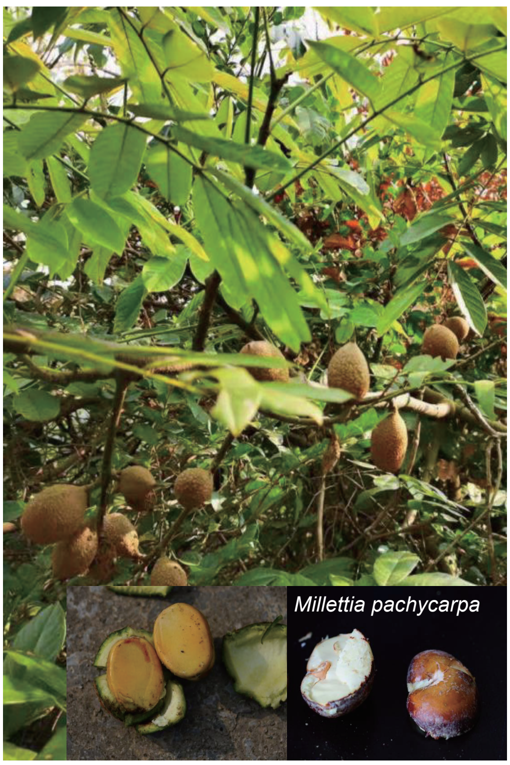
ISSN 2096-7071
CN 10-1629/R1

# CHINA CDC WEEKLY

Vol. 3 No. 14 Apr. 2, 2021

# CCDC weekly

中国疾病预防控制中心周报






ISSN 2096-7071
9 772096 707217 14

Cover Photo: The leaves, fruits, and seeds of Millettia pachycarpa. (See details in the second manuscript of this issue).

Preplanned Studies

# Relationship Between Drug Resistance and Death in HIV-Infected Patients Receiving Antiretroviral Therapy — 7 PLADs, China, 2010–2019

Tianhao Zhang[1]; Lingjie Liao[1]; Yiming Shao[1]; Yi Feng[1]; Yuhua Ruan[1,#]; Hui Xing[1,#]

**Summary**

**What is already known about this topic?**

With increasing coverage of antiretroviral therapy (ART) for HIV-infected patients, more and more attention has been paid to the impact of HIV drug resistance on death in those patients in China.

**What is added by this report?**

Among HIV-infected patients receiving ART, the risk of death is higher in patients with HIV drug resistance [adjusted odds ratio (AOR)=4.25, 95% confidence interval (CI): 2.10–8.62], with viral load ≥1,000 copies/mL but drug resistance untested (AOR=4.65, 95% CI: 1.74–12.39), and with neither viral load nor drug resistance being tested (AOR=17.52, 95% CI: 8.73–35.19) when compared with drug-sensitive patients.

**What are the implications for public health practice?**

It is important to strengthen drug resistance monitoring and prevention in HIV-infected patients. While performing ART for HIV-infected patients, viral load testing and drug resistance testing should be carried out routinely and promptly.

To reduce the mortality rate of HIV-infected patients and improve their quality of life, China has launched the "Four Frees and One Care" policy (Free treatment, free voluntary counseling and testing, free prevention of mother to child transmission, free schooling for AIDS orphans, and one "Care": provision of social assistance for HIV/AIDS patients) to provide lifelong free antiretroviral therapy (ART) for HIV-infected patients who meet the national treatment criteria since 2003 (*1*). In response to the Joint United Nations Programme on HIV/AIDS's (UNAIDS) "Treatment 2.0" strategy, China has implemented a number of targeted strategies to expand the ART coverage in HIV-infected patients since 2010 (*2*). By the end of 2018, a total of 83.4% (748,499/861,042) of HIV-infected patients have received ART (*3*). However, HIV drug resistance (HIVDR) inevitably emerged along with the scale-up of ART, and the drug resistance pattern varied a lot in different regions of China (*4*). This study analyzed data in the national HIV/AIDS Comprehensive Response Information Management System (CRIMS) to investigate the relationship between HIVDR and death in HIV-infected patients receiving ART in seven provincial-level administrative divisions (PLADs) of China. The main finding is that the risk of death was higher in patients with HIV drug resistance or untested resistance compared with drug-sensitive patients. This helps provide a valuable reference for optimizing ART regimens and patient follow-up management in practice.

This study selected seven PLADs that reported and followed-up a large number of HIV/AIDS patients and considered geographical location (eastern and western China) and economic status. Data was collected for patients who received ART, died from all-causes during 2010–2019, and had adequate blood samples that were collected in twelve months prior to death and after ART initiation date. These samples could satisfy the volume requirements for performing viral load and drug resistance tests and were thus selected as death cases. One or two controls were selected for each case from surviving patients who received treatment at the same ART clinic as the case and was registered right before or after the case. The control should have blood samples collected in six months prior to or after the death cases' blood samples. The eligible cases or controls must be people aged 18 years or over when ART initiated, began their ART treatment in 2010 or later, and received ART for more than 6 months.

The data was derived from the CRIMS whose information was collected by local CDCs or HIV hospitals with questionnaires or medical records. Main variables were survival status, gender, age, ethnicity, marital status, education level, occupation, residence, HIV transmission route, ART initiation date, clinic stage according to World Health Organization (WHO) definition, CD4 cell count at the beginning of ART, primary ART regimen, latest ART regimen, ART adherence, latest viral load test result, and latest drug resistance test result.

"HIVDR result" was defined as the main independent variable to analyze the relationship between HIVDR and death (by combining "Latest Viral Load test result" and "Latest drug resistance test result," as shown in Table 1). Due to differences of HIVDR prevalence, quality of medical care services, and sample sizes in regions, multivariate logistic regression analysis was performed for each region, and the adjusted odds ratio (AOR) was obtained. Then, the AORs in different regions were merged by meta-analysis to represent the overall relationship between HIVDR and death in those HIV-infected patients receiving ART. Logistic regression analysis was performed by SAS (version 9.4, SAS Institute, Cary, NC, USA). Meta-analysis was conducted in RevMan (version 5.4, Cochrane Collaboration, Oxford) and NCSS 2004 (Kaysville, UT, USA).

A total of 19,235 HIV-infected patients were enrolled from 7 PLADs (Table 2), with 5,719 in the case group (deaths) and 13,516 in the control group (survived). The proportions of latest viral load untested were 40.0% in the case group and 17.2% in the control group, while 65.6% of case group and 60.8% of control group were latest drug resistance untested. For the HIVDR result, 25.5% of case group and 44.2% of control group were deemed as drug sensitive, and 5.0% of case group and 2.4% of control group were drug resistant. The proportions of patients with viral load ≥1,000 copies/mL but drug resistance untested were 8.6% in the case group and 2.7% in the control group. The proportions of patients who were neither viral load nor drug resistance tested were 28.7% in the case group and 2.9% in the control group, respectively.

The multivariate logistic regression analysis indicated that the correlation between the HIVDR result and death was statistically significant ($P<0.05$) in Anhui, Sichuan, Jiangsu, and Hunan but not in Guangdong ($P>0.05$). No data was shown on the latest compound variable of viral load and drug resistance in Chongqing and Guangxi. After merging AORs of the HIVDR result with deaths in Anhui, Sichuan, Jiangsu, Guangdong, and Hunan, the result suggested that compared with drug-sensitive patients, the risk of death among patients with drug resistance [AOR=4.25, 95% confidence interval (CI): 2.10–8.62], with viral load ≥1,000 copies/mL but drug resistance untested (AOR=4.65, 95% CI: 1.74–12.39), and with neither viral load nor drug resistance being tested (AOR=17.52, 95% CI: 8.73–35.19) were statistically significantly higher (Table 3).

## DISCUSSION

A cross-control survey in seven PLADs in China was conducted to investigate the relationship between HIVDR and death in HIV-infected patients receiving ART. A total of 19,235 participants were included in the analysis. Compared with drug-sensitive patients, the risk of death is higher in patients with HIV drug resistance or untested resistance.

In this large sample study, case-control analysis of patients in seven PLADs showed that HIVDR is significantly associated with death in HIV-infected patients receiving ART. Compared with drug-sensitive HIV-infected patients, the risk of death is 3.25 times

TABLE 1. Operational definition and category of HIVDR result.

| Primary results of viral load and drug resistance test | | Redefined HIVDR categories |
|---|---|---|
| Latest viral load test result (copies/mL) | Latest drug resistance test result | |
| <1,000 | Sensitivity or not be tested | Drug sensitive |
| ≥1,000 | Sensitivity | Drug sensitive |
| Not be tested | Sensitivity | Drug sensitive |
| <1,000 | Resistance | Drug resistant |
| ≥1,000 | Resistance | Drug resistant |
| Not be tested | Resistance | Drug resistant |
| ≥1,000 | Not be tested | Viral load ≥1,000 copies/mL but drug resistance untested |
| Not be tested | Not be tested | Neither viral load nor drug resistance being tested |

Abbreviation: HIVDR=HIV drug resistance.

TABLE 2. Characteristics of participants in 7 PLADs of China between 2010 and 2019, stratified by case group (dead) and control group (survived).

| Item | Anhui | | Chongqing | | Sichuan | | Jiangsu | | Guangxi | | Guangdong | | Hunan | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | | Control group | |
| | n | n | n | n | n | n | n | n | n | n | n | n | n | n | n | % | n | % |
| Total | 1,449 | 2,898 | 1,299 | 5,513 | 1,179 | 2,176 | 897 | 1,628 | 545 | 951 | 200 | 200 | 150 | 150 | 5,719 | 100.0 | 13,516 | 100.0 |
| Age groups (years) | | | | | | | | | | | | | | | | | | |
| 18–29 | 149 | 843 | 45 | 560 | 35 | 189 | 116 | 448 | 38 | 202 | 6 | 12 | 9 | 7 | 398 | 7.0 | 2,261 | 16.7 |
| 30–49 | 578 | 1,410 | 272 | 1,748 | 941 | 1,788 | 348 | 790 | 180 | 455 | 82 | 121 | 62 | 57 | 2,463 | 43.1 | 6,369 | 47.1 |
| ≥50 | 722 | 645 | 982 | 3,205 | 203 | 199 | 433 | 390 | 327 | 294 | 112 | 67 | 79 | 86 | 2,858 | 50.0 | 4,886 | 36.1 |
| Gender | | | | | | | | | | | | | | | | | | |
| Male | 1,194 | 2,249 | 1,047 | 3,679 | 907 | 1,411 | 747 | 1,368 | 432 | 656 | 161 | 134 | 122 | 100 | 4,610 | 80.6 | 9,597 | 71.0 |
| Female | 255 | 649 | 252 | 1,834 | 272 | 765 | 150 | 260 | 113 | 295 | 39 | 66 | 28 | 50 | 1,109 | 19.4 | 3,919 | 29.0 |
| Ethnicity | | | | | | | | | | | | | | | | | | |
| Han | 1,434 | 2,856 | 1,172 | 5,476 | 4 | 11 | 881 | 1,558 | 232 | 438 | 199 | 200 | – | – | 3,922 | 68.6 | 10,539 | 78.0 |
| Other | 13 | 41 | 3 | 16 | 1,175 | 2,165 | 16 | 19 | 313 | 513 | 1 | 0 | – | – | 1,521 | 26.6 | 2,754 | 20.4 |
| Not recorded | 2 | 1 | 124 | 21 | 0 | 0 | 0 | 51 | 0 | 0 | 0 | 0 | – | – | 126 | 2.2 | 73 | 0.5 |
| Marital status | | | | | | | | | | | | | | | | | | |
| Single | 320 | 859 | 104 | 575 | 39 | 102 | 159 | 462 | 99 | 249 | 30 | 47 | 30 | 26 | 781 | 13.7 | 2,320 | 17.2 |
| Married or living with partner | 731 | 1,512 | 799 | 3,899 | 1,091 | 1,966 | 532 | 915 | 320 | 563 | 146 | 142 | 72 | 86 | 3,691 | 64.5 | 9,083 | 67.2 |
| Other | 398 | 527 | 396 | 1,039 | 49 | 108 | 206 | 251 | 126 | 139 | 24 | 11 | 48 | 38 | 1,247 | 21.8 | 2,113 | 15.6 |
| Education* | | | | | | | | | | | | | | | | | | |
| Primary school or less | 735 | 920 | 827 | 2,990 | 1,130 | 2,083 | 293 | 262 | 231 | 283 | 48 | 24 | – | – | 3,264 | 57.1 | 6,562 | 48.5 |
| Junior middle school | 485 | 1,137 | 282 | 1,727 | 41 | 78 | 379 | 612 | 214 | 423 | 109 | 115 | – | – | 1,510 | 26.4 | 4,092 | 30.3 |
| senior middle school or more | 227 | 840 | 66 | 775 | 8 | 15 | 225 | 703 | 77 | 232 | 43 | 61 | – | – | 646 | 11.3 | 2,626 | 19.4 |
| Not recorded | 0 | 0 | 124 | 21 | 0 | 0 | 0 | 51 | 0 | 0 | 0 | 0 | – | – | 124 | 2.2 | 72 | 0.5 |
| Occupation* | | | | | | | | | | | | | | | | | | |
| Famer | 876 | 1,391 | 787 | 3,429 | 985 | 1,981 | 375 | 413 | 281 | 421 | 36 | 36 | – | – | 3,340 | 58.4 | 7,671 | 56.8 |
| Other | 573 | 1,507 | 388 | 2,063 | 194 | 195 | 522 | 1,164 | 264 | 530 | 164 | 164 | – | – | 2,105 | 36.8 | 5,623 | 41.6 |
| Not recorded | 0 | 0 | 124 | 21 | 0 | 0 | 0 | 51 | 0 | 0 | 0 | 0 | – | – | 124 | 2.2 | 72 | 0.5 |
| Residence† | | | | | | | | | | | | | | | | | | |
| Rural | 992 | 1,993 | 797 | 3,328 | – | – | – | – | 96 | 375 | 36 | 37 | – | – | 1,921 | 33.6 | 5,733 | 42.4 |
| Urban | 457 | 905 | 378 | 2,164 | – | – | – | – | 449 | 576 | 164 | 163 | – | – | 1,448 | 25.3 | 3,808 | 28.2 |
| Not recorded | 0 | 0 | 124 | 21 | – | – | – | – | 0 | 0 | 0 | 0 | – | – | 124 | 2.2 | 21 | 0.2 |

TABLE 2. (Continued)

| Item | Anhui | | Chongqing | | Sichuan | | Jiangsu | | Guangxi | | Guangdong | | Hunan | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | | Control group | |
| | n | n | n | n | n | n | n | n | n | n | n | n | n | n | n | % | n | % |
| HIV transmission route | | | | | | | | | | | | | | | | | | |
| Heterosexual | 1,038 | 1,694 | 1,228 | 5,160 | 289 | 797 | 534 | 773 | 444 | 808 | 115 | 132 | 120 | 125 | 3,768 | 65.9 | 9,489 | 70.2 |
| MSM | 282 | 1,019 | 18 | 233 | 847 | 1,284 | 0 | 0 | 9 | 60 | 11 | 35 | 5 | 8 | 1,172 | 20.5 | 2,639 | 19.5 |
| Intravenous drug use | 10 | 7 | 42 | 81 | 43 | 95 | 22 | 30 | 65 | 66 | 59 | 19 | 18 | 9 | 259 | 4.5 | 307 | 2.3 |
| Other | 119 | 178 | 11 | 39 | 0 | 0 | 341 | 825 | 27 | 17 | 15 | 14 | 7 | 8 | 520 | 9.1 | 1,081 | 8.0 |
| WHO clinic stage at the beginning of ART | | | | | | | | | | | | | | | | | | |
| I/II | 837 | 2,212 | 684 | 3,981 | 939 | 1,844 | 555 | 1,172 | 215 | 475 | 0 | 4 | 105 | 120 | 3,335 | 58.3 | 9,808 | 72.6 |
| III/IV | 612 | 686 | 615 | 1,532 | 240 | 332 | 341 | 455 | 120 | 141 | 200 | 196 | 45 | 30 | 2,173 | 38.0 | 3,372 | 24.9 |
| CD4 cell count at the beginning of ART, cells/mm$^3$ | | | | | | | | | | | | | | | | | | |
| <200 | 714 | 902 | 687 | 2,021 | 432 | 431 | 550 | 665 | 355 | 524 | 157 | 129 | 97 | 68 | 2,992 | 52.3 | 4,740 | 35.1 |
| 200–349 | 256 | 925 | 281 | 1,835 | 453 | 877 | 203 | 570 | 137 | 277 | 33 | 54 | 33 | 61 | 1,396 | 24.4 | 4,599 | 34.0 |
| ≥350 | 154 | 608 | 94 | 961 | 261 | 856 | 56 | 253 | 47 | 136 | 10 | 17 | 10 | 17 | 632 | 11.1 | 2,848 | 21.1 |
| Not recorded | 325 | 463 | 237 | 696 | 33 | 12 | 88 | 140 | 0 | 0 | 0 | 0 | 10 | 4 | 693 | 12.1 | 1,315 | 9.7 |
| ART initiation date | | | | | | | | | | | | | | | | | | |
| Before 2015 | 541 | 1,510 | 529 | 1,329 | 974 | 1,619 | 548 | 963 | 312 | 527 | 194 | 192 | 125 | 126 | 3,223 | 56.4 | 6,266 | 46.4 |
| 2015 or later | 908 | 1,388 | 770 | 4,184 | 205 | 557 | 349 | 665 | 233 | 424 | 6 | 8 | 25 | 24 | 2,496 | 43.6 | 7,250 | 53.6 |
| Initial ART regimen | | | | | | | | | | | | | | | | | | |
| D4T-based | 69 | 242 | 83 | 108 | 46 | 39 | 89 | 137 | 100 | 161 | 106 | 88 | 25 | 28 | 518 | 9.1 | 803 | 5.9 |
| AZT-based | 455 | 1,063 | 218 | 719 | 432 | 556 | 467 | 956 | 188 | 352 | 57 | 65 | 62 | 73 | 1,879 | 32.9 | 3,784 | 28.0 |
| TDF-based | 828 | 1,407 | 988 | 4,643 | 682 | 1,483 | 339 | 533 | 218 | 390 | 35 | 45 | 52 | 44 | 3,142 | 54.9 | 8,545 | 63.2 |
| LPV/r-based | 95 | 166 | 1 | 27 | 18 | 96 | 1 | 2 | 0 | 0 | 12 | 13 | 11 | 5 | 138 | 2.4 | 309 | 2.3 |
| Other | 12 | 20 | 9 | 16 | 1 | 2 | 1 | 0 | 39 | 48 | 0 | 3 | 0 | 0 | 62 | 1.1 | 89 | 0.7 |
| Latest ART regimen | | | | | | | | | | | | | | | | | | |
| D4T-based | 0 | 0 | 0 | 0 | 32 | 2 | 46 | 20 | 56 | 3 | 16 | 0 | 10 | 0 | 160 | 2.8 | 25 | 0.2 |
| AZT-based | 535 | 1,110 | 3 | 393 | 369 | 307 | 325 | 751 | 134 | 355 | 34 | 54 | 33 | 49 | 1,433 | 25.1 | 3,019 | 22.3 |
| TDF-based | 505 | 980 | 77 | 4,867 | 679 | 1,353 | 500 | 815 | 226 | 522 | 105 | 123 | 59 | 73 | 2,151 | 37.6 | 8,733 | 64.6 |
| LPV/r-based | 303 | 650 | 1 | 109 | 96 | 514 | 16 | 28 | 0 | 0 | 71 | 49 | 48 | 28 | 535 | 9.4 | 1,378 | 10.2 |
| Other | 106 | 158 | 1 | 55 | 3 | 0 | 10 | 14 | 129 | 71 | 23 | 8 | 0 | 0 | 272 | 4.8 | 306 | 2.3 |
| Not recorded | 0 | 0 | 1,217 | 89 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1,217 | 21.3 | 89 | 0.7 |

TABLE 2. (Continued)

| Item | Anhui | | Chongqing | | Sichuan | | Jiangsu | | Guangxi | | Guangdong | | Hunan | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | Control group | Case group | | Control group | |
| | n | n | n | n | n | n | n | n | n | n | n | n | n | n | n | % | n | % |
| Stop ART or lost to follow-up | | | | | | | | | | | | | | | | | | |
| No | 1,242 | 2,461 | 261 | 708 | 664 | 1,202 | 198 | 260 | 348 | 155 | 88 | 54 | 0 | 0 | 2,801 | 49.0 | 4,840 | 35.8 |
| Yes | 207 | 437 | 1,038 | 4,805 | 515 | 974 | 699 | 1,368 | 197 | 796 | 112 | 146 | 150 | 150 | 2,918 | 51.0 | 8,676 | 64.2 |
| Latest viral load test result, copies/mL§ | | | | | | | | | | | | | | | | | | |
| <1,000 | – | – | 569 | 4,425 | 96 | 701 | 352 | 1,424 | 258 | 893 | 169 | 197 | 8 | 146 | 1,452 | 25.4 | 7,786 | 57.6 |
| ≥1,000 | – | – | 88 | 78 | 58 | 324 | 194 | 78 | 22 | 17 | 27 | 0 | 142 | 4 | 531 | 9.3 | 501 | 3.7 |
| Not be tested | – | – | 642 | 1,010 | 1,025 | 1,151 | 351 | 126 | 265 | 41 | 4 | 3 | 0 | 0 | 2,287 | 40.0 | 2,331 | 17.2 |
| Latest drug resistance test result§ | | | | | | | | | | | | | | | | | | |
| Sensitivity | – | – | 0 | 0 | 96 | 1,841 | 71 | 83 | 2 | 6 | 24 | 1 | 73 | 147 | 266 | 4.7 | 2,078 | 15.4 |
| Resistance | – | – | 0 | 0 | 58 | 66 | 99 | 86 | 4 | 5 | 13 | 11 | 77 | 3 | 251 | 4.4 | 171 | 1.3 |
| Not be tested | – | – | 1,299 | 5,513 | 1,025 | 111 | 727 | 1,459 | 539 | 940 | 163 | 188 | 0 | 0 | 3,753 | 65.6 | 8,211 | 60.8 |
| HIVDR result ¶ | | | | | | | | | | | | | | | | | | |
| Sensitivity | 448 | 2,411 | – | – | 374 | 1,841 | 390 | 1,388 | – | – | 175 | 187 | 73 | 147 | 1,460 | 25.5 | 5,974 | 44.2 |
| Resistance | 59 | 152 | – | – | 36 | 66 | 99 | 86 | – | – | 13 | 11 | 77 | 3 | 284 | 5.0 | 318 | 2.4 |
| Viral load ≥1,000 copies/mL but resistance not being tested | 107 | 221 | – | – | 291 | 111 | 86 | 30 | – | – | 8 | 0 | 0 | 0 | 492 | 8.6 | 362 | 2.7 |
| Neither viral load nor drug resistance being tested | 835 | 114 | – | – | 478 | 158 | 322 | 124 | – | – | 4 | 2 | 0 | 0 | 1,639 | 28.7 | 398 | 2.9 |

Abbreviations: PLADs=provincial-level administrative divisions; ART=Antiretroviral therapy; HIVDR=HIV drug resistance; MSM=men who have sex with men; D4T=2′,3′-Didehydro-3′-deoxythymidine; AZT=azidothymidine; TDF=Tenofovir; LPV/r=Lopinavir/Ritonavir.

* Lack of Hunan region data, the sum of proportion is not 100%.

† Lack of Sichuan, Jiangsu and Hunan region data, the sum of proportion is not 100%.

§ Lack of Anhui region data, the sum of proportion is not 100%.

¶ Lack of Chongqing and Guangxi region data, the sum of proportion is not 100%.

TABLE 3. Relationship between HIVDR and death in HIV-infected patients receiving ART.

| HIVDR result | AOR (95% CI)* |
|---|---|
| Sensitivity | 1 |
| Resistance | 4.25 (2.10, 8.62) |
| Viral load ≥1,000 copies/mL but resistance not being tested | 4.65 (1.74, 12.39) |
| Neither viral load nor drug resistance being tested | 17.52 (8.73, 35.19) |

Abbreviations: ART=Antiretroviral therapy; HIVDR=HIV drug resistance; AOR=multivariate adjusted odds ratio; CI=confidence interval.
* AOR was conducted by meta-analysis to merge the results of PLADs.

higher than that of the drug-resistant HIV-infected patients. Drug-resistant patients are prone to have poor adherence to ART treatment (*5*) and higher incidence of virological failure (*6*), which could accelerate deaths of HIV-infected patients. A previous study showed that the risk of mortality in drug-resistant patients was 3.26 times higher than that of the drug-sensitive population (95% CI: 1.77–6.01), which was similar to the results of this study (*7*). This paper indicated that it is highly important to strengthen the drug resistance monitoring and prevention in HIV-infected patients receiving ART.

In accordance to the requirements of “Manual of the National Free Antiretroviral Treatment” (*8*), all treated HIV-infected patients with viral load ≥1,000 copies/mL should get drug resistance tested. However, the proportions of treated HIV patients with viral load ≥1,000 copies/mL but with drug resistance untested in some regions remained high in this study. Compared with drug-sensitive HIV-infected patients receiving ART, the risk of death was 3.65 times higher in patients with latest viral load ≥1,000 copies/mL but drug resistance untested. This result suggested that for those with viral load ≥1,000 copies/mL, drug resistance tests should be routinely conducted to know patients’ most updated drug resistance status. Therefore, ART regimens could be adjusted accordingly to improve treatment effectiveness.

Constant adherence is vital to effective ART for reducing viral load and HIV/AIDS-related opportunistic infections and mortality which used to be assessed by self-reported data of “missed doses in the past month” in previous studies (*9*–*10*). In this study, required viral load testing was used as a proxy for treatment compliance as it could promptly detect virological failure and drug resistance. The proportion of patients with latest viral load untested in the case group was higher than that in control group (40.0% *vs.* 17.2%). Compared with drug-sensitive HIV-infected patients receiving ART, the risk of death was 17.52 times higher than that of HIV-infected patients with neither viral load nor drug resistance being tested (95% CI: 8.73–35.19). This result indicates that during the ART follow-up management period, more attention should be paid on improving the adherence of patients, strengthening the follow-up quality of HIV clinics, and performing viral load and drug resistance testing promptly as required.

This study was subject to some limitations. First, the case-control design limited the ability to make causal inference about the proposed association. Second, some information of participants was not collected in some regions. Lack of these data may partly affect the analysis for the corresponding regions.

In summary, associations between drug resistance and death in HIV-infected patients receiving ART are highly related. It is important to strengthen the drug resistance monitoring and prevention in those patients. When conducting follow-up management of HIV-infected patients, adherence to antiviral treatment should be improved and viral load testing should be carried out as required. All treated HIV-infected patients with viral load ≥1,000 copies/mL should get drug resistance tested in a timely manner.

**Acknowledgement:** Anhui CDC, Chongqing CDC, Sichuan CDC, Jiangsu CDC, Guangxi CDC, Guangzhou Eighth People’s Hospital, and Hunan CDC.

**Conflicts of interest:** The authors who have taken part in this study declared that they did not have any other potential conflicts of interest.

**Funding:** The Ministry of Science and Technology of China (2017ZX10201101, 2018ZX10721102-006) and National Natural Science Foundation of China (11971479).

**doi:** 10.46234/ccdcw2021.068

# Corresponding authors: Yuhua Ruan, ruanyuhua92@163.com; Hui Xing, xingh09@163.com.

[1] State Key Laboratory of Infectious Disease Prevention and Control (SKLID), National Center for AIDS/STD Control and Prevention (NCAIDS), Chinese Center for Disease Control and Prevention (China CDC), Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Beijing, China.

Submitted: December 16, 2020; Accepted: March 10, 2021

## REFERENCES


1. Zhang FJ, Pan J, Yu L, Wen Y, Zhao Y. Current progress of China's free ART program. Cell Res 2005;15(11 – 12):877 – 82. http://dx.doi.org/10.1038/sj.cr.7290362.
2. Dou ZH, Zhang FJ, Zhao Y, Jin CR, Zhao DC, Gan XM, et al. Progress on China’s national free antiretroviral therapy strategy in 2002-2014. Chin J Epidemiol 2015;36(12):1345 – 50. http://dx.doi.org/10.3760/cma.j.issn.0254-6450.2015.12.005. (In Chinese).
3. Zhao Y, Han MJ, Ma Y, Li DM. Preplanned Studies: progress towards the 90-90-90 targets for controlling HIV—China, 2018. China CDC Wkly 2019;1(1):5 – 7. http://dx.doi.org/10.46234/ccdcw2019.003.
4. Zuo LL, Liu K, Liu HL, Hu YH, Zhang ZJ, Qin JR, et al. Trend of HIV-1 drug resistance in China: a systematic review and meta-analysis of data accumulated over 17 years (2001–2017). EClinicalMedicine 2020;18:100238. http://dx.doi.org/10.1016/j.eclinm.2019.100238.
5. Bayu B, Tariku A, Bulti AB, Habitu YA, Derso T, Teshome DF. Determinants of virological failure among patients on highly active antiretroviral therapy in University of Gondar Referral Hospital, Northwest Ethiopia: a case–control study. HIV/AIDS Res Palliat Care 2017;9:153 – 9. http://dx.doi.org/10.2147/HIV.S139516.
6. Zuo ZB, Liang S, Sun XG, Bussell S, Yan J, Kan W, et al. Drug resistance and virological failure among HIV-infected patients after a decade of antiretroviral treatment expansion in eight provinces of China. PLoS One 2016;11(12):e0166661. http://dx.doi.org/10.1371/journal.pone.0166661.
7. Zhang JH, Li HL, Shi HB, Jiang HB, Hong H, Dong HJ. Survival analysis of HIV/AIDS patients with access to highly antiretroviral therapy in Ningbo during 2004-2015. Chin J Epidemiol 2016;37(9):1262 – 7. http://dx.doi.org/10.3760/cma.j.issn.0254-6450.2016.09.016. (In Chinese).
8. Manual of the national free antiretroviral treatment. 4th ed. Beijing: People’s Medical Publishing House.
9. Kan W, Teng T, Liang SJ, Ma YL, Tang H, Zuohela T, et al. Predictors of HIV virological failure and drug resistance in Chinese patients after 48 months of antiretroviral treatment, 2008–2012: a prospective cohort study. BMJ Open 2017;7(9):e016012. http://dx.doi.org/10.1136/bmjopen-2017-016012.
10. Liu PT, Liao LJ, Xu W, Yan J, Zuo ZB, Leng XB, et al. Adherence, virological outcome, and drug resistance in Chinese HIV patients receiving first-line antiretroviral therapy from 2011 to 2015. Medicine (Baltimore) 2018;97(50):e13555. http://dx.doi.org/10.1097/MD.0000000000013555.

Outbreak Reports

# A Poisoning Outbreak Caused by *Millettia Pachycarpa* — Chongqing Municipality, December 2020

Qian He[1]; Xun Tang[2]; Shisong Wang[3]; Maolin Zhang[3]; Hongshun Zhang[4,#]

**Summary**

**What is already known about this topic?**

*Millettia pachycarpa* belongs to the Fabaceae family and is widely distributed in the southern China. It is toxic for the rotenone contained in its roots and seeds, and ingesting its seeds could result in poisoning.

**What is added by this report?**

In December, 2020, a poisoning from plant seeds occurred in Chongqing Municipality. The etiological association was confirmed based on epidemiological investigation, clinical manifestation, plant species identification, and rotenone analysis. The patient rapidly developed central nervous and respiratory depression with metabolic acidosis. The plant was identified as *Millettia pachycarpa*, and toxin analysis indicated that the rotenone content contained in the seeds was high enough to cause intoxication.

**What are the implications for public health practice?**

*Millettia pachycarpa* poisoning is rare but could be fatal. Efforts should be made to educate and communicate with the public, doctors, and public health practitioners that the toxic effects the seeds could be life-threating when swallowed, both accidentally or intentionally.

On December 18, 2020, the National Poison Control Center received notification that a poisoning accident occurred due to ingestion of plant seeds, and the patients were admitted to Fengdu County People's Hospital of Chongqing Municipality. The plant seemed to stem from the *Millettia* genus based on the pictures provided by one patient's wife. To further clarify the causality of the intoxication outbreak and provide control measures, an investigation into the outbreak was conducted in collaboration with Chongqing Poison Control Center. The plants with fruits were collected at the site where the poisoning occurred, and the doctors and patients were interviewed to obtain the clinical course and treatments. Then, the species of plants was identified, and the rotenone contents of the seeds and gastric lavage samples were analyzed.

## INVESTIGATION AND FINDINGS

Around 11∶30 on December 18, 2020, 2 workers picked fruits thinking they were edible on the hillside besides their workplace in a village in Fengdu County, Chongqing Municipality. Subsequently, they grilled the fruits and shared several fruits with another worker, and all the three workers ate the seeds after peeling the pericarp. They developed discomfort a few minutes after ingesting the seeds. Two of the workers spit out most of the seeds due to poor taste and experienced slightly transient nausea and dizziness but recovered relatively quickly. In contrast, the other 32-year-old male worker who swallowed a whole seed unsuccessfully tried to induce vomiting for himself. He underwent limb weakness and dizziness and rapidly lost consciousness and progressed to coma about ten minutes later. He was then sent to Fengdu County People's Hospital immediately. The patient was unconsciousness on the way to the hospital and admitted to hospital in about fifty minutes.

The patient experienced central nervous system depression and respiratory failure when arriving at the hospital. He presented deep coma, mydriasis, and had no light reflection. His breath was slow, averaging 6 breaths per minute, and the blood oxygen saturation was 67%. Physical examination showed breathing sounds were rough and that wet rales (crackling sounds) were present in both lower lungs. The patient was intubated and treated with ventilator-assisted ventilation to stabilize the vital signs immediately, during which scarlet foam was ejected from the trachea, and gastric lavage was performed to decrease toxin absorption. Chest computed tomography (CT) showed patchy shadows and pleural effusion in both lower lungs. Blood gas analysis indicated metabolic acidosis with pH: 7.09; lactic acid: 11.76 mmol/L. The patient was admitted to the intensive care unit after emergency treatment, underwent hemoperfusion therapy once, and was administrated intravenous sodium bicarbonate to maintain electrolyte balance. The patient took off the ventilator 28 hours after admission and resumed spontaneous breathing, and his consciousness recovered. He was treated and observed in the hospital until his chest CT completely recovered and was discharged.

The plant specimens were collected at the scene of the poisoning incident and testified as the ingested plants by the patient. It was identified as the *Millettia pachycarpa* (Figure 1) using morphological and DNA barcoding method, which belongs to Fabaceae family. The specimen was deposited in the Poisonous Plants Herbarium affiliated with the National Poison Control Center (No. 2020121801).

The primary toxin rotenone in *Millettia pachycarpa* seeds and biological samples were analyzed used liquid chromatography coupled to mass spectrometry method. The rotenone content in *Millettia pachycarpa* seeds (n=2) were 1,389.46 mg/kg and 928.88 mg/kg, and the rotenone content in gastric fluid sample was 3.16 μg/mL. In addition, there were others rotenoid compounds found in the seeds with untargeted screening.

## DISCUSSION

China CDC collaborated with the local poison control center to conduct an investigation to clarify how this poisoning occurred. This outbreak was exactly attributed to the ingestion of *Millettia pachycarpa* seeds, and the etiological association was confirmed based on the evidence in epidemiological correlation, clinical manifestations, plant species identification and rotenone toxin analysis. This work demonstrated that *Millettia pachycarpa* has potential for poisoning and that the public should be warned about the severe toxic effects and potential fatal effects.

Although ingestion of *Millettia pachycarpa* seeds is relatively rare, it may be fatal without appropriate and timely treatment. This incident involved 3 persons, 2 of whom experienced slightly transient dizziness and recovered fast, while the other suffered severe central nervous and respiratory depression, due to the difference in intake amount. The neurological symptoms of the 32-year-old male patient progressed rapidly from dizziness to coma with respiratory depression in about 10 minutes after the ingestion. The scarlet foam ejected from the trachea and the chest CT indicated aspiration pneumonia developed, which was accounted for the central nervous depression and vomiting caused by gastrointestinal irritation. The patient was intubated and ventilated immediately after admission to the emergency department, then, the gastric lavage was carried out to break off more toxin absorption. In addition, the patient underwent hemoperfusion therapy and administered sodium

FIGURE 1. The leaves, fruits, and seeds of *Millettia pachycarpa*.

bicarbonate to maintain acid-base balance.

The toxicity of *Millettia pachycarpa* seeds is attributed to its rotenone and rotenoids. Rotenone mainly exerts toxicity to the nervous, respiratory, and gastrointestinal systems when ingested orally. There is no specific antidote available for rotenone poisoning, and treatment mainly relies on symptomatic and supportive measures (*1*), including intubation, mechanically-assisted ventilation, maintenance of acid-base balance, and stabilizing the vital signs. Gastrointestinal decontamination, such as emetic and gastric lavage, should be used to prevent more toxin absorption even when the patient is unconsciousness. There is insufficient evidence that hemoperfusion therapy is effective for eliminating rotenone, but it is one of the choices for the treatment of rotenone poisoning. The recognition and treatment of the inhalation of pneumonia should be a priority when such patients are encountered.

*Millettia pachycarpa* is a rotenone-containing plant and is widely distributed in the south of China. Reports of *Millettia pachycarpa* poisoning were uncommon in China, but 2 incidents occurred in Guizhou and Hunan provinces in 2020. Another rotenone-containing plant, *Pachyrhizus erosus*, has an edible root and is cultivated extensively in southeastern China, but its rotenone-containing seeds can cause occasional poisonings by accidental ingestion. Additionally, there were several reports of poisonings caused by rotenone-containing plants in other countries and regions. In China (Taiwan) (*2–3*) and Thailand (*4*), *Pachyrhizus erosus* seeds, also called “yam beans,” were reported to result in life-threating poisonings and deaths. In French Guiana (*5*), a woman ingesting another rotenone-containing plant belonging to *Lonchocarpus* genus committed suicide, and the exact species was unable to be determined.

In the region where *Millettia pachycarpa* and other rotenone-containing plants were distributed, ingestion and misuse of the plants should be prevented. Therefore, the public should be educated to distinguish the plants and recognize its toxic effects. Clinicians should be aware and trained to recognize clinical toxicological characteristics and treatment of rotenone-containing plants intoxication. In addition, the pathophysiological, toxicokinetic, and treatment strategy of rotenone-containing plants poisoning should be further reviewed and studied.

**doi:** 10.46234/ccdcw2021.075

[#] Corresponding author: Hongshun Zhang, zhanghs@niohp.chinacdc.cn.

[1] National Institute of Occupational Health and Poison Control, China CDC, Beijing, China; [2] Fengdu County People’s Hospital, Chongqing, China; [3] The First Affiliated Hospital of Chongqing Medical and Pharmaceutical College, Chongqing, China; [4] National Institute of Occupational Health and Poison Control, China CDC, Beijing, China.

Submitted: February 19, 2021; Accepted: March 19, 2021

## REFERENCES

1. Gupta RC. Rotenone. In: Gupta RC, editor. Veterinary toxicology. 2nd ed. Oxford: Academic Press. 2012; p. 620-3. http://dx.doi.org/10.1016/B978-0-12-385926-6.00052-1.
2. Yu JH, Huang CF, Wang TH, Hung DZ, Mu HW, Pan CS. Oxidative storm in a patient with acute rotenone-containing plant poisoning. Am J Emerg Med 2020;38(6):1296.e1 – 3. http://dx.doi.org/10.1016/j.ajem.2020.01.019.
3. Hung YM, Hung SY, Olson KR, Chou KJ, Lin SL, Chung HM, et al. Yam bean seed poisoning mimicking cyanide intoxication. Intern Med J 2007;37(2):130 – 2. http://dx.doi.org/10.1111/j.1445-5994.2007.01245.x.
4. Narongchai P, Narongchai S, Thampituk S. The first fatal case of yam bean and rotenone toxicity in Thailand. J Med Assoc Thai 2005;88(7):984-7. https://www.ncbi.nlm.nih.gov/pubmed/16241030.
5. Chesneau P, Knibiehly M, Tichadou L, Calvez M, Joubert M, Hayek-Lanthois M, et al. Suicide attempt by ingestion of rotenone-containing plant extracts: one case report in French Guiana. Clin Toxicol 2009;47(8):830 – 3. http://dx.doi.org/10.1080/15563650903146818.

Outbreak Reports

# Epidemiological Survey of First Human Brucellosis Outbreak Caused by the Sika Deer (*Cervus nippon*) — Guizhou Province, China, 2019

Zhongfa Tao[1,2,3,&]; Zhangping Yang[4,&]; Yishan Chen[2,5]; Shufeng Yang[6]; Jingchao Xu[7]; Yue Wang[1]; Mingyu Lei[1]; Yun Gou[1]; Qiulan Chen[2,3,#]; Yan Huang[1,#]

**Summary**

**What is already known on this topic?**

Brucellosis is a zoonotic infectious disease caused by *Brucella* spp. The main source of infection in human brucellosis is sick animals, mainly including sheep, goat, and cattle, but sika deer (*Cervus nippon*) can also cause human brucellosis. The first human brucellosis case in Guizhou Province was reported in 2009, and no brucellosis outbreak was reported caused by sika deer ever before.

**What is added by this report?**

This is the first reported outbreak of human brucellosis caused by sika deer in Guizhou Province. Inappropriate regulation of animal movement may be the main driver of introducing and spreading brucellosis in southern areas. The ability to diagnose brucellosis in both humans and animals was weak in the county where the outbreak took place.

**What are the implications for public health practice?**

It was suggested to prioritize occupational protection and health education for sika deer breeders. The inspection of the movement of animals and the reimbursement policy need to be improved.

On June 24, 2019, 6 villagers from a sika deer (*Cervus nippon*) farm came to their local CDC for consultation about brucellosis. After onsite inquiry, three of the six villagers had repeated fever, joint pain, low back pain, and other symptoms. Three villagers tested positive for the Rose Bengal precipitation test (RBPT) for brucellosis. Two of the three villagers tested positive in the standard agglutinating test (SAT). According to the national diagnostic standard on human brucellosis (*1*), two were confirmed cases and one was a clinical case. Therefore, they were considered to be infected with human brucellosis, suspected coming from sika deer. Since sika deer were rarely reported as an infection source to human in southern provinces and even none in Guizhou Province before (*2*–*3*), the provincial CDC staff conducted an onsite epidemiological investigation to verify the outbreak and the infection source.

According to the earliest date of illness onset in the three cases, investigators reviewed the outpatient log of nearby hospitals with a period ranging from September 1, 2018 to June 28, 2019. This study also conducted interviews with a uniform questionnaire and used RBPT and SAT, to identify potential cases among farm workers, the family members of the patients, and other people who had contacted sika deer and other livestock in the village during this period. Lastly, one more clinical case was found according to the national diagnostic standard, making the total number of cases four (*1*). They were 3 males and 1 female breeders in the sika deer farm. None of the patients' family members and other villagers were found to have human brucellosis.

The earliest illness onset time of the patients was October 2018, while the latest onset time was February 2019, and three patients out of the total four presented symptoms from October to November 2018. The 3 of them first visited the local people's hospital in October, December 2018, and February 2019, respectively, but all failed to be confirmed with human brucellosis (Figure 1). The blood samples of the patients were collected for bacteria cultivation in June 2019, but the results were negative due to the former history of antibacterial drug use before diagnosis.

The farm was separated from the village by a river and a mountain (Figure 1). Sika deer were introduced in two batches: the first batch was purchased from Guangxi Zhuang Autonomous Region in June 2016 with an inspection and quarantine certificate; the second batch was introduced in January 2018 from another township in the county without a quarantine certificate. The two batches of imported sika deer were


FIGURE 1. The farm where the sika deer were bred.
Note: The farm was located at the foot of a mountain, which was separated from the village.

kept separately in different but adjacent fences. In May 2018, several sika deer began to suffer from leg suppuration, diarrhea, miscarriage, and even death.

A total of 7 staff were in the farm, and the incidence of human brucellosis in the farm was 57.1% (4/7). All staff had no history of contact with other livestock or other animals except for sika deer since June 2016. All denied ever drinking raw cow/goat milk or eating raw meat. During the breeding process, they had handled the abortion placenta of the sika deer by bare hands without wearing any personal protection equipment. A case-control study was conducted to determine the risk factors of infection, taking people who had contacted sika deer but not diagnosed as human brucellosis case as a control group and staff who had different exposed channels as case group. The study indicated that the regular feeding (OR=99, 95% CI: 1.6–6,053.1) and treatment of abortion placenta exposure (OR=99, 95 % CI: 1.6–6,053.1) were risk factors for the infection in this cluster (Table 1).

The local animal CDC collected 9 blood specimens of living sika deer from the first batch in the farm for *Brucella* antibody detection and cultivation but failed to have positive results. No specimen could be taken from the second batch of the sika deer, since the deer were all sold by the farm owner for the economic incentive soon after the farm staff were confirmed with brucellosis. Local health department disinfected the farm and educated the farm staff and the owner about the prevention measures of brucellosis. No sika deer were killed as the farm owner sold out all the sika deer at last for the reason of no reimbursement for the killed sick deer paid by the local government. The local animal CDC failed to trace the sika deer due to lack of ability to contact the buyer.

## DISCUSSION

Human brucellosis is common zoonosis and is currently endemic in Asia, the Eastern Mediterranean Region, and the Caribbean Region and reemerges in developed countries with the rapidly increasing international travel and business (*4–6*). China faces an increasing burden of human brucellosis since the 21st century (*2–3*). The majority of cases emerged in northern China, where husbandry is more developed, but the southern provinces were also increasing due to the movement of ill animals (*7–8*). The disease causes flu-like symptoms, including fever, weakness, malaise, and weight loss, which are easy to be neglected and misdiagnosed by patients and clinicians (*9–10*). Delayed diagnosis was prone to cause chronic brucellosis, leading to great harm to the patients and their families (*10*). Brucellosis is caused by various *Brucella* species, which mainly infect cattle, swine, goats, sheep, and dogs (*11*). However, sika deer were reported to cause cases in humans both internationally and domestically (*12–14*). Humans become infected with *Brucella* species mainly by contact with sick animals and ingestion of contaminated milk and cheese (*12*). Having contact with the miscarriage material of sick animals is a common infection channel as *Brucella* is prone to be located at the genital tract of animals and cause animal miscarriage (*15*).

TABLE 1. The case study of controlled exposure of an outbreak of brucellosis in Guizhou Province, China, 2019*.

| Exposure pathway | Case group | | Control group | | *p* | OR | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | | | Lower | Upper |
| Breeding deer | 4 | 0 | 2 | 3 | 0.14 | 12.6 | 0.4 | 356.4 |
| Regular feeding | 4 | 0 | 0 | 5 | 0.03 | 99 | 1.6 | 6,053.1 |
| Treatment of abortion placenta | 4 | 0 | 0 | 5 | 0.03 | 99 | 1.6 | 6,053.1 |
| Treatment of sick and dead sika deer | 3 | 1 | 1 | 4 | 0.12 | 12 | 0.5 | 280.1 |
| Delivery | 2 | 2 | 0 | 5 | 0.16 | 11 | 0.4 | 324.5 |

* Where zeros cause problems with computation of the odds or its standard error, 0.5 is added to all cells (a, b, c, d).

Based on literature review and the results of the investigation, this cluster of human brucellosis was likely caused by sika deer. First, the sika deer of the farm had typical symptoms of animal brucellosis such as miscarriage before the patients become ill. Second, all four patients were staff of the sika deer farm. Except for breeding sika deer, no other epidemiological history of infection with brucellosis was detected. Third, the case-control study suggested that handling the abortion placenta of sika deer and regular breeding of sika deer were risk factors for infection.

This study was subject to some limitations. Neither serological nor etiological evidence of brucellosis for the sika deer was required. The negative test results of sika deer specimens in this investigation may be due to insufficient detection capabilities of the county-level animal CDC or sampling bias (that is, the samples collected were all from healthy sika deer). Delays in diagnosis were also a prominent problem in this event and were common in southern China, especially where no human brucellosis was reported before like in this county (*2*). It is important to strengthen the diagnostic ability of both local veterinarians and clinicians.

This was the first report of human brucellosis caused by deer in Guizhou Province. With the development of sika deer breeding industry in China, sika deer are increasingly a risk factor for human brucellosis. The occupational protection and health education of the sika deer breeders should be prioritized. In addition, illegal sales of sick animals were also found in this investigation. This phenomenon is the main driver of introducing and spreading brucellosis in southern areas. Consequently, the inspection of the movement of animals needs improvement, as does the reimbursement policy.

**Acknowledgments:** Staff of the Leishan County Center for Disease Control and Prevention; Village Committee of Datang Village; Datang Village Health Room.

**Conflicts of interest**: No conflicts of interest were reported.

**doi:** 10.46234/ccdcw2021.081

# Corresponding authors: Qiulan Chen, Chenql@chinacdc.com; Yan Huang, cdchuangyan@163.com.

[1] Guizhou Provincial Center for Disease Control and Prevention, Guiyang, Guizhou, China; [2] Division of Infectious Disease, Key Laboratory of Surveillance and Early Warning on Infectious Disease, China Center for Disease Control and Prevention, Beijing, China; [3] China Field Epidemiology Training Project, Beijing, China; [4] Qiandongnan Prefecture Center for Disease Control and Prevention, Kaili,Guizhou, China; [5] Emory University, America; [6] Leishan County Center for Disease Control and Prevention, Leishan, Guizhou, China; [7] Qiannan Prefecture Center for Disease Control and Prevention, Duyun, Guizhou, China.

[&] Joint first authors.

Submitted: November 03, 2020; Accepted: March 23, 2021

## REFERENCES

1. National Health Commission of the People's Republic of China. WS 269-2019 Diagnosis for brucellosis. Beijing: China Standards Press, 2019. (In Chinese).
2. Shang DQ, Xiao DL, Yin JM. Epidemiology and control of brucellosis in China. Vet Microbiol 2002;90(1 – 4):165 – 82. http://dx.doi.org/10.1016/s0378-1135(02)00252-3.
3. Lai SJ, Zhou H, Xiong WY, Yu HJ, Huang ZJ, Yu JX, et al. Changing epidemiology of human brucellosis, China, 1955-2014. Emerg Infect Dis 2017;23(2):184 – 94. http://dx.doi.org/10.3201/eid2302.151710.
4. Franc KA, Krecek RC, Häsler BN, Arenas-Gamboa AM. Brucellosis remains a neglected disease in the developing world: a call for interdisciplinary action. BMC Public Health 2018;18:125. http://dx.doi.org/10.1186/s12889-017-5016-y.
5. Dean AS, Crump L, Greter H, Schelling E, Zinsstag J. Global burden of human brucellosis: a systematic review of disease frequency. PLoS Negl Trop Dis 2012;6(10):e1865. http://dx.doi.org/10.1371/journal.pntd.0001865.
6. Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. Lancet Infect Dis 2006;6(2):91 – 9. http://dx.doi.org/10.1016/S1473-3099(06)70382-6.
7. Chen ZL, Zhang WY, Ke YH, Wang YF, Tian BL, Wang DL, et al. High-risk regions of human brucellosis in China: implications for prevention and early diagnosis of travel-related infections. Clin Infect Dis 2013;57(2):330 – 2. http://dx.doi.org/10.1093/cid/cit251.
8. Shi YJ, Lai SJ, Chen QL, Mou D, Li Y, Li XX, et al. Analysis on the epidemiological features of human brucellosis in northern and southern areas of China, 2015–2016. Chin J Epidemiol 2017;38(4):435 – 40. http://dx.doi.org/10.3760/cma.j.issn.0254-6450.2017.04.005. (In Chinese).
9. Zheng RJ, Xie SS, Lu XB, Sun LH, Zhou Y, Zhang YX, et al. A systematic review and meta-analysis of epidemiology and clinical manifestations of human brucellosis in China. Biomed Res Int 2018;2018:5712920. http://dx.doi.org/10.1155/2018/5712920.
10. Dean AS, Crump L, Greter H, Hattendorf J, Schelling E, Zinsstag J. Clinical manifestations of human brucellosis: a systematic review and meta-analysis. PLoS Negl Trop Dis 2012;6(12):e1929. http://dx.doi.org/10.1371/journal.pntd.0001929.
11. World Health Organization. Brucellosis. 2020. https://www.who.int/news-room/fact-sheets/detail/brucellosis. [2021-1-17].
12. Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. Lancet Infect Dis 2007;7(12):775 – 86. http://dx.doi.org/10.1016/S1473-3099(07)70286-4.
13. Cui BY, Li JY, Yin JM, Li YK, Liang ZH. Epidemiological survey of brucellosis in a deer farm in Shanxi Province. Chin J Epidemiol 2004;25(2):172. https://kns.cnki.net/kcms/detail/detail.aspx?FileName=ZHLX200402027&DbNameCJFQ2004. (In Chinese).
14. He YP, Wang DL. Survey of deer as a source of infection in brucellosis. Chin J Endemiol Prev 1998;13(5):278-80. https://kns.cnki.net/kcms/detail/detail.aspx?FileName=DYBF199805012&DbNameCJFQ1998. (In Chinese).
15. Musallam II, Abo-Shehada MN, Hegazy YM, Holt HR, Guitian FJ. Systematic review of brucellosis in the Middle East: disease frequency in ruminants and humans and risk factors for human infection. Epidemiol Infect 2016;144(4):671 – 85. http://dx.doi.org/10.1017/S0950268815002575.

Healthy China

# Prevention and Control of Cardiac Arrest in Healthy China

Lei Hou[1,#]; Yumeng Wang[1,2]; Wenlei Wang[3]

**Summary**
Cardiac arrest (CA) usually occurs out of hospitals, comprising approximately 50% of all cardiovascular deaths, which may delay achievement for Healthy China 2030 goals for life expectancy and premature death from major chronic diseases. In this review of Chinese law and health policy, challenges and opportunities are explored for CA prevention and control. A considerable gap would remain even if the CA target in Healthy China 2030 are to be achieved on schedule. Therefore, CA should be included in the national disease prevention and control system and national projects, such as the Healthy Cities Initiative and the Primary Public Health Services to accelerate population-wide Cardiopulmonary Resuscitation training and Automatic External Defibrillation availability. Principles of CA prevention and control should be integrated into all relevant policies.

## BACKGROUND

Cardiac arrest (CA) is a serious clinical condition and the initial symptom in one-fourth of cases of cardiac disease, contributing to approximately 50% of all cardiovascular deaths worldwide (*1–2*). CA usually occurs out of hospitals and is often unrecognized in patients with a low risk of cardiovascular disease or who have occult heart disease (*2*). The rate of emergency medical services (EMS) attending out-of-hospital cardiac arrest (OHCA) varies substantially, from 20.9 per 100,000 people in Singapore to 186.0 per 100,000 people in Rochester, United States. The estimated annual mortality from CA is as high as 4–5 million deaths worldwide, with 544,000 deaths in China (*2–3*). An autopsy study showed that only 20% of sudden cardiac deaths — a common outcome of CA — were associated with cardiovascular risk factors. Therefore, much about the etiology of CA is unknown, and CA remains unpredictable (*4*).

One intervention that may reduce mortality from OHCA in non-hospital scenarios is "bystander" cardiopulmonary resuscitation (CPR). However, bystander CPR is underutilized in China, with implementation rates of only 11.4% in Beijing and 4.2% in Shanghai, which are much lower than 46.1% in the United States and 32.2% in Japan (*5*). As a result, the success rate of OHCA rescue is as low as less than 1% in China, compared with approximately 10% in other developed countries (*6*).

High incidence of and mortality from CA may delay achievement of the Healthy China 2030 goals on life expectancy and premature mortality from major chronic diseases. Here, the aim of this article is to discuss challenges and opportunities for CA prevention and control by reviewing the laws and health policies related to CA in China.

## KEY CONTENTS & TARGETS

The *Healthy China Initiative (2019–2030)*, including two government-driven campaigns related to CA — health literacy and cardiovascular/cerebrovascular disease prevention and treatment — will guide our work over the next 10 years (Table 1). CA-related first aid is the first topic of the *Campaign of Cardiovascular and Cerebrovascular Disease Prevention and Treatment*, but there is only one quantitative assessment indicator monitored by the government, which is the rate of emergency rescue training among residents, with training of teachers being the primary strategy chosen to achieve improvement of this indicator. In 2020, the Red Cross Society and the Ministry of Education of China issued a joint notice to strengthen CPR training and train teachers specialized in emergency education. The plans involve installing automatic external defibrillations (AED) in crowded places, including schools, workplaces and institutions, airports, transport stations, shopping malls, and cinemas. Organizations involved in implementation of this effort include the National Health Commission, the Ministry of Education, the Ministry of Finance, and the Red Cross Society of China.

TABLE 1. Campaigns related to cardiac arrest in the *Healthy China Initiative (2019−2030)*.

| Campaign | Government-monitored indicators | Main practices |
|---|---|---|
| Health literacy campaign | Mastering basic knowledge and skills on of first aid including CPR | Encouraging professional institutions and media to educate the public; encouraging residents to master essential skills, such as making an emergency call and CPR; encouraging families to have the first aid kits |
| Cardiovascular and cerebrovascular disease prevention and treatment campaign | Percent of residents with certification in emergency rescue training: ≥ 1% in 2022 and ≥ 3% in 2030 | Supporting professional institutions to carry out mass emergency rescue training; training teachers in primary and secondary schools, 1 teacher trained for each 50 students in the first aid |
| | Outside the monitored indicator system | Providing the first aid drugs and AEDs in crowded places; providing an ambulance for every 50 thousand people; achieving 100% of 10-second answering rate for pre-hospital medical emergency institutions; increasing the 5-minute departure rate of ambulances |

Abbreviations: CPR=cardiopulmonary resuscitation; AED=automatic external defibrillation.

## STRATEGIES

Timely and effective bystander CPR may be the best hope for survival once CA occurs. Initiating CPR within 1 minute of CA and use of AEDs within 3–5 minutes can increase CA survival rate to 50%–70% (*7*). Currently, there are four national laws closely related to increase in CA survival (Table 2). Among these, the *Civil Code* implemented in 2021 is particularly important for legally protecting bystanders who are not medical staff when witnessing a CA and providing onsite first aid. The *Primary Healthcare, Medicine, and Health Promotion Law* implemented in 2020 guarantees comprehensive measures to improve onsite first aid in terms of training potential bystanders, public participation, availability of equipment, and mechanisms for legal protection. The ongoing *Law for Medical Practitioners* is anticipated to play a key role in encouraging and protecting medical practitioners to implement a rescue for OHCA by exempting medical practices from restrictions on place, category, and specialty. Lastly, the *Law of the Red Cross Society* revised in 2017 authorizes the Red Cross Society of China — a non-governmental organization (NGO) — to establish an emergency rescue system in an attempt to improve likelihood of successful rescue from CA.

To supplement national laws, some local governments have enacted detailed regulations to support CA rescue. For example, considering people who are likely to become witnesses of a CA, public transportation drivers and attendants, teachers, tourist guides, firemen, policemen, security staff, and pension service personnel are designated as specific recipients of CPR training in Hunan Province, Shanghai Municipality, Hainan Province, and Nanjing City. The *Regulations of Hunan Province on Spot Rescue* stipulates that CPR training should be included in all types of school curriculum. As the availability of AED devices is essential for onsite first aid for CA, the above regulations require or encourage provision of AEDs in crowded or high-CA-risk places such as transportation hubs, tourist attractions, stadiums, conference and exhibition centers, nursing homes, and schools.

## PERSPECTIVE

Considering that the average response time of pre-hospital emergency medical services is usually more than 15 minutes in urban areas of China, earlier initiation of high quality bystander CPR and AED use are crucial for saving the lives of OHCA victims (*6*,*8*). However, the current CPR training rate among Chinese residents is less than 1%, much lower than the 33% reported in the United States and 40% in France (*5*). Moreover, the number of AEDs per 100,000 Chinese residents is dramatically lower than that in many industrialized countries (17.5, 13, and 5 in the developed Chinese cities of Shenzhen, Haikou, and Shanghai, respectively, *vs.* 700, 276, and as high as 3,399 in the United States, Japan, and in parts of France, respectively) (*7*). These gaps between China and other industrialized countries must be overcome by developing laws and policies. In particular, the key elements of CPR training and provision of AED equipment specified in some local laws should be raised to the level of national laws.

In terms of CPR training, it remains to be determined who should be trained, who should conduct the training, and who should support the training. Health practitioners and people likely to be first to witness CA events are prime candidates for

TABLE 2. Current national laws closely related to cardiac arrest in China.

| Name | Basic description | Function in cardiac arrest |
|---|---|---|
| *Law for Medical Practitioners* | A draft of this law, issued on January 27, 2021, is based on a revision of a similar 1999 law | We suggest that medical practitioners should be encouraged and protected to implement OHCA by exemption from restrictions on their medical practice such as place, category, and specialty by this law, although this draft includes rescue for patients in case of emergency. |
| *Civil Code* | China's first law named after the code occupies a fundamental position in the legal system; implemented on January 1, 2021 | Articles 183 and 184 provide a basic guarantee of civil rights for any bystander who conducts out-of-hospital CPR; Article 1,005 requires organizations or individuals with legal obligations to fulfill their own rescue duties. |
| *Primary Health Care, Medicine and Health Promotion Law* | China's first basic and comprehensive law in the field of health; implemented on June 1, 2020 | Article 27 establishes and improves a pre-hospital first aid system, defining what the jobs of the government as following: 1) carrying out first aid training and public education; 2) encouraging onsite first aid; 3) providing first aid facilities in public places; 4) forbidding refusal and delay from first aid centers due to fees. |
| *Law of the Red Cross Society* | 2017 revised version with functions of the Red Cross Society in non-war or non-armed conflict scenes added. | Article 11 defines the functions of the Red Cross Society, including establishing an emergency rescue system, carrying out emergency rescue training, popularizing emergency rescue and health knowledge, and organizing volunteers to participate in onsite rescue. |

Abbreviations: OHCA=out-of-hospital cardiac arrest; CPR=cardiopulmonary resuscitation.

CPR training. CA training should be considered for inclusion in the national disease prevention and control system, where professional public health institutions such as CDCs can more effectively organize and mobilize the general population. This would not only be responsive to requirements of recent legislation, but also helps offset limitations of the Red Cross Society as an NGO. Establishing permanent professional positions for CPR trainers will help address deficiencies in the availability of training for the public. In terms of AEDs, it is essential to increase the number of AEDs and optimize the placement of AED sites. For example, the local laws noted above suggest many locations for AED sites; however, in communities where the majority of OHCAs occur at home [e.g., 84.7% and 92% before and after the COVID-19 pandemic in Lombardy, Italy, respectively (*9*)], this may be insufficient, as community-based AED placement does not feature in any of China's laws or policies.

Current CA-related policy measures in the *Healthy China Initiative* lag behind the law, despite priority being placed on health and prevention in rapidly developing legislation - likely due to the locus of CA prevention and control being largely beyond the reach of the healthcare system. Even if the *2030 Healthy China* targets are achieved on schedule, a significant gap with other countries will remain. Therefore, we suggest that CPR training and placement of AEDs be featured in the index systems of the National Healthy Cities, the National Demonstration Areas for the Comprehensive Prevention and Control of Chronic Diseases, and the National Primary Public Health Services projects. These projects either effectively mobilize government resources or cover a large number of people, which will help to dramatically increase coverage of CPR training and AEDs among the population. Furthermore, in adherence to the principle of including health promotion in all policies, standards for the placement of AEDs should be considered and integrated into all types of building codes, including specifications for construction of civilized cities and beautiful villages to improve AED coverage for CAs.

Since the beginning of the COVID-19 pandemic, CA cases have increased and the rate of restoration of spontaneous circulation (ROSC) from OHCA has dramatically decreased. This may be because the coronavirus attacks the cardiopulmonary system and because of the strain the pandemic has placed on medical resources. For example, 19.8% of patients with severe COVID-19 pneumonia experienced an in-hospital CA in a single-centered, retrospective, observational study conducted in Wuhan City, Hubei Province; mortality due to CA increased by 58% in the Lombardy region of Italy; and the ROSC rate dropped to 0.4% in February 2020 from about 4.5% before the COVID-19 outbreak in Hangzhou City (*9*–*10*). It is therefore urgent to add CA to the monitoring and early warning mechanisms of public health emergencies, required by the Central Committee of the Communist Party of China, in accordance with the principle of "people first and life first."

**Conflicts of Interest:** No conflicts of interest were reported.

**Funding:** Special Foundation for National Science and Technology Basic Research Program of China (2018FY10060002).

**doi:** 10.46234/ccdcw2021.076

# Corresponding author: Lei Hou, houlei@ncncd.chinacdc.cn.

[1] National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; [2] Public Health School, Baotou Medical College, Baotou, Inner Mongolia, China; [3] The Center for Disease Control and Prevention of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang, China.

Submitted: February 02, 2021; Accepted: March 18, 2021

## REFERENCES

1. Krokhaleva Y, Vaseghi M. Update on prevention and treatment of sudden cardiac arrest. Trends Cardiovasc Med 2019;29(7):394 – 400. http://dx.doi.org/10.1016/j.tcm.2018.11.002.
2. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the american college of cardiology/american heart association task force on clinical practice guidelines and the heart rhythm society. J Am Coll Cardiol 2018;72(14):e91 – e220. http://dx.doi.org/10.1016/j.jacc.2017.10.054.
3. Hua W, Zhang LF, Wu YF, Liu XQ, Guo DS, Zhou HL, et al. Incidence of sudden cardiac death in China: analysis of 4 regional populations. J Am Coll Cardiol 2009;54(12):1110 – 8. http://dx.doi.org/10.1016/j.jacc.2009.06.016.
4. Ifteni P, Barabas B, Gavris C, Moga M, Burtea V, Dracea L, et al. Sudden cardiac death: autopsy findings in 7200 cases between 2001 and 2015. Am J Forensic Med Pathol 2017;38(1):49 – 53. http://dx.doi.org/10.1097/PAF.0000000000000274.
5. Xu F, Zhang Y, Chen YG. Cardiopulmonary resuscitation training in China: current situation and future development. JAMA Cardiol 2017;2(5):469 – 70. http://dx.doi.org/10.1001/jamacardio.2017.0035.
6. Shao F, Li CS, Liang LR, Li D, Ma SK. Outcome of out-of-hospital cardiac arrests in Beijing, China. Resuscitation 2014;85(11):1411 – 7. http://dx.doi.org/10.1016/j.resuscitation.2014.08.008.
7. Lyv CZ, Zhang H, Chen S, Liu XR, Tian GG, Yan SJ. Expert consensus on layout and delivery of AED in China. Clin J Crit Care Sep, 2020;40(9): 813-9. https://doi.org/10.3969/j.issn.1002-1949.2020.09.003. (In Chinese).
8. Qi TF, Jing J. Response time of pre-hospital first aid in urban regions in China, 1996-2015: a meta-analysis. Chin J Public Health 2017;33(10):1466 – 8. http://dx.doi.org/10.11847/zgggws2017-33-10-12. (In Chinese).
9. Shao F, Xu S, Ma XD, Xu ZM, Lyu JY, Ng M, et al. In-hospital cardiac arrest outcomes among patients with COVID-19 pneumonia in Wuhan, China. Resuscitation 2020;151:18 – 23. http://dx.doi.org/10.1016/j.resuscitation.2020.04.005.
10. Yang FL, Yuan YJ, Song YL, Lu X. The Effect on the out-of-hospital system of patients with out-of-hospital cardiac arrest during the COVID-19 outbreak in one city in China. Ann Emerg Med 2020;76(5):687 – 9. http://dx.doi.org/10.1016/j.annemergmed.2020.05.032.

Notifiable Infectious Diseases Reports

# Reported Cases and Deaths of National Notifiable Infectious Diseases — China, February, 2021

| Diseases | Cases | Deaths |
|---|---|---|
| Plague | 0 | 0 |
| Cholera | 0 | 0 |
| SARS-CoV | 0 | 0 |
| Acquired immune deficiency syndrome | 3,051 | 1,052 |
| Hepatitis | 101,058 | 36 |
| Hepatitis A | 745 | 0 |
| Hepatitis B | 83,014 | 30 |
| Hepatitis C | 14,714 | 6 |
| Hepatitis D | 23 | 0 |
| Hepatitis E | 1,849 | 0 |
| Other hepatitis | 713 | 0 |
| Poliomyelitis | 0 | 0 |
| Human infection with H5N1 virus | 0 | 0 |
| Measles | 38 | 0 |
| Epidemic hemorrhagic fever | 365 | 1 |
| Rabies* | 14 | 10 |
| Japanese encephalitis | 0 | 0 |
| Dengue | 2 | 0 |
| Anthrax | 10 | 0 |
| Dysentery | 2,623 | 1 |
| Tuberculosis | 55,425 | 56 |
| Typhoid fever and paratyphoid fever | 327 | 0 |
| Meningococcal meningitis | 10 | 1 |
| Pertussis | 115 | 1 |
| Diphtheria | 0 | 0 |
| Neonatal tetanus | 3 | 0 |
| Scarlet fever | 989 | 0 |
| Brucellosis | 3,425 | 0 |
| Gonorrhea | 7,650 | 0 |
| Syphilis | 33,615 | 5 |
| Leptospirosis | 3 | 0 |
| Schistosomiasis | 1 | 0 |
| Malaria | 58 | 0 |
| Human infection with H7N9 virus | 0 | 0 |
| COVID-19† | 348 | 0 |
| Influenza | 10,894 | 1 |
| Mumps | 4,393 | 0 |

Continued

| Diseases | Cases | Deaths |
|---|---|---|
| Rubella | 46 | 0 |
| Acute hemorrhagic conjunctivitis | 1,873 | 0 |
| Leprosy | 30 | 0 |
| Typhus | 37 | 0 |
| Kala azar | 15 | 0 |
| Echinococcosis | 224 | 0 |
| Filariasis | 0 | 0 |
| Infectious diarrhea[§] | 144,447 | 0 |
| Hand, foot, and mouth disease | 18,529 | 1 |
| **Total** | **389,618** | **1,165** |

[*] Of the 10 reported death cases of rabies, there were 7 reported in Feburary, the other were reported previously.

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

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

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

**doi:** 10.46234/ccdcw2021.082

The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).

CCDC weekly

Vol. 3 No. 14 Apr. 2, 2021

**Responsible Authority**

National Health Commission of the People's Republic of China

**Sponsor**

Chinese Center for Disease Control and Prevention

**Editing and Publishing**

China CDC Weekly Editorial Office

No.155 Changbai Road, Changping District, Beijing, China

Tel: 86-10-63150501, 63150701

Email: weekly@chinacdc.cn

**CSSN**

ISSN 2096-7071

CN 10-1629/R1