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## Viewpoint

Emerging macrolide resistance in *Bordetella pertussis* in mainland China: Findings and warning from the global pertussis initiativeYe Feng<sup>a,b</sup>, Cheng-Hsun Chiu<sup>c,d,\*</sup>, Ulrich Heininger<sup>e</sup>, Daniela Flavia Hozbor<sup>f</sup>, Tina Quanbee Tan<sup>g</sup>, Carl-Heinz Wirsing von König<sup>h</sup><sup>a</sup> Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China<sup>b</sup> Institute for Translational Medicine, Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China<sup>c</sup> Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan, Republic of China<sup>d</sup> Molecular Infectious Disease Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan, Republic of China<sup>e</sup> Department of Pediatric Infectious Diseases and Vaccinology, University of Basel Children's Hospital, Basel, Switzerland<sup>f</sup> Laboratorio VacSal, Instituto de Biotecnología y Biología Molecular, Universidad Nacional de La Plata y CCT de La Plata, CONICET de La Plata, Argentina<sup>g</sup> Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago and Feinberg School of Medicine, Northwestern University, Chicago, IL, USA<sup>h</sup> Krefeld, Germany

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## ABSTRACT

Whooping cough, or pertussis, is a highly communicable infectious disease caused by the bacterium *Bordetella pertussis*. Vaccination once reduced the incidence of the disease, but a global resurgence of the infection happened during the past two decades, likely due to the waning immunity of vaccination. Macrolides such as erythromycin and azithromycin are the drugs of primary choice for treatment. In this personal view, we call for attention to macrolide-resistant *B. pertussis* (MRBP), which has emerged and prevailed in mainland China for years and are exclusively mediated by mutations in the 23S rRNA gene. Whether the prevalence of MRBP in China results from overuse of azithromycin in clinical medicine remains unknown. The incidence of MRBP is low in other countries, but this could be a technical illusion since China employs culture as the mainstream diagnostic method whereas nucleic-acid amplification test being widely used in other countries fail to test antimicrobial susceptibility. Given the increasingly frequent global travel that facilitates microbial transmission worldwide, there is a pressing need to perform international surveillance on MRBP to prevent the potential circulation of the organism. Finding alternative agents that possess good activity against *B. pertussis* is also urgently required.

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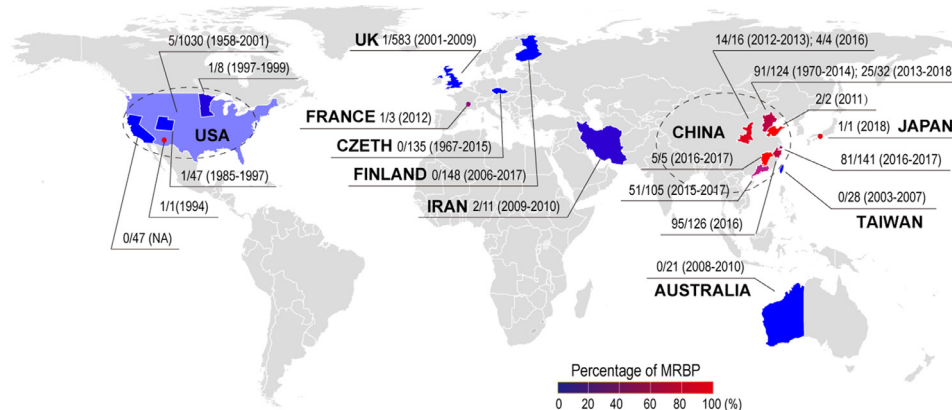
## 1. Introduction

Pertussis (whooping cough), a highly contagious respiratory illness caused by *Bordetella pertussis*, is characterized by outbursts of coughing followed by whooping inhalation. Vaccination for pertussis, introduced in the 1950s, dramatically reduced the incidence of the disease. The past two decades, however, has seen a global resurgence of the infection, in particular in countries with high vaccination coverage [1,2]. Pertussis remains primarily a disease of

childhood, but the distribution of cases has shifted to adolescents and adults [3]. A diminishing duration in the protection afforded by acellular vaccines (ACVs) is believed to be a major cause for the infection's revival, which may then further spread to non- or partially immunized infants. What is worse is the emergence of macrolide resistance in *B. pertussis* (MRBP) in China, which has not attracted enough attention yet. The Global Pertussis Initiative (GPI) is an expert scientific forum that publishes consensus recommendations or viewpoints concerning pertussis for many regions of the world [4]. This Personal View article from GPI is calling a global concerted effort upon MRBP since its development may challenge the current treatment of pertussis and worsen the already serious threat of this organism to public health.

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**Fig. 1.** Percentage of macrolide-resistant *B. pertussis* (MRBP) worldwide. Included in this figure are data from literatures about MRBP searched from PubMed. The information including country, number of MRBP and all *B. pertussis* tested, as well as the isolates' collection time are marked. The detailed information for these literatures is listed in appendix.

## 2. Emergence of macrolide-resistant *B. pertussis* in China

The first macrolide resistant *B. pertussis* (MRBP) was identified in Arizona in the United States in 1994, with a minimum inhibitory concentration of  $> 64 \mu\text{g/mL}$  [5]. We searched PubMed using the terms, “*Bordetella pertussis*”, “pertussis”, “macrolide resistance”, and their combinations, and limited our search to English language papers published as of June 2020. Consequently, we discovered that during the past 60 years of the history of the use of macrolides for treatment of pertussis in the US, less than 15 MRBP have been detected, accounting for  $< 0.5\%$  of the total *B. pertussis* isolates examined (Fig. 1 and appendix) [6–9]. The incidence of MRBP in other countries, except China, also appears to be very low according to previous studies [10–13]. In China, erythromycin has been used for treatment of pertussis since the 1980s, with few MRBP being isolated prior to 2008 [14]. However, since then, a steep rise in macrolide resistance has been observed in hospitals in east, north and northwest China, where over 50% of *B. pertussis* isolates were found to be resistant to macrolides [14–19]. Thus, MRBP is expected to have prevailed throughout China.

There are two known mechanisms for resistance to erythromycin in bacteria: the acquisition of erythromycin-resistant methylase (*erm*) genes, [20] and the mutations in the 23S rRNA (*rrn*) gene leading to structural changes that prevent the binding of erythromycin [7]. To date, nearly all studies have confirmed that the resistance of MRBP is mediated by the latter mechanism, and the mutation concentrates on the A2047G transition [6,7,12,14,16–19,21] This mutation is likely to occur in more than one of the three copies of the *rrn* operon in the *B. pertussis* genome. More copies may result in higher resistance level, but a single copy is already sufficient to raise the MIC to  $> 64 \mu\text{g/mL}$  [5,6,12,16] It is therefore not feasible to attempt to treat the MRBP infection with an increased dose of erythromycin. Furthermore, the resistance mediated by this mutation is not only to erythromycin but also to other macrolides, including azithromycin [19]. Thus azithromycin is also no longer effective for MRBP treatment.

Usually antimicrobial resistance is selected and driven by antimicrobial exposure in healthcare, agriculture, and the environment [22,23]. Macrolide is one of the most extensively used veterinary antimicrobials in China [24–26]. But *B. pertussis* is a strict human pathogen with no known animal or environmental reservoir. Combined with the knowledge that macrolide resistance in *B. pertussis* is not conferred through plasmid-mediated lateral transfer, the use of macrolides in animal husbandry appears less likely to serve as a selection pressure to contribute towards the prevalence of MRBP. Thus, the rise of MRBP is probably attributed to

the overuse of azithromycin in pediatrics, [27–29] since the empirical treatment of bacterial or even viral infectious diseases has relied too heavily on this antimicrobial agent in China. The high population density may also help to accelerate the dissemination of MRBP.

Antimicrobial resistance is often associated with a reduced bacterial fitness and virulence; this phenomenon is often referred to as “epistasis” or “fitness cost” [23,30]. Whether the MRBP strains exhibit a diminished virulence is unknown. Also unknown is whether the weakened antimicrobial selective pressure, brought by a more strictly control of antibiotics use in China, would reduce the macrolide resistance, and accordingly, enhance the virulence.

## 3. Will MRBP prevail worldwide?

Before making this prediction, the first question we need to answer is whether China is the only country where MRBP has already prevailed. In China, culture remains the mainstream diagnostic method employed. Despite such problems as lengthy culture time and false negatives, the culture method can obtain isolates that allow for the subsequent antimicrobial resistance testing. In contrast, in most of other countries, PCR or serology are the gold standard of identification. Being rapid and sensitive, the two methods fail to provide any susceptibility information, and the chance of missing resistant strains is high. It is therefore likely, at least in theory, that in other countries than China, the MRBP rate is high but being ignored due to inadequate diagnostic methods.

The evidence from previous genomic epidemiological studies supports the notion that the MRBP in China are less likely to cause epidemic in other countries [21]. The MRBP isolates in China can be mostly assigned into the ptxP1 lineage, which further split into three independent sub-lineages based on their genome sequences; [21,31] whereas the ptxP3 lineage is currently endemic in other countries [32,33]. The dated phylogeny revealed that the three ptxP1 sub-lineages emerged in 2008, coinciding with the time when the co-purified acellular vaccines (cp-ACVs) were applied and began replacing whole cell vaccines (WCVs) for the national immunization program in China. Compared to WCVs and the separated purification ACVs (sp-ACVs) which have been adopted by most of other countries worldwide, cp-ACVs induce a lower level of antibodies and stimulate a lower concentration of cytokines [34]. As expected, much less antigen variations have been observed in the genomes of the ptxP1 lineage resulting from the cp-ACV-induced selection pressure than in the ptxP3 lineage from the WCV- and sp-ACV-induced selection pressure [21]. Because the ptxP1 strains probably failed to deal with strong immunization se-

lection pressure in a population vaccinated with WCVs or sp-ACVs, it is reasonable to speculate that the current MRBP in China may not become a pandemic pathogen.

Even if the Chinese MRBP strains is less likely to spread abroad, public should be on the alert against the emergence of any novel MRBP clones. The three ptxP1 sub-lineages in China has evolved independently to each other, suggesting a not low frequency of the spontaneous mutations in 23S *rrn*. The global resurgence of pertussis infers a more common use of macrolides. This enhanced antimicrobial pressure may drive more mutations to form novel MRBP strains anywhere in the world.

#### 4. Clinical and vaccination implications

Three stages of illness are noted for pertussis: catarrhal, paroxysmal, and convalescent. The transmissibility of pertussis is greatest early after onset of illness, occurring during the catarrhal and early paroxysmal phases [35]. Before the emergence of MRBP, the drug of primary choice is a macrolide, such as erythromycin, azithromycin, or clarithromycin. Treatment with macrolides during the catarrhal stage of illness shortens the duration of symptoms and eliminate the organism from the upper respiratory tract within 5 days of the initiation of treatment [36]. Previous studies also confirmed the efficacy of erythromycin for the chemoprophylaxis of pertussis; in a prospective study, chemoprophylaxis with 10 days of the erythromycin achieved an efficacy of 67.6% [37,38].

For MRBP, sulfamethoxazole-trimethoprim remains effective and can be used for patients aged > 2 months of age [39]. A number of other antimicrobial agents have been tested for in vitro activity against *B. pertussis*. While there is no substantial activity of oral penicillin and cephalosporins, a number of fluoroquinolones and parenteral cephalosporins showing low MIC deserve future evaluation [38]. An oral carbapenem, faropenem, was tested to show good activity against *B. pertussis*, [40] whereas other parenteral  $\beta$ -lactams, such as meropenem, are unlikely to play role.

The vaccines, including WCVs and ACVs, have greatly reduced the incidence of pertussis, and will continue to be the most powerful weapon against MRBP. One effect of vaccination in the countries with high vaccination coverage has been a shift in the incidence of the disease from children aged 1–9 years in unvaccinated populations to adolescents and adults in vaccinated populations [41,42]. This is probably because the duration of protective immunity provided by ACVs is between 10 and 15 years [43]. Disease incidence is also increasing in infants because adolescents and adults can serve as reservoirs for *B. pertussis* and transmit the disease to vulnerable infants who are too young to be protected by vaccination [44–48]. When MRBP leaves few antimicrobials for treatment, measures should be taken in order to reduce transmission and develop herd immunity. The recommendations include adolescent booster and cocooning; the latter refers to the vaccination of mothers and other contacts of infants [49,50].

Comparison between the existing vaccines and development of novel vaccines are still required, since vaccines with different technique, formula and schedule may produce different reactogenicity and efficacy. We suggest that China should carry out a clinical trial to switch to a vaccine with a different immunogenic profile from the currently used cp-ACVs and see whether the prevalence of MRBP can be hindered.

#### 5. Global surveillance needed for control of MRBP

Currently, two aspects require particular attention in the surveillance of *B. pertussis*. One is macrolide resistance. Culture is not the only diagnostic method for detection of MRBP. Given the uniform resistance mechanism of MRBP, it is recommended that a PCR technique be developed that simultaneously targets

the A2047G mutation, [10] therefore combining the availability of susceptibility information with the advantage of PCR diagnosis. The other is subspecies typing, which may facilitate source tracing when an endemic occurs. To date, genome sequencing is the only approach that can achieve enough resolution for the determination of clonal relationship [51]. Unfortunately, the current genome resources aimed at epidemiological source tracing, such as BacWGSTdb [52] and NCBI Pathogen Detection (<https://www.ncbi.nlm.nih.gov/pathogens/>), are not available for *B. Pertussis*. However, such resources are of particular importance for assessing the potential threat that whether MRBP will disseminate worldwide to become a pandemic, given the context of increasing international travel and globalization.

To date there are two global consortia which aim to raise awareness about pertussis and to recommend effective vaccination strategies for disease control. One is GPI, [4] and the other is the PERTussIS Correlates Of Protection Europe (PERISCOPE) [53]. Both consortia organized regular forums to gather experts worldwide and collect epidemiological information evaluation and prioritization of immunization strategies.

Economic hurdle remains to be the biggest challenge for controlling pertussis. Most countries have a passive surveillance system where cases are reported through general practitioners and hospitals to regional and national health board. Due to its wide variation in clinical presentation, pertussis cases in adolescents and adults are often not reported. As a result, the incidence of the disease is underestimated, not to mention MRBP which relies heavily on diagnostic facilities. Meanwhile, even if adolescent booster and cocooning strategy are known to be beneficial, they are difficult to implement because of funding requirements. Targeted application in high-risk populations may increase their feasibility.

#### 6. Conclusions

Taken together, the emergence of MRBP may evolve to be a looming threat to the global public health that may further complicate the current worldwide epidemiology of pertussis. Development of accurate and low-cost diagnostic, surveillance and vaccination methods/resources appear critical at this moment. Finding alternative agents that possess good activity against *B. pertussis* should also become areas of interest for research in the coming resistance era.

#### Author Contributions

YF and C-HC wrote the initial draft. C-HC collated input from all other authors. UH, DFH, TQT, and CWvK provided discussions and reviewed the manuscript. UH and DFH in formulating the table and panel. UH also helped in organizing the panel and post-meeting discussions

#### Declaration of Interests

Dr Feng declares no competing interests. During the conduct of the study, Dr. Chiu has received honoraria from Sanofi Pasteur, MSD, and Pfizer; Dr. Heininger and Dr. Hozbor have received honoraria from Sanofi Pasteur; Dr. von König has received honoraria from Sanofi Pasteur, GSK Biologicals SA, MSD, and Novartis Vaccines. Dr. Tan has received grant from Sanofi Pasteur. Outside the submitted work, Dr. Tan has received grants from Merck, Pfizer, and Glaxo-Smith Kline.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2021.100098.

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