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Short Communication

Phase-shifting of the transmissibility of macrolide-sensitive and resistant *Mycoplasma pneumoniae* epidemics in Hong Kong, from 2015 to 2018

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ABSTRACT

Mycoplasma pneumoniae is a threat to public health. This pathogen caused an epidemic in Hong Kong during the years 2015–2018. The reproduction number during the initial epidemic was estimated to be 1.7 for macrolide-resistant *M. pneumoniae* (MRMP) and 1.4 for macrolide-sensitive *M. pneumoniae* (MSMP). During 2016–2018, the reproduction number remained stable at around 1.0 for both MRMP and MSMP. Phase-shifting and changes in the leading-status between the transmissibilities of MSMP and MRMP were found.

Introduction

Mycoplasma pneumoniae is one of the common causes of community-acquired pneumonia (CAP). *M. pneumoniae* epidemics occur every 3–5 years in the general population, with the highest infection rates among individuals aged 5–20 years (Bradley et al., 2011; the Centre for Health Protection, the Department of Health, the government of Hong Kong, 2019; Centers for Disease Control and Prevention, 2019; Atkinson et al., 2008). There is no effective vaccine (Centers for Disease Control and Prevention, 2019; Atkinson et al., 2008) and a macrolide is usually used for the antibiotic treatment of *M. pneumoniae* infections. However, macrolide resistance is an emerging threat worldwide (Bradley et al., 2011; the Centre for Health Protection, the Department of Health, the government of Hong Kong, 2019; Centers for Disease Control and Prevention, 2019; Atkinson et al., 2008).

An increasing trend in the macrolide-resistant *M. pneumoniae* (MRMP) rate was reported in a previous outbreak of *M. pneumoniae* occurring in 2011–2014. The rate increased from 13.6% in 2011 to 47.1% in 2014 (Ho et al., 2015). Starting in January 2015, an *M. pneumoniae* epidemic caused 1060 cumulative *M. pneumoniae* cases (5.54%) among 19 134 CAP cases and gradually faded away in 2018 (Figure 1a, b). The rate of diagnosis of positive macrolide resistance showed one pEeak in the summer of 2016 (green curve in Figure 1a), while there were two peaks of *M. pneumoniae* cases, one in the summer of 2016 and the other in the summer of 2017 (grey line in Figure 1b). The average MRMP rate was 29.38%, i.e., 307 out of 1045 *M. pneumoniae* cases processed; 15 *M. pneumoniae* cases were not processed for macrolide resistance testing (Centers for Disease Control and Prevention, 2019).

This study was performed to estimate the transmissibility of *M. pneumoniae* infections using a standard approach and to compare the transmissibilities of MRMP cases and macrolide-sensitive *M. pneumoniae* (MSMP) cases. Differences in the changing dynamics of MRMP and MSMP infection transmissibilities across different periods during 2015–2018 were explored. The aim was to understand the non-stationary association between MRMP and MSMP. Such an understanding is crucial for the future design of forecasting approaches and control measures.

Data and methods

Monthly *M. pneumoniae* cases and macrolide resistance testing records were obtained from the Centre for Health Protection in Hong Kong (the Centre for Health Protection, the Department of

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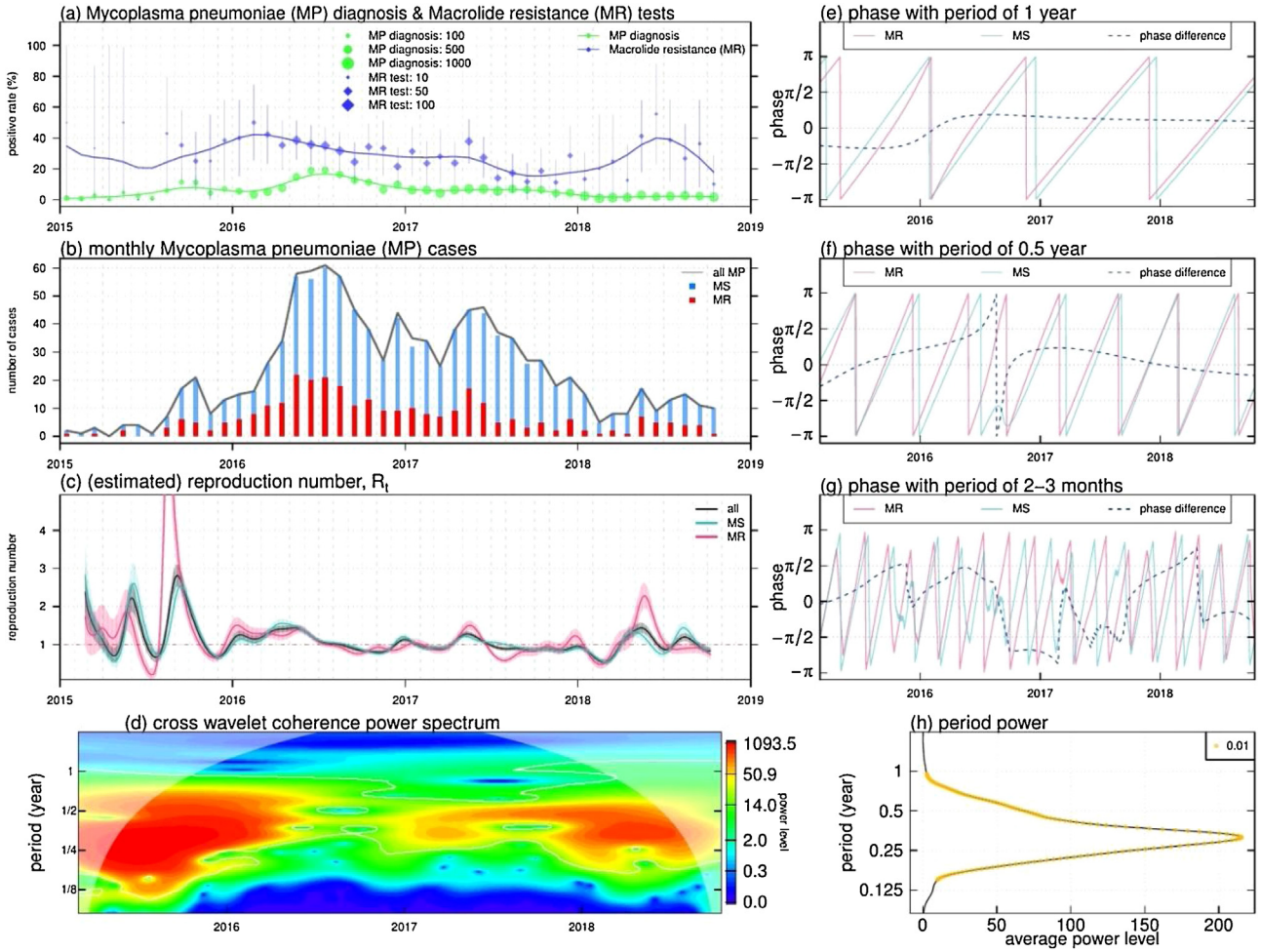

Figure 1. *Mycoplasma pneumoniae* diagnosis and macrolide resistance testing records, monthly numbers of cases, estimated transmissibility (R_t), and cross-wavelet power spectrum analysis results, Hong Kong, 2015–2018. (a) Reported (dots) and smoothed (curves) rates of positive *M. pneumoniae* diagnostic testing (green circles) and macrolide resistance (MR, blue diamonds); the vertical bars are the 95% confidence intervals (CI) and the sizes of the dots indicate the test sample sizes. (b) Monthly number of total (grey), macrolide-resistant (MR, red), and macrolide-sensitive (MS, blue) *M. pneumoniae* cases. (c) Estimated instantaneous transmissibility in terms of the reproduction number (R_t) of total (black), MR (pink), and MS (cyan) *M. pneumoniae* cases; the horizontal red dashed line is the level of $R_t = 1.0$ and the shaded areas are the 95% CI. (d) Cross-wavelet power spectrum: the colour key is on the right; the area in which the cross-wavelet transform results could be distorted by edge effects is indicated by a lighter shade. (e–g) Cross-wavelet phase plot of MR (pink) and MS (cyan) *M. pneumoniae* reproduction numbers with a period of (e) 1 year, (f) 0.5 year, and (g) 2–3 months; the indigo dashed curves are the phase difference dynamics over time. (h) Average wavelet period spectrum power; significant periods ($p < 0.01$) are highlighted in gold.

Health, the government of Hong Kong, 2019) (Figure 1a, b). These *M. pneumoniae* cases were laboratory confirmed through the testing of respiratory secretion specimens obtained from all CAP patients in Hong Kong. Macrolide resistance tests were conducted based on the 23S rRNA gene for all specimen samples from most of the confirmed *M. pneumoniae* patients, except for 15 out of 1060 cases (the Centre for Health Protection, the Department of Health, the government of Hong Kong, 2019).

The instantaneous reproduction number, R_t, was calculated using the serial interval (SI) approach (Cori et al., 2013; Wallinga and Teunis, 2004) (see Supplementary material, Appendix A1). The estimated R_t allowed the transmissibilities of MRMP and MSMP infections to be studied. Cross-wavelet analysis was then utilized to investigate the temporal patterns of the R_t series obtained (Tang et al., 2017; Grenfell et al., 2001; Chiu et al., 2018) in the frequency spectrum, and particularly on the phases of the R_t obtained. Furthermore, the observed patterns were verified via the Granger causality test (GCT). The GCT was conducted on the entire estimated R_t series and on the parts before and after mid-2016 (see Supplementary material, Appendix A2), separately. Finally, sensitivity analyses were conducted to check the sensitivity of R_t estimation and observed phase-shifting patterns in various ranges of the SI (see Supplementary material, Appendix A3).

Results and discussion

Results are shown in Figure 1c–h. In the initial epidemic in 2015, R_t was relatively high (due to the high proportion of susceptibles). Note that R_t equals the basic reproductive number of the pathogen multiplied by the proportion of susceptibles. In 2015, the R_t was estimated to be 1.4 (95% confidence interval (CI) 1.2–1.6) for all *M. pneumoniae* cases, 1.7 (95% CI 1.3–2.1) for MRMP infections, and 1.4 (95% CI 1.2–1.7) for MSMP infections. The estimates were in line with those of a previous study (Nguipdop-Djomo et al., 2013), which reported a basic reproduction number (R_0) of 1.7 (95% CI 1.6–1.9) (see Supplementary material, Appendix A4). During 2016–2018, the R_t was stable at around 1.0 for both MRMP infections (95% CI 0.9–1.2) and MSMP infections (95% CI 1.0–1.1). This decrease could have been due to the reduction of susceptibles. The estimated daily R_t of MRMP and MSMP differed significantly on most of the days during the study period (estimated 98.9%) (see Supplementary material, Appendix A1).

Cross-wavelet analysis revealed that the periodicity of the R_t of MRMP and MSMP was significant between 2 months and 1 year (Figure 1d, h). In particular, their phases showed rich patterns (Figure 1e–g). Figure 1e (period 1 year channel) shows that the R_t of MRMP and MSMP were largely in-phase, although a leading-status change is evident when the phase difference crosses zero. Here, 'leading-status' means that the change in one (leading) pathogen is ahead of the change in the other (following) pathogen. In Figure 1e, the phase differences between the two were largely between $-\pi/4$ and $\pi/4$. Figure 1f (period 0.5 year channel) shows that at one time point in 2016, the two pathogens were close to anti-phase (a phase difference of π or $-\pi$). Figure 1g (period 2–3 months channel) shows that an MR-led in-phase pattern occurred before 2016, followed by an out-of-phase period and an MS-led in-phase in the winter and spring of the 2016–2017 season, then followed by another period of MR-led in-phase, ending with an MS-led in-phase pattern. For the period of 2–3 months, the most dominant periodicity channel, the R_t of MRMP and MSMP showed rich dynamics, e.g., transitions from MR-led in-phase to out-of-phase then to MS-led in-phase, which could be speculatively associated with competition between the two pathogens. This phenomenon mimics those observed among different influenza strains (Chiu et al., 2018).

The results of GCT were only significant under the hypotheses that MR Granger causes MS before 2016 and MS Granger causes MR after 2016 (see Supplementary material, Appendix A3). This should be interpreted in Granger-causality sense, but not necessarily in biological sense. Nevertheless, the GCT results corroborated the results (phase-shifting in 2016) found via the cross-wavelet analyses.

Hypothetically, it is speculated that competition between the MRMP and MSMP pathogens could have been responsible for the rich anti-phase dynamics revealed here. This competition might be associated with competition on the susceptibles or interference between MSMP and MRMP. Thus, the change in the leading pathogen could (partly) cause the change in the following pathogen. Such a competition could be caused by the convalescence effect after infection with one pathogen, and thus individuals had a lower chance of becoming infected by another pathogen. Other possible mechanisms include the evolution of the *M. pneumoniae* pathogens, changes in the build-up of immunity in the host population, and interference between MSMP and MRMP, and other respiratory pathogens. Alternatively, it is possible that a common driving force caused the changes in both pathogens, but one of them responded more swiftly than the other. In addition, it could also be a combined effect in which both causality (between MSMP and MRMP) and a common driving force exist.

Detailed information and follow-up data for the *M. pneumoniae* patients could improve these analyses. With the available patient information, a case–control study could be conducted to explore the factors influencing the MSMP or MRMP infections. With patient follow-up details, including contact history, the source of *M. pneumoniae* infection could be explored and a further analysis conducted using mechanistic compartmental modelling approaches, providing more precise estimate results.

The findings of this study indicate the possible existence of a biological mechanism behind the rich patterns of MSMP and MRMP. Future studies and clinical investigations are needed to explore the biological mechanisms behind these rich patterns, which could be helpful for *M. pneumoniae* control. The framework used here could be applied to other infectious diseases, in particular those in which multiple strains/pathogens potentially compete.

Author contributions

SZ conceived and carried out the study. All authors drafted and revised the manuscript, and gave final approval for publication.

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Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2019.02.030.

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