Unique factors to consider when exploring the surge in reported pertussis cases in China

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The increasing number of pertussis cases and fatalities in China is concerning, with decreased immunity after acellular vaccination being a key reason for the increase.[1] However, to understand the current increase in the number of pertussis cases in China, attention should be paid to the resurgence of cases before the COVID-19 pandemic and the apparent change in the *Bordetella pertussis* pathogen.

Although China is among the few countries using copurified acellular pertussis vaccines in national immunisation programmes, declining protection after inoculation is not a unique problem. Reduced vaccine-induced immunity contributes to the resurgence of pertussis. Remarkably, the coverage of the diphtheria, tetanus, and acellular pertussis vaccine in China has remained above 98% during 2009–22, despite the COVID-19 pandemic.[2] If waning immunity was solely responsible, logically more cases would be observed in adolescents and adults.

The rise in pertussis cases over the past decade is closely linked to increased vigilance among paediatricians within passive surveillance frameworks. The widespread use of PCR assays during the COVID-19 pandemic has helped in identifying more pertussis cases. Doctors in general hospitals treating adolescents and adults need to be more vigilant regarding pertussis because the disease can be challenging to identify in adolescents and adults owing to frequent atypical manifestations. This increased awareness can help to mitigate future increases in reported cases of pertussis.[3]

Before the COVID-19 pandemic, numerous studies involving serological analyses and enhanced clinical surveillance suggested that reported pertussis rates in China were likely to be substantially underestimated.[4] The actual number of cases could be tens to thousands of times greater than the reported cases. A serological study revealed that the incidence of pertussis in individuals older than 15 years was 25 625 times higher than the reported incidence.[5] Hence, despite a potential ten-fold increase in reported pertussis cases compared with the number of cases reported in the same period in the past year, the incidence likely remains underestimated relative to the actual incidence. Furthermore, whether the actual incidence of pertussis is rising in line with the increase in reported cases remains unclear. Another crucial epidemiological factor is the evident resurgence in reported pertussis cases before the COVID-19 pandemic. By 2019, national reports registered 30 027 cases, reverting to levels not observed since the late 1980s. Strict pandemic control measures sharply disrupted this upward trend.[6]

There are no published data available regarding the current surge in cases, including information on demographics and distribution.[1] Nevertheless, select single-centre data indicated no marked increase in infant cases compared with pre-pandemic cases.[3] Additionally, the national statistics of 2022 have maintained a decline in infant cases observed since 2018–21.[6] Given the decrease in infant cases, the question arises: why the increase in fatalities? In this context, associating the sudden surge in pertussis-related deaths with the circulation of highly virulent strains resistant to erythromycin is logical. The *ptxP3* variant of *B pertussis* is more virulent than *ptxP1* strains. In China, the erythromycin-sensitive *ptxP3* strain has been identified since 2002, and the first erythromycin-resistant *ptxP3* strain (*ERBP-ptxP3*) was identified in 2017, marking a shift in strain characteristics.

One possible explanation is that before developing drug resistance, the highly virulent *ptxP3* strain paradoxically caused milder clinical symptoms in infected individuals compared with the *ptxP1* strain—contrary to findings of previous research.[7] Ongoing surveillance has identified a shift in dominance among clinical isolates; between 2020 and 2022, *ERBP-ptxP3 B pertussis* supplanted that expressing *ptxP1* (*ERBP-ptxP1*). In 2019, *ERBP-ptxP1* accounted for 91·6% of pertussis cases (109 of 119), and *ERBP-ptxP3* was not detected. Conversely, in 2022, the proportions changed considerably to 19·6% (18 of 92) for *ERBP-ptxP1* and 80·4% (74 of 92) for *ERBP-ptxP3*.[6] *ERBP-ptxP3* has a stronger ability to evade immune selection pressure because the *ptxP3* strain with the same genetic background belonging to lineage IV has greater antigen variations and deficiencies.[7] A study reported that all 44 *B pertussis* isolates collected in Beijing during 2022–23 were identified as *ERBP-ptxP3*. Two of the isolates showed a deficiency in the vaccine antigen filamentous hemagglutinin (Fha), 30 showed a deficiency

in pertactin (Prn), and one showed multiple immunogen deficiencies.[8] This widespread prevalence of *ERBP-ptxP3* strains poses a substantial challenge to both clinical therapies and the effectiveness of the pertussis vaccination programme.

To address the increasing prevalence of *ERBP-ptxP3*, we have advocated exploring alternative antibiotic options.[9] On May 25, 2024, the National Disease Control and Prevention Administration issued an updated pertussis prevention and control strategy,[10] which could initially lead to an increase in reported cases. However, the update represents a crucial step towards devising targeted interventions that include the optimisation of vaccination schedules for comprehensive lifetime protection or focused strategies for newborn immunity in China.

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