Review

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Incidence and prevalence of 121 rare diseases in China: Current status and challenges: 2022 revision

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SUMMARY The current study updated data on the incidence and prevalence of 121 rare diseases listed in *China's First List of Rare Diseases* to provide rationales and references for the development and promotion of rare-disease-related policies. The National Health Commission of the People's Republic of China issued the *Rare Disease Diagnosis and Treatment Guide* (2019) (denoted here as *China's Rare Disease Diagnosis and Treatment Guide*). Then 121 diseases were registered with the national rare disease diagnosis and treatment network. The incidence/prevalence of 121 rare diseases varied from country to country. Data are available for a total of 76 rare diseases (76 of 121 rare diseases, 62.81%) in China, including data on the incidence of 23 rare diseases (19.01%) and data on the prevalence of 66 (54.55%). There are data on the incidence/prevalence of 112 rare diseases (112 of 121 rare diseases, 92.56%) at the global level, including data on the incidence of 86 rare diseases (71.07%) and data on the prevalence of 91 (75.21%). On average, the incidence of progressive muscular dystrophies, hyperphenylalaninemia, citrullinemia, and methylmalonic acidemia is over 1/10,000 in China. The prevalence of coronary artery ectasia, congenital scoliosis, retinitis pigmentosa, severe congenital neutropenia, congenital hyperinsulinemic hypoglycemia, and osteogenesis imperfecta is over 1/10,000 in China. All of these figures are beyond the cut-off of 1/10,000 according to the 2021 definition of rare diseases in China. As registration and investigation of rare diseases continues, the spectrum of rare diseases in some provinces is expanding. Diseases such as idiopathic pulmonary arterial hypertension, hepatolenticular degeneration, hemophilia, amyotrophic lateral sclerosis, idiopathic pulmonary fibrosis, and multiple sclerosis are relatively prevalent in some regions and cities of China. Registration efforts promote the correction of incidence/prevalence data, development of orphan drugs, coverage by medical insurance, and development of clinical and diagnostic pathways.

Keywords rare disease, incidence, prevalence, definition, *China's Rare Disease Diagnosis and Treatment Guide*

1. Introduction

Rare diseases are defined by the World Health Organization (WHO) as diseases with a prevalence between 0.65-1‰ (*1*). Different definitions of rare diseases have been adopted in some countries. The European Union defines a rare disease as a life-threatening or chronically debilitating disease with a prevalence of 5/10,000; in the US, a rare disease is defined as a disease with a prevalence of less than 7.5 per 10,000 and affecting fewer than 200,000 patients (*2*). In 2021, a rare disease was defined as a disease with an incidence of less than 1/10,000 in newborns, a prevalence of less than 1/10,000, or a condition that affects fewer than 200,000 people in China (*3*). Currently, there are roughly 7,000 different rare diseases affecting 3.5–5.9% of individuals worldwide, which amounts to 263–446 million individuals (*4*).

Rare diseases are hard to assess due to the large number and diversity of conditions; this is especially true

in China, which has a large population. Epidemiological data on rare diseases are limited, and the incidence or prevalence of most major rare diseases is still unclear worldwide. Over the last few years, the Chinese Government has announced a series of policies to support diagnosis and treatment of rare diseases, including fast-tracking orphan drugs, coverage by medical insurance, and disease registration. In 2018, five bodies including the National Health Commission of the People's Republic of China and the National Medical Products Administration issued *China's First List of Rare Diseases* in May 2018 (denoted here as *China's Rare Disease List*) (*5,6*).

The release of *China's Rare Disease List* has greatly promoted the diagnosis and treatment of rare diseases. At present, more than 40 types of drugs for rare diseases have been included in the national medical insurance drug catalogue. Some policies and laws have been drafted to facilitate scientific research, diagnosis and treatment, drug access, and medical care for rare diseases.

The current study updated the incidence and prevalence of 121 rare diseases with recent registration numbers for these rare diseases based on the 2019 version (*3*). The OMIM database was searched for genetic information on 121 rare diseases in *China's Rare Disease List*. Incidence and prevalence data and case numbers in *China's Rare Disease List* were collected from the *China's Rare Disease Diagnosis and Treatment Guide*, the *Research Report on the definition of rare diseases in China,* Taiwan's National Health Insurance Research Database, Orphanet (www.orpha.net), MalaCards (https://www.malacards.org/) and literature in CNKI, Wanfang, and PubMed. Here, diseases in the list were mapped to a standard ICD 10 (International Classification of Diseases), disease classification and code (National Clinical Version 1.1), and ORPHA code.

2. Current incidence/prevalence of 121 rare diseases in China

One hundred and twenty-one rare diseases in 10 different categories and their genetic information are listed in Supplementary Table S1 (*http://www.irdrjournal.com/action/getSupplementalData.php?ID=114*). Most of these rare diseases are genetic in origin. The use of high-throughout sequencing technology in rare diseases has accelerated the discovery of the genes causing these diseases. Genotypic and phenotypic variation contributes to the complexity of rare diseases. Clinical symptoms of rare diseases overlap those of common diseases, leading to the misdiagnosis of rare diseases. The codes for 121 rare diseases are listed in Supplementary Table S2 (*http://www.irdrjournal.com/action/getSupplementalData.php?ID=115*).

Based on a comprehensive analysis of the literature, official websites, and *China's Rare Disease Diagnosis and Treatment Guide,* data on the incidence/prevalence of 76 rare diseases (62.81%) were available for 121 rare diseases in China. Data on the incidence of 23 rare diseases (19.01%) was reported, along with data on the prevalence of 66 (54.55%). The incidence/prevalence of 21 rare diseases (17.36%) was cited from *China's Rare Disease Diagnosis and Treatment Guide.* Data on 73 diseases (60.33%) were retrieved from articles, literature databases, and official websites. Global data on the incidence/prevalence of 112 rare diseases (112 of 121 rare diseases, 92.56%) were available, including data on the incidence of 86 rare diseases (71.07%) and data on the prevalence of 91 (75.21%). The incidence/prevalence of 64 of 121 rare diseases (52.89%) has been reported in Europe, including the incidence of 30 rare diseases (24.79%) and the prevalence of 46 (38.02%). The incidence/prevalence of 37 of 121 rare diseases (30.58%) has been reported in the US, including the incidence of 18 rare diseases (14.88%) and the prevalence of 25 (20.66%). Details are shown in Table 1 and Supplementary Table S3 (*http://www.irdrjournal.com/action/getSupplementalData.php?ID=116*) (*3,7-24*).

The cut-off of 1/10,000 in newborns was adopted as a unique criterion for the 2021 definition of rare diseases in China. In the past, the newborn incidence of 8 different rare diseases was available in China and 31 rare diseases (0.26%) were cited in *China's Rare Disease Diagnosis and Treatment Guide* (Table 1).

Incidence/prevalence data in China is mainly from Taiwan and Shanghai. Data on the incidence of 10 (8.26%) of 121 rare diseases and the prevalence of 53 (43.80%) were available from Taiwan, compared to data on the incidence of 19 rare diseases (15.70%) and the prevalence of 36 (29.75%) from the Chinese mainland. Regional trends are evident in some rare diseases, *e.g.*, the incidence of citrullinemia is 1.87/100,000 in South China and 0.03/100,000 in North China. A high incidence of 1/100,000 was reported for methylmalonic acidemia (MMA) in North China and 1.27/100,000 in Yacheng, Jiangsu Province. The prevalence of Larson syndrome is 4.86/100,000 in Shanghai and 0.021/100,000 in Taiwan (Table 1).

3. Rare diseases with a high incidence/prevalence in the first list of 121 rare diseases

In the first list of 121 rare diseases, some diseases have a relatively high incidence or prevalence in China. Hyperphenylalaninemia, phenylketonuria, albinism, 21-hydroxylase deficiency, progressive muscular dystrophies, citrullinemia, and methylmalonic acidemia are relatively prevalent. The incidence of progressive muscular dystrophies is 2.53/10,000 (Table 1), which is close to the worldwide incidence of 2.19. Duchenne muscular dystrophy (DMD) is reported to have an incidence of 2/10,000 and Becker muscular dystrophy (BMD) is reported to have an incidence

Table 1. Newborn incidence, incidence, and prevalence of 121 rare diseases in *China's First List of Rare Disease*

No.	Disease	Newborn incidence /100,000 persons	Incidence /100,000 persons	Prevalence /100,000 persons
1	21-Hydroxylase deficiency	5-10 (*10*)	3.08 (Dongguan, Guangzhou) (*18*) 3.03 (Liuzhou, Guangxi) (*19*)	/
2	Albinism	/	5.56[b]	/
3	Alport syndrome	/	/	/
4	Amyotrophic lateral sclerosis	/	0.6 (Hong Kong)[b] 0.51 (Taiwan) (*42*)	3.1 (Hong Kong)[b] 1-9 (Taiwan)[a] 3.33 (Taiwan) (*9*)
5	Angelman syndrome	/	/	0.29 (Taiwan) (*9*)
6	Arginase deficiency	0.1-0.33 (*10*)	/	0.43 (Zhejiang) (*43*)
7	Asphyxiating thoracic dystrophy (Jeune syndrome)	0.77-1 (*10*)	/	/
8	Atypical hemolytic uremic syndrome	/	/	0.03 (Shanghai) (*40*) 0.068 (Taiwan) (*9*)
9	Autoimmune encephalitis	/	/	/
10	Autoimmune hypophysitis	/	/	/
11	Autoimmune insulin receptopathy (Type B insulin resistance)	/	/	/
12	β-ketothiolase deficiency	/	0.10 (*10*)	/
13	Biotinidase deficiency	/	/	0.025 (Taiwan) (*9*)
14	Cardiac ion channelopathies	2.5 (*10*)	/	/
15	Carnitine deficiency	/	1.27 (Yancheng, Jiangsu) (*44*)	2.4 (Shanghai)[b] 3.1 (Zhejiang)[b] 1.1 (Hongkong)[b] 0.8 (China, Taiwan)[b] 2.5 (*21*) 0.60 (Taiwan) (*9*)
16	Castleman disease	/	/	/
17	Charcot-Marie-Tooth disease	/	/	1.44 (Taiwan) (*9*)
18	Citrullinemia	/	10.87 (South China)[b] 0.03 (North China)[b] 8.66 (Taiwan) (*43*)	/
19	Congenital adrenal hypoplasia	/	/	/
20	Congenital hyperinsulinemic hypoglycemia	/	/	23.2 (Shanghai) (*40*) 0.29 (Taiwan) (*9*)
21	Congenital myasthenic syndrome	/	/	/
22	Congenital myotonia syndrome (Non-dystrophic myotonia)	/	/	/
23	Congenital scoliosis	/	/	202.43 (Luohe He'nan) (*45*) 295.98 (Females, Luohe, He'nan) (*45*) 110.63 (Males, Luohe, He'nan) (*45*)
24	Coronary artery ectasia	/	/	656 (Beijing) (*3*)
25	Diamond-Blackfan anemia	/	/	0.19 (Shanghai) (*40*)
26	Erdheim-Chester disease	/	/	/
27	Fabry disease	0.91-2.5 (*10*)	/	0.12 (Shanghai) (*40*) 1.34 (Taiwan) (*9*)
28	Familial Mediterranean fever	/	/	/
29	Fanconi anemia	/	/	0.11 (Shanghai) (*3*)
30	Galactosemia	2.08 (*10*) 0.53 (China) (*10*)	0.25 (Taiwan) (*21*)	0.53 (Zhejiang)[b] 0.11 (Taiwan) (*9*)
31	Gaucher's disease	1.25 (China) (*10*)	1.24 (Shanghai)[b]	0.22 (Shanghai) (*40*) 0.15 (Taiwan) (*9*)
32	General myasthenia gravis	/	0.68 (*11, 13*) 0.89 (Taiwan) (*11, 13*)	/
33	Gitelman syndrome	/	/	/
34	Glutaric acidemia type I	/ /	1.67[b] 0.77 (Zhejiang) (*21*)	/
35	Glycogen storage disease (Type I or II)	/	2 (Taiwan)[b] 1 (Taiwan) (*21*)	1.51 (Shanghai) (*40*)

Note: [a]data from MalaCards; [b]data from *China's Rare Disease Diagnosis and Treatment Guide (2019)*.

of 0.5/10,000 (Supplementary Table S3, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=116*). The global incidence of familial Mediterranean fever, idiopathic pulmonary fibrosis, hyperornithinemia-hyperammoniemia-homocitrullinuria syndrome, congenital scoliosis, multiple sclerosis, cardiac ion channelopathies, Charcot-Marie-Tooth disease, pulmonary cystic fibrosis, Marfan syndrome, retinitis pigmentosa, hemophilia, and Fabry disease is relatively high (greater than 2/10,000), but there are no data on these diseases from China (Supplementary Table S3, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=116*).

Some diseases have a relatively high prevalence, such as coronary artery ectasia, congenital scoliosis, retinitis pigmentosa, severe congenital neutropenia, congenital

Table 1. Newborn incidence, incidence, and prevalence of 121 rare diseases in *China's First List of Rare Disease* (continued)

No.	Disease	Newborn incidence /100,000 persons	Incidence /100,000 persons	Prevalence /100,000 persons
36	Hemophilia	/	/	2.73[b] 2.7 (Chinese mainland) (*46*) 6.46 (Shanghai) (*40*) 5.5 (Males, Chinese mainland) (*47*) 2.0 (Blood group A, 8 Chinese provinces) (*48*) 9.1 (Males, Taiwan) (*49*) 6.4 (Hong Kong) (*50*)
37	Hepatolenticular degeneration (Wilson's disease)	/	/	2.85 (8 Chinese provinces) (*48*) 3.69 (Shanghai) (*40*)
38	Hereditary angioedema	/	/	0.034 (Taiwan) (*9*)
39	Hereditary epidermolysis bullosa	/	/	0.30 (Taiwan) (*9*)
40	Hereditary fructose intolerance	5 (*10*)	/	/
41	Hereditary hypomagnesemia	/	/	/
42	Hereditary multi-infarct dementia (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	/	/	/
43	Hereditary spastic paraplegia	/	/	0.48 (Taiwan) (*9*)
44	Holocarboxylase synthetase deficiency	/	/	/
45	Homocystinuria	0.33-0.5 (*10*)	/	/
46	Homozygous hypercholesterolemia	/	/	0.20 (Taiwan) (*9*)
47	Huntington's disease	/	/	1.23 (Taiwan) (*9*)
48	Hyperornithinemia-hyperammoniemia-homocitrullinuria syndrome	/	/	/
49	Hyperphenylalaninemia	9.62 (China) (*10*)	9.62 (China, 1985-2011)[b] 12.67 (Yancheng, Jiangsu) (*44*)	/
50	Hypophosphatasia	1 (*10*)	/	0.02 (Shanghai) (*40*) 0.017 (Taiwan) (*9*)
51	Hypophosphatemic rickets	/	/	0.52 (Taiwan) (*9*)
52	Idiopathic cardiomyopathy	/	/	/
53	Idiopathic hypogonadotropic hypogonadism	/	/	/
54	Idiopathic pulmonary arterial hypertension	/	/	1.56 (Taiwan) (*9*) 6.25 (Shanghai) (*40*)
55	Idiopathic pulmonary fibrosis	/	/	/
56	IgG4-related disease	/	/	/
57	Inborn errors of bile acid synthesis	/	/	0.013 (Taiwan) (*9*)
58	Isovaleric acidemia	0.63 (China) (*10*)	0.63[b] 0.063 (Shanghai) (*21*) 0.027 (Taiwan) (*21*)	0.047 (Taiwan) (*9*)
59	Kallmann syndrome	/	/	0.20 (Taiwan) (*9*)
60	Langerhans cell histiocytosis	/	/	/
61	Laron syndrome	/	0.021 (Taiwan) *(9)*	4.86 (Shanghai) (*40*) 0.021 (Taiwan) (*9*)
62	Leber hereditary optic neuropathy	/	/	1.092 (Xingtai)[b]
63	Long chain 3-hydroxyacyl coA dehydrogenase deficiency	/	0.4[b]	/
64	Lymphangioleiomyomatosis	10-16.67 (TSC) (*10*)	/	/
65	Lysine urinary protein intolerance	1-1.75 (*10*)	/	/
66	Lysosomal acid lipase deficiency	/	/	0.0042 (Taiwan) (*9*)
67	Maple syrup urine disease	0.2-0.59 (*10*) 0.72 (China) (*10*) 1 (Taiwan) (*10*)	0.72 (Shanghai) (*21*)	0.72[b] 1 (Taiwan)[b] 0.1-0.9 (Taiwan)[a] 0.12 (Taiwan) (*9*)
68	Marfan syndrome	/	/	0.75 (8 Chinese provinces) (*48*)
69	McCune-Albright syndrome	/	0.1-0.9 (Taiwan)[a]	0.089 (Taiwan) (*9*)
70	Medium chain Acyl coA dehydrogenase deficiency	1.9-9.4 (*10*) 0.66 (China) (*10*)	0.67 (Chinese mainland) (*43*) 0.28 (Zhejiang) (*21*) 1.43 (Shanghai) (*51*) 2.13 (Shandong) (*51*) 0.38 (Taiwan) (*43*)	0.034 (Taiwan) (*9*) 0.74 (Shanghai) (*21*)

Note: [a]data from MalaCards; [b]data from *China's Rare Disease Diagnosis and Treatment Guide (2019)*.

Table 1. Newborn incidence, incidence, and prevalence of 121 rare diseases in *China's First List of Rare Disease* (continued)

No.	Disease	Newborn incidence /100,000 persons	Incidence /100,000 persons	Prevalence /100,000 persons
71	Methylmalonic acidemia	0.59-2 (*10*) 3.57-10 (China) (*10*) 1.16 (Taiwan) (*10*)	10 (North China)[b] 1.27 (Yancheng, Jiangsu) (*44*)	1.16 (Taiwan)[b] 3.57 (Chinese mainland)[b] 3 (Shanghai) (*21*) 1.5 (Zhejiang) (*21*) 0.22 (Taiwan) (*9*)
72	Mitochondrial encephalomyopathy	/	/	/
73	Mucopolysaccharidosis	/	/	0.46 (Taiwan) (*9*)
74	Multi-focal motor neuropathy	/	/	/
75	Multiple Acyl coA dehydrogenase deficiency	/	/	/
76	Multiple sclerosis	/	/	3.4 (Males, 8 Chinese provinces) (*48*) 6.3 (Females, 8 Chinese provinces) (*48*) 7.02 (Taiwan) (*9*) 4.8 (Hong Kong) (*52*)
77	Multiple system atrophy	/	/	0.65 (8 Chinese provinces) (*48*)
78	Myotonic dystrophy	/	/	0.70 (Taiwan) (*9*)
79	N acetylglutamate synthase deficiency	/	/	/
80	Neonatal diabetes mellitus	/	/	0.0042 (Taiwan) (*9*)
81	Neuromyelitis optica	/	0.278 (*7*)	/
82	Niemann-Pick disease	/	/	0.12 (Shanghai) (*40*) 0.059 (Taiwan) (*9*)
83	Non-syndromic deafness	186 (*10*)	/	/
84	Noonan syndrome	40-100 (*10*)	/	/
85	Ornithine transcarbamylase deficiency	7.14 (*10*)	/	0.089 (Taiwan) (*9*)
86	Osteogenesis imperfecta (Brittle bone disease)	5-6.67 (*10*)	/	11.3 (8 Chinese provinces) (*48*) 1.45 (Taiwan) (*9*) 0.38 (Shanghai) (*40*)
87	Parkinson's disease (Young-onset, Early-onset)	/	/	7.39 (Taiwan) (*3*)
88	Paroxysmal nocturnal hemoglobinuria	/	1[b] 2.7(Mudanjiang, Heilongjiang)[b]	0.8 (8 Chinese provinces) (*48*) 1.419 (6 Chinese provinces) (*20*) 0.45 (Taiwan) (*9*)
89	Peutz-Jeghers syndrome	/	/	/
90	Phenylketonuria	/	8.48[b] 1.82 (Taiwan) (*21*)	1.17 (Taiwan) (*9*) 0.10 (Shanghai) (*40*)
91	POEMS syndrome	/	/	/
92	Porphyria	/	/	0.44 (Taiwan) (*9*)
93	Prader-Willi syndrome	/	/	1.22 (Taiwan) (*3*) 0.23 (Shanghai) (*40*)
94	Primary combined immune deficiency	1-1.33 (*10*)	/	/
95	Primary hereditary dystonia	/	/	/
96	Primary light chain amyloidosis	/	/	/
97	Progressive familial intrahepatic cholestasis	/	/	0.059 (Taiwan) (*9*)
98	Progressive muscular dystrophies	16.67-27.78 (*10*)	25.30[b]	/
99	Propionic acidemia	/	/	0.6-0.7[b] 0.03 (Shanghai) (*40*) 0.055 (Taiwan) (*9*)
100	Pulmonary alveolar proteinosis	/	/	/
101	Pulmonary cystic fibrosis	4-55.56 (*10*)	/	0.064 (Taiwan) (*9*)
102	Retinitis pigmentosa	/	/	26.43[b] 23.38 (Rural areas around Beijing) (*53*)
103	Retinoblastoma	5-6.67 (*10*)	/	1-9 (Taiwan)[c]
104	Severe congenital neutropenia	0.4 (*10*)	/	25.7 (Shanghai) (*40*)
105	Severe myoclonic epilepsy in infancy (Dravet syndrome)	/	/	0.25 (Taiwan) (*9*)
106	Sickle cell disease	/	/	/
107	Silver-Russell syndrome	1-3.33 (*10*)	/	/
108	Sitosterolemia	/	/	0.017 (Taiwan) (*9*)
109	Spinal bulbar muscular atrophy (Kennedy disease)	/	/	/
110	Spinal muscular atrophy	/	/	1.71 (Taiwan) (*9*)
111	Spinocerebellar ataxia	/	/	4.41 (Taiwan) (*9*)

Note: [a]data from MalaCards; [b]data from *China's Rare Disease Diagnosis and Treatment Guide (2019)*.

Table 1. Newborn incidence, incidence, and prevalence of 121 rare diseases in *China's First List of Rare Disease* (continued)

No.	Disease	Newborn incidence /100,000 persons	Incidence /100,000 persons	Prevalence /100,000 persons
112	Systemic sclerosis	/	/	/
113	Tetrahydrobiopterin deficiency	/	/	0.021 (Taiwan) (*9*)
114	Tuberous sclerosis complex	10-16.67 (*10*)	/	1-9 (Taiwan)[a] 2.16 (Taiwan) (*9*)
115	Tyrosinemia	/	/	0.042 (Taiwan) (*9*)
116	Very long chain acyl coA dehydrogenase deficiency	/	/	/
117	Williams syndrome	4.26 (Hong Kong) (*10*)	/	1.07 (Taiwan) (*9*)
118	Wiskott-Aldrich syndrome	0.4-1 (*10*)	/	0.03 (Shanghai) (*40*) 0.064 (Taiwan) (*9*)
119	X-Linked agammaglobulinemia	/	/	/
120	X-linked adrenoleukodystrophy	0.26 (*10*)	/	/
121	X-linked lymphoproliferative disease	/	/	0.03 (Shanghai) (*40*)

Note: [a]data from MalaCards; [b]data from *China's Rare Disease Diagnosis and Treatment Guide (2019)*.

hyperinsulinemic hypoglycemia, Laron syndrome, spinocerebellar ataxia, multiple sclerosis, amyotrophic lateral sclerosis, hepatolenticular degeneration (Wilson's disease), hemophilia, osteogenesis imperfecta, and tuberous sclerosis complex. The prevalence of coronary artery ectasia, congenital scoliosis, retinitis pigmentosa, severe congenital neutropenia, congenital hyperinsulinemic hypoglycemia, and osteogenesis imperfecta is higher than 1/10,000, according to the new 2021 definition of rare diseases in China, though some data are limited by region (Table 1). The prevalence of congenital hyperinsulinemic hypoglycemia is 2.32/10,000 in Shanghai and 0.029/10,000 in Taiwan. Like the incidence, the global prevalence of rare diseases differs greatly from that in China (Table 1, Supplementary Table S3, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=116*).

4. The development and promotion of the rare disease list and registration: Data collection and information sharing

Before the release of *China's Rare Disease List,* the Shanghai Municipal Health Commission published the "*Major Rare Diseases in Shanghai (2016 Edition)*" that included 56 rare diseases (Supplementary Table S4, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=117*) (*25*). After excluding infectious diseases, tumors, poisoning, and traumatic diseases in the Orphanet catalogue, searching the literature and websites, and comparing diseases to the Chinese version of ICD-10, a catalogue of 4,299 rare diseases and 1,049 ICD codes was created in 2016 by the Shandong Association for the Prevention and Treatment of Rare Diseases. On March 1, 2017, the Shandong Provincial Health Commission began registering cases of 68 rare diseases according to their prevalence and drug availability (Supplementary Table S4, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=117*) (*26*). Provincial Grade-III Class-A hospitals (according to the Chinese Hospital Ranking System) including maternal and child health hospitals, children's hospitals, and general hospitals were required to register these 68 diseases. This was later expanded to 121 rare diseases under the national rare disease diagnosis and treatment network. Thus far, more than 29,000 cases have been registered (unpublished data). The Chinese Organization for Rare Disorders (CORD), the largest non-official rare disease organization, has advocated for a list of 147 rare diseases. The criteria used for inclusion of these disorders included the following: (a) the global incidence of rare diseases; (b) rare diseases that have been treated with drugs at home and abroad; (c) diseases recognized by domestic organizations for rare diseases; (d) the list of rare diseases in Taiwan; (e) the rate of clinical detection by domestic genetic testing facilities; (f) the list of major rare diseases in Shanghai; and (g) rare diseases of great social concern (Supplementary Table S2, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=115*) (*27*).

Despite the lack of epidemiological data on and registration of rare diseases, rare diseases have been specifically defined in China, and this has greatly affected their diagnosis and treatment. In February 2019, the National Health Commission issued the *Rare Disease Diagnosis and Treatment Guide* (2019), which cited data on the incidence/prevalence of rare diseases based on *China's Rare Disease List* (*28*). The national rare disease diagnosis and treatment network was created at the same time, and it included 1 leading national hospital (Beijing Union Medical College Hospital), 32 leading provincial hospitals, and 291 member hospitals in the network (*29*). In October 2019, member hospitals in the network were encouraged to start registering 121 rare diseases on November 1, 2019. Registration was dated back to the beginning of 2015 (*30*). Nearly 500,000 cases have been registered according to a notice from the National Health Commission (*31*). The first national rare disease

registry (the National Rare Diseases Registry System of China; NRDRS) was created in 2016; it includes a total of 62,590 cases of 166 diseases or types of diseases (*32*).

5. The relationship between the rare disease list and the 2021 definition

There is no unified standard for the definition and classification of rare diseases. The definition is dynamic, and it changes from nation to nation. Initially, rare diseases were defined despite the lack of epidemiological data in China. Then, they were defined based on prevalence and the number of people affected or the incidence in newborns (*33*). A rare disease is a disease with an incidence less than 1/10,000, as recognized by the Rare Disease and Drug Review Committee, and it is documented by a relevant department in Taiwan. The definition benefited from the rare disease reporting system that was established in 2000, which covers disease incidence, treatment fees, and treatment outcomes (*34*). As national registration continues, more reports of rare diseases will be collected. The emphasis will be on rare diseases with a relatively high incidence/prevalence, drug availability, and greater recognition. The 2021 definition will definitely increase the understanding of more rare diseases as more epidemiological data becomes available. Moreover, it will guide medical insurance coverage, orphan drug R&D, and designations.

China is a country with a high prevalence of birth defects, with an estimated prevalence of 5.6% (*35*) . Birth defects keep rising with the high growth rate. The number of children with birth defects was 977,000 in 1996, but that figure jumped to 1.53 million in 2011, with a growth rate as high as 70.9% (*35*). Newborn screening is an important policy in China, and it started in 1980. In 2016, the Department of Maternal and Child Health Care and Community Health of the National Health Commission and the Foundation for Foundation for Intervention in and Relief of Birth Defects in China jointly launched a relief project for birth defects (genetic metabolic diseases); the project included 78 diseases, 43 of which were listed in *China's First List of Rare Diseases (36)* . The incidence in newborns was included in the definition of rare diseases in China. Epidemiological data on rare diseases will help to tally the number of patients with rare diseases. This will facilitate interventions in and help to prevent birth defects and improving the health of the population.

6. Rare diseases beyond the 121 diseases in the list and their spectrum

As part of a "Project to Study and Attempt to Control Rare Diseases in China" (no. 2013BAI07B00) under the "Twelfth Five-year Plan" National Program to Support Science and Technology, the Shandong Association for the Prevention and Treatment of Rare Diseases conducted an epidemiology study of rare diseases in nearly 100 tertiary hospitals in China in collaboration with research institutes in Shandong and 6 other provinces. A total of 40,5589 patients with 952 rare diseases (2.27% of all hospitalized patients) were recorded by 93 hospitals in the 7 provinces and at least half of the rare diseases were congenital diseases (*37*). A survey and literature review revealed that 5,749 cases of 323 rare diseases were identified in Shandong Province (*38*). The Rare Disease Branch of the Beijing Medical Association has conducted studies of rare diseases since 2013; using the rare diseases listed on European websites related to rare diseases as a template, the Rare Disease Branch has collected and analyzed 404,312 cases from tertiary hospitals in Beijing. As a result, the Rare Disease Branch identified 1,423 rare diseases (*37*). Preliminary research by the Rare Disease Branch yielded information on 121 diseases in *China's First List of Rare Diseases*, including the number of inpatients, the disease distribution by province/municipality, affected age groups, and the rate of repeated hospitalization at 96 level A tertiary hospitals. Although national epidemiological data are lacking, data on diseases in the database have been mined, which is also an effective approach for an epidemiological study (*39*).

Out of over 15 million hospitalized patients, a total of 54,468 patients with 102 rare diseases were identified. Sixty-nine-point-seven-two percent of those cases involved the ten leading rare diseases, including idiopathic pulmonary arterial hypertension, Langerhans cell histiocytosis, amyotrophic lateral sclerosis, idiopathic pulmonary fibrosis, systemic sclerosis, hepatolenticular degeneration, retinitis pigmentosa, Marfan syndrome, homozygous familial hypercholesterolemia, and congenital scoliosis (*39*). In the NRDRS, hemophilia, idiopathic pulmonary arterial hypertension, spinocerebellar ataxia, Alport syndrome, myasthenia gravis, phenylketonuria, methylmalonic acidemia, multiple sclerosis, osteogenesis imperfecta, and spinal muscular atrophy were the ten leading rare diseases, accounting for 71.19% of total cases (*32*) . From the Shanghai list of 33 rare diseases, 16,933 cases were identified from 2013 to 2016. The disease spectrum in terms of age, gender, and yearly changes was described. The proportion of inpatients and outpatients and the burden of hospitalization were analyzed. Severe congenital neutropenia, congenital hyperinsulinemic hypoglycemia, hemophilia, hepatolenticular degeneration, idiopathic pulmonary arterial hypertension, and congenital adrenal hyperplasia were identified as the most prevalent rare diseases in Shanghai (*40*). In December 2021, Tongji Hospital, a leading provincial hospital and member of the network, released an *Investigation on rare diseases in Hubei Province* that included 109 rare diseases; amyotrophic lateral sclerosis, multiple sclerosis, hemophilia, multiple system atrophy, autoimmune encephalitis, Marfan syndrome, Castleman

disease, idiopathic pulmonary fibrosis, coronary artery ectasia, and optical neuromyelitis were the most prevalent rare diseases (*41*). Taking this spectrum in different regions and cities into consideration, idiopathic pulmonary arterial hypertension, hepatolenticular degeneration, hemophilia, amyotrophic lateral sclerosis, idiopathic pulmonary fibrosis, and multiple sclerosis are relatively prevalent.

7. Conclusion

In light of the drafting of *China's First List of Rare Diseases* and the promotion of national or regional registration of rare diseases, the number of registered cases has increased massively, and especially for 121 rare diseases. More cases will be assembled and disease and epidemiological data will be collected as registration continues, though there are limited data on the incidence and prevalence of 121 rare diseases. Since there are more than 7,000 rare diseases, the rare disease list should be continuously updated. With the 2021 definition of rare diseases in China, the number of registered rare diseases will increase. The national rare disease diagnosis and treatment network is expected to expand as more hospitals are enrolled and expert knowledge on rare diseases spreads. Hence, different types of rare diseases will be identified and registered. Based on updated registration data, highly prevalent diseases should be removed from the list of 121 rare diseases. Registration could promote the development of orphan drugs, improve medical insurance coverage, and enhance diagnosis and treatment. In addition to registration, the conducting of follow-ups and collection of biosamples should be enhanced.

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References

1. Melnikova I. Rare diseases and orphan drugs. Nature Reviews Drug Discovery. 2012; 11:267-268.
2. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, Murphy D, Le Cam Y, Rath A. Estimating cumulative point prevalence of rare diseases: Analysis of the Orphanet database. Eur J Hum Genet. 2020; 28:165-173.
3. He J, Tang M, Zhang X, Chen D, Kang Q, Yang Y, Hu J, Jin C, Song P. Incidence and prevalence of 121 rare diseases in China: Current status and challenges. Intractable Rare Dis Res. 2019; 8:89-97.
4. Shourick J, Wack M, Jannot AS. Assessing rare diseases prevalence using literature quantification. Orphanet J Rare Dis. 2021; 16:139.
5. He J, Kang Q, Hu J, Song P, Jin C. China has officially released its first national list of rare diseases. Intractable Rare Dis Res. 2018; 7:145-147.
6. Bureau of Medical Administration, National Health Commission. Notice on issuance of the first list of rare diseases. *http://www.nhc.gov.cn/yzygj/s7659/201806/393a9a37f39c4b458d6e830f40a4bb99.shtml* (accessed March 10, 2022). (in Chinese)
7. Yuan P, Li Z, Xia T, Li H. Population investigation of albinism in China for 25 years- Review and future. Chin J Birth Health & Heredity. 2006; 4-6.
8. Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011; 6:60.
9. Taiwan Health Promotion Administration. Statistical Table of Reported Cases of Rare Diseases. *https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=1559&pid=10254* (accessed March 10, 2019). (in Chinese)
10. Ding J, Wang L. 121 Rare Diseases Handbook. China Medical Science and Technology Press. Beijing, 2019.
11. Zhan S, Siu J, Wang Z, Yu H, Bezabeh T, Deng Y, Du W, Fei P. Focal point of Fanconi anemia signaling. Int J Mol Sci. 2021; 22.
12. Berry GT. Classic galactosemia and clinical variant galactosemia. In: GeneReviews (Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, eds.). Seattle (WA), 1993.
13. Pillai NR, Stroup BM, Poliner A, Rossetti L, Rawls B, Shayota BJ, Soler-Alfonso C, Tunuguntala HP, Goss J, Craigen W, Scaglia F, Sutton VR, Himes RW, Burrage LC. Liver transplantation in propionic and methylmalonic acidemia: A single center study with literature review. Mol Genet Metab. 2019; 128:431-443.
14. Li Q, Yang C, Feng L, Zhao Y, Su Y, Liu H, Men H, Huang Y, Korner H, Wang X. Glutaric acidemia, pathogenesis and nutritional therapy. Front Nutr. 2021; 8:704-984.
15. Racis L, Tessa A, Di Fabio R, Storti E, Agnetti V, Casali C, Santorelli FM, Pugliatti M. The high prevalence of hereditary spastic paraplegia in Sardinia, insular Italy. J Neurol. 2014; 261:52-59.
16. The Subspecialty Group of Endocrinology H, and Metabolic Diseases, Society of Pediatrics, Chinese Medical Association. Common sense in diagnosis and treatment of hyperphenylalaninemia. Chin J Ped. 2014; 420-425.
17. Tournis S, Yavropoulou MP, Polyzos SA, Doulgeraki A. Hypophosphatasia. J Clin Med. 2021; 10.
18. Ye L, Yuan H, Cai X. Analysis of screening results for 21-hydroxylase deficiency in newborns in the Dongguan area. Contemporary Medicine Forum. 2014; 164-165.
19. Pan L, Zheng M, Xie L, Cai R, Tan J, Yang J, Huang L. Screening for 21-hydroxylase deficiency in newborns in Liuzhou. Chin J Birth Health & Heredity. 2013; 68-69.
20. Wang C. A retrospective study of rare diseases in China Biology Medicine Database. Master's Thesis, Jinan University. 2015.
21. Chen J. Treatable Rare Diseases (Chen J, eds.). Shanghai Jiao Tong University Press, Shanghai, China. 2017; 38-136.
22. Roberts AE. Noonan syndrome. In: GeneReviews (Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, eds.). University of Washington, Seattle (WA), 1993.
23. Zhang SY. Compendium of China's First List of Rare Disease. People's Medical Publishing House. Beijing, 2018.

24. Hosahalli Vasanna S, Pereda MA, Dalal J. Clinical features, cancer biology, transplant approach and other integrated management strategies for Wiskott-Aldrich syndrome. J Multidiscip Healthc. 2021; 14:3497-3512.
25. Shanghai Municipal Health Commission. Notice on printing and distribution of the *List of Major Rare Diseases in Shanghai* (2016 Edition). *http://wsjkw.sh.gov.cn/fybj2/20180815/0012-59645.html* (accessed March 10, 2022). (in Chinese)
26. Liu X. Descriptive epidemiology investigation and analysis of the rare diseases in eight provinces, China. China Academic Journal Electronic Publishing House. 2016.
27. Chinese Organization for Rare Disorders. Reference list of rare diseases in China. https://www.sohu.com/a/114982149_119250 (accessed March 10, 2022). (in Chinese)
28. General Office, National Health Commission. Notice on publication of the Rare Diseases Diagnosis and Treatment Guide (2019). *http://www.nhc.gov.cn/yzygj/s7659/201902/61d06b4916c348e0810ce1fceb844333.shtml* (accessed March 10, 2022). (in Chinese)
29. Bureau of Medical Administration, National Health Commission. Notice on the establishment of a national cooperative network for the diagnosis and treatment of rare diseases. *http://www.nhc.gov.cn/yzygj/s7659/201910/be9343380e414adb8c8d641ae8967492.shtml* (accessed March 10, 2022). (in Chinese)
30. Bureau of Medical Administration, National Health Commission. Notice on the registration of information on the diagnosis and treatment of rare diseases. *http://www.nhc.gov.cn/yzygj/s7659/201910/be9343380e414adb8c8d641ae8967492.shtml* (accessed March 10, 2022). (in Chinese)
31. Department of Publicity, National Health Commission. Transcript of the State Council Information Office's regular policy briefing on July 8, 2021. *http://www.nhc.gov.cn/xcs/s3574/202107/8c7bce96b85c48498df15fb1bd0434eb.shtml* (accessed March 10, 2022). (in Chinese)
32. Guo J, Liu P, Chen L, Lv H, Li J, Yu W, Xu K, Zhu Y, Wu Z, Tian Z, Jin Y, Yang R, Gu W, Zhang S. National Rare Diseases Registry System (NRDRS): China's first nationwide rare diseases demographic analyses. Orphanet J Rare Dis. 2021; 16:515.
33. Lu Y, Han J. The definition of rare disease in China and its prospects. Intractable Rare Dis Res. 2022; 11:29-30.
34. Xiao J, Wang C. Support system for rare disease prevention and protection: Experience in Taiwan and insights. Social Security Studies. 2018; 2:92-105.
35. Ministry of Health of the People's Republic of China. Report on the control of birth defects in China 2012. *http://www.gov.cn/gzdt/att/att/site1/20120912/1c6f6506c7f811bacf9301.pdf* (accessed March 10, 2022). (in Chinese)
36. Foundation for Intervention in and Relief of Birth Defects in China. Birth defect (genetic metabolic disease) relief project. *http://www.csqx.org.cn/list.aspx?id=877919995095&prjid=48###* (accessed March 10, 2022). (in Chinese)
37. Ding J WL. Report of rare diseases in China (2018) (Ding J, Wang L, eds). China Medical Science Press, Beijing, 2018; 9.
38. Zhao H, Cui Y, Zhou X, Pang J, Zhang X, Xu S, Han J. Study and analysis of the state of rare disease research in Shandong Province, China. Intractable Rare Dis Res. 2012; 1:161-166.
39. Shi XM LH, Wang L, Wang ZX, Dong CY, Wang YF, Yao C, Zhan SY, Ding J, Li Y. Study on the current situation of China's First List of Rare Diseases based on 15 million hospitalizations. Natl Med J China 2018; 98:3274-3278.
40. Cai X, Genchev GZ, He P, Lu H, Yu G. Demographics, in-hospital analysis, and prevalence of 33 rare diseases with effective treatment in Shanghai. Orphanet J Rare Dis. 2021; 16:262.
41. Hubei Daily. "Survey of rare diseases in Hubei Province" released. *http://www.shandong.gov.cn/art/2017/3/2/art_97564_280621.html?from=singlemessage&isappinstalled=0* (accessed March 10, 2022). (in Chinese)
42. Tsai CP, Wang KC, Hwang CS, Lee IT, Lee CT. Incidence, prevalence, and medical expenditures of classical amyotrophic lateral sclerosis in Taiwan, 1999-2008. J Formos Med Assoc. 2015; 114:612-619.
43. Zhang SY. Compendium of China's First List of Rare Disease (Zhang SY, eds.). People's Medical Publishing House, Beijing, 2018; 86-503.
44. Lu H, Zheng J, Yao Y, Yang M, Ya S, Shi N, Lu J. Retrospective analysis of screening results using TMS to identify inherited metabolic diseases in newborns in Yancheng. Chin J Birth Health & Heredity. 2016; 83-85.
45. Li Y, Cui W, Ya X, Wang H. Epidemiology of congenital scoliosis in Luohe. Chin J Ped Surg. 2017; 221-224.
46. Qu Y, Nie X, Yang Z, Zhan S. Meta-analysis of the prevalence of hemophilia in mainland China. Chin J Hematol. 2014; 65-68.
47. Zhao Z. Advances in screening newborns for inherited metabolic diseases. Chin J Pract Ped. 2014; 586-589.
48. Liu X. Descriptive epidemiology investigation and analysis of the rare disease in eight provinces, China. Master's Thesis, Pharmacy, Jinan University. 2016.
49. Tu TC, Liou WS, Chou TY, Lin TK, Lee CF, Chen JD, Cham TM, Chung MI. Prevalence, incidence, and factor concentrate usage trends of hemophiliacs in Taiwan. Yonsei Med J. 2013; 54:71-80.
50. Ling S, Chan G, Shing M, Yue H, Lee A, Chan C, Lee C, Kwong K, Li C. Children and adolescents with haemophilia in Hong Kong: An epidemiological and clinical review. Hong Kong J Paed. 2006; 13-19.
51. Zhou H, Li Y, Tian L. Progress in diagnosis and treatment of medium-chain acyl-coenzyme A dehydrogenase deficiency. Chin J Pract Ped. 2019; 22-25.
52. Lau KK, Wong WW, Sheng B, Yu IT, Fung BH, Li HL, Ma KF, Wong LK, Li PC. The clinical course of multiple sclerosis patients in Hong Kong. J Neurol Sci. 2008; 268:78-82.
53. You QS, Xu L, Wang YX, Liang QF, Cui TT, Yang XH, Wang S, Yang H, Jonas JB. Prevalence of retinitis pigmentosa in North China: The Beijing Eye Public Health Care Project. Acta Ophthalmol. 2013; 91:e499-500.

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