Classification of Diseases (tenth revision) (ICD-10) code (C81–85, C88, C90, C96) and text-based diagnosis (using a dictionary of lymphoma diagnosis constructed by reviewing the Chinese version of the ICD-10 and extracting all keywords indicating lymphoma cases) (*7*). The period between 2012 and 2018 was set as the 7-year time window for identifying prevalent cases in 2019, and the year 2020 was also included to avoid missing 2019 incident cases due to reimbursement delay (*7*). The standard procedure for identifying incident cancer cases (lymphoma) in 2019 has been described previously (Figure 1) (*7*). In brief, among the extracted claims records, those from primary or unrated healthcare facilities were excluded due to insufficient diagnostic qualifications (consistent with the criteria adopted in BCR). Lymphoma diagnoses were then determined using both ICD-10 codes and text-based diagnoses. When either was missing or inconsistency occurred, manual evaluation was performed through group discussion among 3 trained investigators specialized in lymphoma and/or epidemiology. For patients with multiple records, only the first one with definite lymphoma diagnosis was retained for each patient. Finally, the new records from January 1, 2019 to December 31, 2019 were kept, and the corresponding patients were defined as incident lymphoma cases in this study. The corresponding admission date of each lymphoma case was defined as its incidence date, which was in accordance with the BCR (*10*).

Out of regard for confidentiality, individual-level identifiable personal information (name, identity number, telephone number, home address, and so on) were masked, and a unique encrypted identification code was generated for each case in order to eliminate duplicate records.

Statistical Analysis

In this study, incidence rate generated from MIS-CASS referred to the number of new lymphoma cases occurring in a given year (2019) in the insured population in Beijing [see the following formula (*11*)].

$$\text{Incidence rate} = \frac{\text{Number of new lymphoma cases}}{\text{Insured population at risk}} \text{ in 2019}$$

Crude incidence rate, age-specific incidence rate, and age-standardized incidence rate (ASR) were calculated by gender and subtype. Lymphoma was generally categorized into Hodgkin lymphoma (C81), non-Hodgkin lymphoma (C82–85, C96), and multiple myeloma (C88, C90) (consistent with the method used for the BCR and other PBCRs in China), and was further subdivided when describing morphologic distribution. The China standard population in 2000 (ASR China) and the Segi standard population (ASR World) were applied for calculation of ASRs. We then compared MIS-CASS estimates of 2019 with the latest BCR-reported lymphoma incidence data of 2017 which was published in April, 2021 (*12*). This study was approved by the Institutional Review Board of the Peking University School of Oncology, China (No. 2019KT44).

RESULTS

The lymphoma incidence in Beijing estimated by MIS-CASS was close to that reported by BCR (crude incidence rate: 9.8/100,000 *vs.* 10.6/100,000) (Table 1), and no significant difference in morphologic distribution was detected between MIS-CASS and BCR (Hodgkin lymphoma: 5.1% *vs.* 4.6%, non-

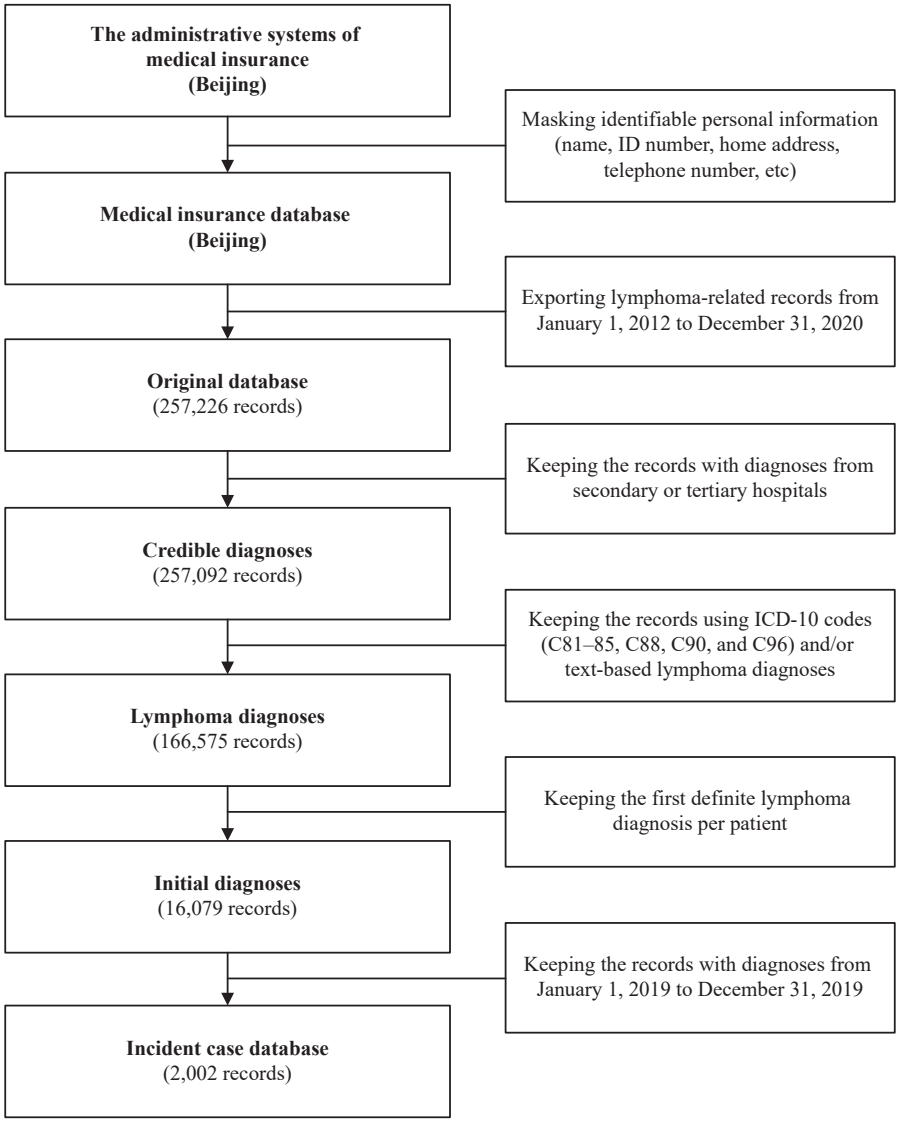

FIGURE 1. The procedure for capturing incident lymphoma cases in 2019 from the administrative systems of medical insurance in Beijing (MIS-CASS).
Abbreviations: ICD-10=International Classification of Diseases (tenth revision); MIS-CASS=Medical-Insurance-System-based Cancer Surveillance System.

Hodgkin lymphoma: 70.6% *vs.* 69.8%, multiple myeloma: 24.3% *vs.* 25.6%, *P*=0.559) (Figure 2) (*12*).

However, the absolute number of new lymphoma cases identified by MIS-CASS was 39.1% higher than that reported by the BCR (2,002 *vs.* 1,439) (still 34.1% higher when only claims data from BCR-designated hospitals were included for analysis) (Table 1). Further analysis revealed that, among the 110 hospitals where the new lymphoma cases were diagnosed in 2019 according to MIS-CASS, only 90 were BCR-designated hospitals (*12*), and the remaining 20 hospitals contributed 22.2% of the excess patients (125/563). In addition, due to differences in target population between MIS-CASS (insured population) and BCR (household registered population), the population covered by MIS-CASS was 6.5 million larger than that for BCR in the age group of 20–49 years (Supplementary Figure S1, available in http://weekly.chinacdc.cn/).

Regarding age distribution, the incidence rate of lymphoma was relatively low in patients aged below 50 years and peaked at 75–84 years (Figure 3). The MIS-CASS-estimated number of new lymphoma cases peaked at age 60–69 years for both males and females, which was similar with the age distribution reported by the BCR, but was notably higher for the majority of the age groups, especially for men of 30–69 years and for women of 20–69 years (Figure 4).

TABLE 1. Comparison of the latest lymphoma incidence estimates in Beijing between MIS-CASS (2019) and BCR (2017).

Surveillance approach	Subtype	ICD-10 of lymphoma	Gender	No. of cases	Crude incidence rate ($1/10^5$)	ASR China ($1/10^5$)	ASR World ($1/10^5$)
MIS-CASS	All	C81–85, C88, C90, C96	Both	2,002	9.8	6.8	6.6
			Male	1,090	10.3	7.3	7.3
			Female	912	9.3	6.3	5.9
	Hodgkin lymphoma	C81	Both	103	0.5	0.4	0.4
			Male	48	0.5	0.4	0.3
			Female	55	0.6	0.5	0.4
	Non-Hodgkin lymphoma	C82–85, C96	Both	1,413	6.9	4.8	4.7
			Male	754	7.1	5.1	5.1
			Female	659	6.7	4.5	4.3
	Multiple myeloma	C88, C90	Both	486	2.4	1.5	1.5
			Male	288	2.7	1.8	1.8
			Female	198	2.0	1.3	1.2
BCR*	All	C81–85, C88, C90, C96	Both	1,439	10.6	5.9	5.6
			Male	814	12.0	6.8	6.6
			Female	625	9.2	4.9	4.7

Abbreviations: MIS-CASS=Medical-Insurance-System-based Cancer Surveillance System; BCR=Beijing Cancer Registry; ICD-10=International Classification of Diseases (tenth revision); ASR China=age-standardized incidence rate by China standard population in 2000; ASR World=age-standardized incidence rate by world standard population (Segi population).

* The latest lymphoma incidence data of BCR (year of 2017) were derived from *Beijing Cancer Registry Annual Report 2020* (*12*).

DISCUSSION

We have previously demonstrated that MIS-CASS could efficiently reflect cancer burden with a shorter reporting delay than the current cancer registries in China (6 months *vs*. 3 years) (*5*–*7*). In addition to timeliness, accuracy and completeness were also crucial for cancer surveillance (*13*–*15*). In this head-to-head comparative study conducted in an area covered by one of the highest-quality PBCRs (BCR) in China, we evaluated the performance of the MIS-CASS approach in estimating the most current cancer incidence (2019), using lymphoma as an example neoplasm.

As shown in this study, the incidence rate of lymphoma estimated by MIS-CASS was close to that reported by the BCR, and these 2 approaches were also consistent in terms of morphologic distribution as well as in the pattern of lymphoma burden across age groups. However, the absolute number of new lymphoma cases estimated by MIS-CASS was notably higher than that of the BCR. A more in-depth analysis of the numerator and denominator for calculation of cancer incidence reveals the following 2 crucial findings:

First, MIS-CASS covers more designated hospitals than the BCR. For BCR, the information on cancer cases were merely collected from BCR-designated hospitals (e.g., 168 hospitals in 2017). Basic medical insurance covers a broader range of hospitals in Beijing specialized in cancer diagnosis and treatment, including a series of top-level military hospitals in China which are not covered by the BCR. Of the newly occurred lymphoma cases missed by the BCR, as many as 72% were diagnosed in these military hospitals. Absence of cancer diagnoses in these health facilities leads to underestimation of the absolute number of incident lymphoma cases in Beijing.

Secondly, all cancer cases reported by the BCR were restricted to the registered population, i.e., those with a local household registration (*hukou*), which is a fundamental social management system in China initiated in the 1950s. Hence, new cancer cases that occur in residents in Beijing but registered in other

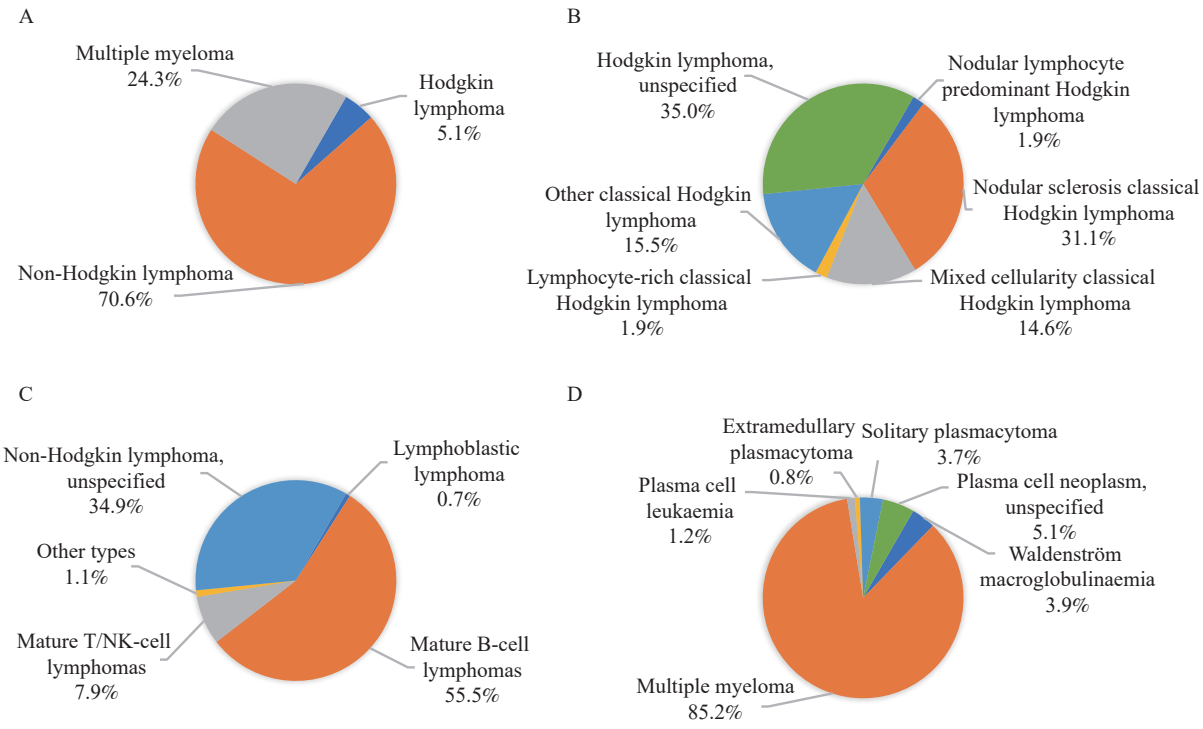

FIGURE 2. Morphologic distribution of incident lymphoma cases in Beijing, 2019 (MIS-CASS). (A) Lymphoma (C81–85, C88, C90, C96); (B) Hodgkin lymphoma (C81); (C) Non-Hodgkin lymphoma (C82–85, C96); (D) Multiple myeloma (C88, C90).
Abbreviation: MIS-CASS=Medical-Insurance-System-based Cancer Surveillance System.

areas would not be counted by BCR (*8*). However, Beijing is characterized by high population mobility due to its central role in economic and cultural development, and many individuals from other provinces work and reside in Beijing for long periods of time. They are not registered in the Beijing household registration system, but are insured by the local medical insurance system. As a result, the population covered by MIS-CASS represents the permanent population in Beijing to a greater extent than that covered in BCR. This study revealed that the current BCR failed to capture millions of these individuals, especially for young and middle-aged groups (20–49 years) in local area (Supplementary Figure S1). More importantly, as the cancer patients in this group are generally diagnosed and treated in Beijing, they would also be missed by any cancer registry in places where they registered their household according to the current regulation of PBCRs in China. The fact that PBCRs in China are based on the household registration system would further lead to underestimation of both the number of newly detected cancer cases and the size of the target population simultaneously, that is, the numerator and denominator of the cancer incidence rate. It is worth noting that the degree of underestimation may be further magnified for the high-incidence cancer types in the middle-age population such as breast cancer, cervical cancer, and thyroid cancer (*7*).

Therefore, the MIS-CASS approach could provide a more complete picture of cancer incidence and actual consumption of corresponding medical resources. The unique advantage of MIS-CASS for cancer incidence surveillance is due to the fact that basic medical insurance systems in China are administrated and operated by central and local governments and that the submitted claims data are highly standardized with the establishment of the National Healthcare Security Administration and integration of major medical insurance systems (covering 95% of national population). Despite that, efforts should also be continuously made to further improve the quality of the original claims data through training and supervising doctors entering the diagnosis in real-world clinical practice and the staff responsible for submission of claims records, especially those in lower grade hospitals. The approach to identify cancer cases using medical insurance claims data has been explored in several countries in the past decades; however, few

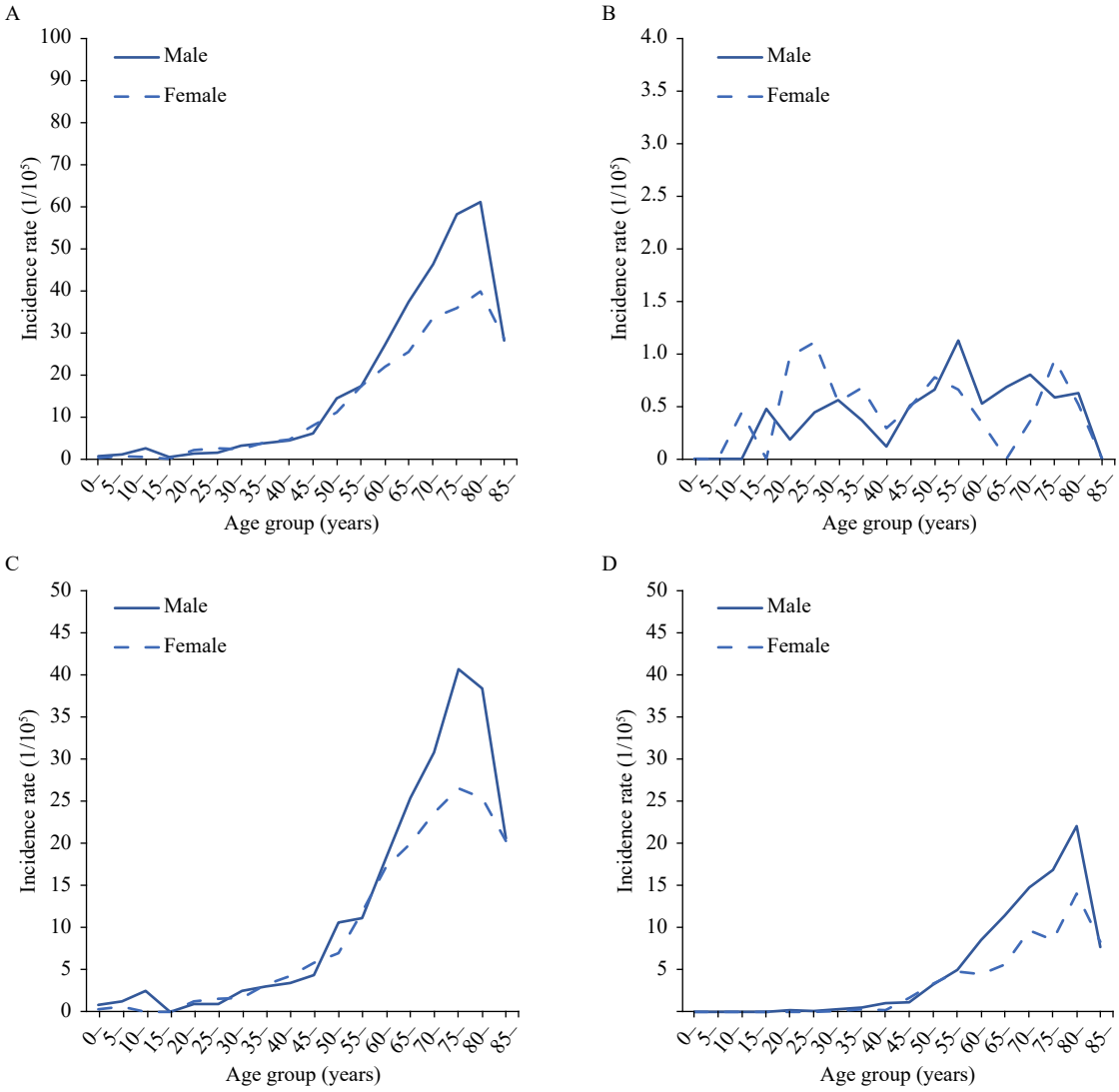

FIGURE 3. Age-specific incidence rates of lymphoma by gender and subtype in Beijing, 2019 (MIS-CASS). (A) Lymphoma (C81–85, C88, C90, C96); (B) Hodgkin lymphoma (C81); (C) Non-Hodgkin lymphoma (C82–85, C96); (D) Multiple myeloma (C88, C90).
Abbreviation: MIS-CASS=Medical-Insurance-System-based Cancer Surveillance System.

countries have established the national or subnational cancer incidence surveillance system based on this data source, partly due to relatively low coverage of health insurance, popularity of private insurance, decentralization of data management, etc. In this regard, this study provided a new insight into the improvement of cancer incidence surveillance strategies for countries or regions with uniform and high-quality health insurance system covering the whole population.

This study was subject to at least two limitations. First, this was still a single-center study focusing only on lymphoma, and similar comparative studies including more cancer types are warranted in other regions in China that are similarly covered by high-quality PBCRs. Second, the inclusion of more diagnosis-related information (such as ICD-O-3 codes and grading) into the claims database is deemed necessary to further enhance the accuracy of cancer diagnosis ascertainment and to enrich the application of MIS-CASS.

In conclusion, the present head-to-head comparative study provides direct evidence that MIS-CASS can estimate cancer incidence in a complete and timely manner. Compared with the current PBCRs in China that rely upon incomplete designated hospitals and a strict household registration system, the MIS-CASS has more comprehensive coverage of incident cancer cases and local population, and thus better reflects the actual cancer burden and consumption of medical

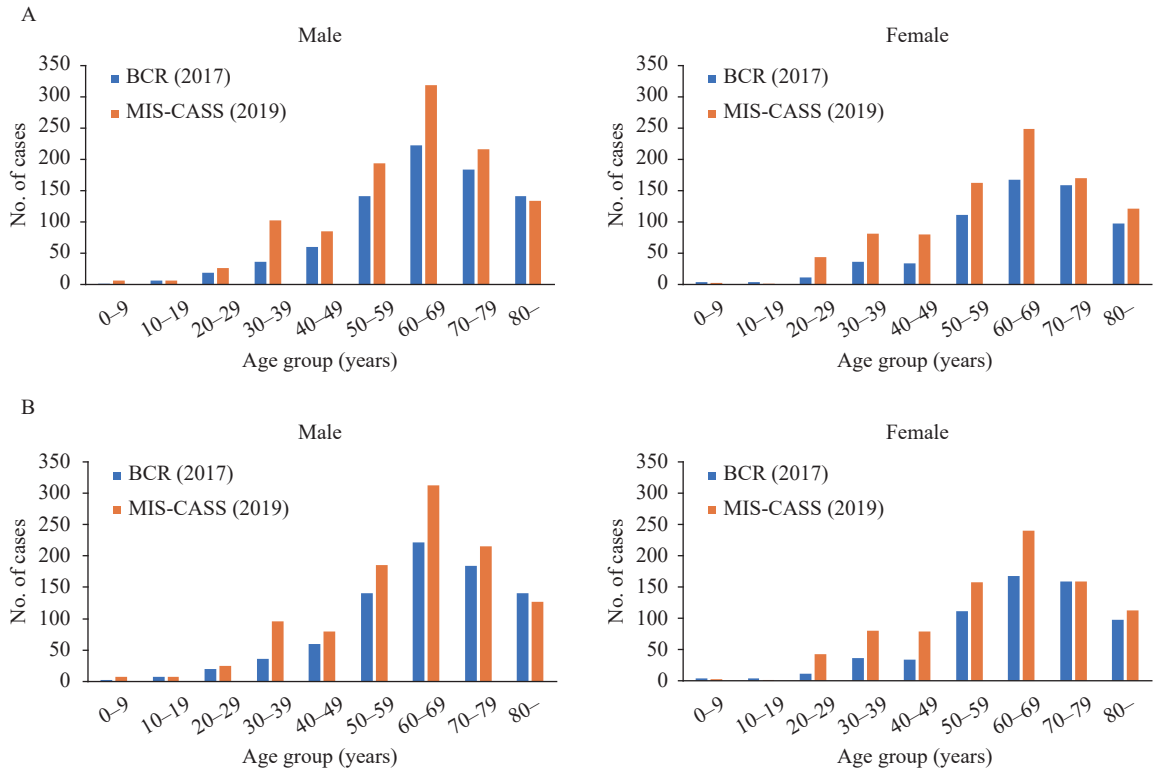

FIGURE 4. Comparison of the absolute number of new lymphoma cases by age group in Beijing between MIS-CASS (2019) and BCR (2017). (A) Including all designated medical insurance hospitals for MIS-CASS. (B) Including only BCR-designated hospitals for MIS-CASS.
Note: The latest lymphoma incidence data of BCR (year of 2017) were derived from *Beijing Cancer Registry Annual Report 2020* (*12*).
Abbreviations: MIS-CASS=Medical-Insurance-System-based Cancer Surveillance System; BCR=Beijing Cancer Registry.

resources in a given area. With the advent of the era of big data and the increasing availability of standardized electronic health-related records, MIS-CASS should have more importance attached in reforming the nationwide cancer incidence surveillance. We advocate sharing claims data by medical insurance administration departments with disease control departments, so that this new approach for cancer incidence surveillance can be efficiently implemented in broader areas in China, especially where PBCRs have not been established so far.

Conflicts of interest: No conflicts of interest.

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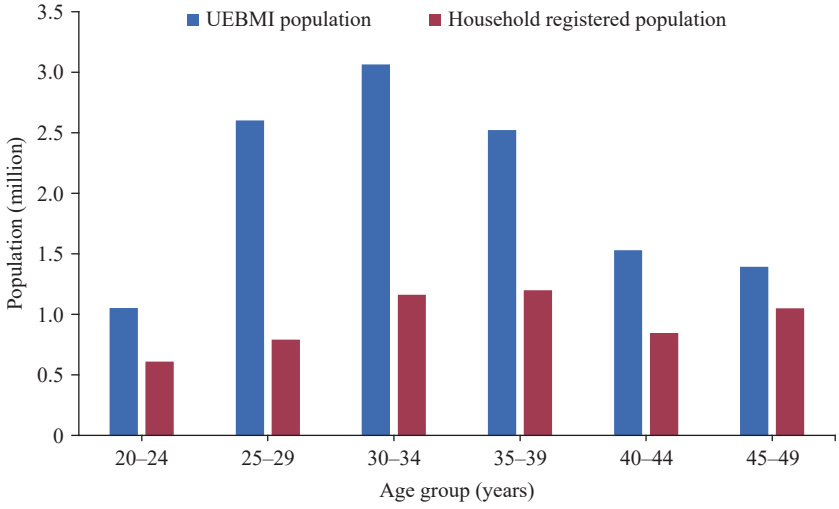
SUPPLEMENTARY MATERIAL



SUPPLEMENTARY FIGURE S1. The age distribution of UEBMI population and household registered population (the young and the middle-aged, 20–49 years) in Beijing, 2019.
Abbreviation: UEBMI=Urban Employee Basic Medical Insurance.

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