Age-period-cohort analysis of tuberculosis notifications in Hong Kong from 1961 to 2005

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SUMMARY
Background: Hong Kong, despite its wealth, excellent vital indices and robust health care infrastructure has a relatively high incidence of tuberculosis (TB) (85.4 per 100,000). Hong Kong residents have also experienced a very rapid and recent epidemiologic transition; the population largely originated from migration by southern Chinese in the mid 20th century. Given, the potentially long latency period of TB infection, we investigated to what extent TB incidence rates reflected the population history and the impact of public health interventions.

Methods: We used an age-period-cohort model to decompose the Hong Kong TB notification rates from 1961 to 2005 into the effects of age, calendar period and birth cohort.

Results: Analysis by age showed a consistent pattern across all the cohorts by year of birth, with a peak in relative risk of TB at 20-24 years of age. Analysis by year of birth showed an increase in relative risk of TB from 1880 to 1900, stable risk until 1910 and then a linear rate of decline from 1910, with an inflection point at 1990 for a steeper rate of decline, while period effects yielded only one inflection during the calendar years 1971-75.

Conclusions: Economic development, social change and DOTS have contributed to TB control in Hong Kong. The linear cohort effect until 1990 suggests that a relatively high, but slowly falling, incidence of TB in Hong Kong will continue into the next few decades.
INTRODUCTION
Tuberculosis (TB) has been declared a global health emergency since 1993.[1] Hong Kong, despite its wealth (GDP per capita was approximately US$33,000 in 2005), excellent vital indices (longest life expectancies at birth for both sexes) and robust health care infrastructure, is classed as having an intermediate TB burden[2] reporting notification rate of TB of all forms of 85.4 per 100,000 population in 2006.[3] While it is not facing the same critical situation as some Southeast Asian and African countries, local notification rates are considerably higher than in most other developed countries.[2] This apparent paradox of high wealth yet high burden may be due to Hong Kong’s unique social history, where population growth has been driven by waves of immigration from southern China mainly after 1945, given that migration has been found to drive TB incidence in other industrialised countries.[4-6]

The age-period-cohort (APC) modelling framework[7] has previously been used to study secular trends typically in chronic disease incidence[8,9] but also in infectious disease incidence.[10-13] The APC model decomposes the time trends in disease incidence into effects of age, year of birth and calendar period. For instance, changes in risk by age can reflect pathogenesis of disease, while those by birth cohort can show the effect of prevalence of an infectious disease over a lifetime, and period effects can show changes in diagnostic efficiency. APC models have been applied to TB mortality,[14] although we are unaware of previous applications to TB incidence. While models for infectious disease incidence will typically describe transmission dynamics, these dynamics may be less important for TB given the chronic characteristics of infection, particularly the slow time course between infection and onset of symptoms and the high proportion of latent infections. In the following sections we apply APC modelling techniques to TB notification rates in Hong Kong and interpret the results in terms of the impact of demographic shifts, socioeconomic development and intervention programmes on trends in TB incidence.

METHODS

Sources of data
Age- and gender-specific TB notifications from 1961 to 2005 were obtained from the Department of Health of the Hong Kong Government.[15] Tuberculosis has been a notifiable infectious disease in Hong Kong since 1939 and notifications from the private and public sectors are centrally collated in the Department of Health. The annual age- and gender-specific mid-year population of Hong Kong from 1961 to 2005 were derived from official statistics published by the Census and Statistics Department.[16] Cases were notified if they met a clinical case definition or a laboratory case definition of active tuberculosis infection.[17]

Statistical analysis
Annual notification rates were standardized to the World Standard Population[18] to investigate the changes in disease reporting rates over time allowing for changes in the underlying population age structure.
In order to estimate the independent effects of age, period and birth cohort factors on TB notification, we fitted a negative binomial log-linear regression model[19] with age, period and cohort terms included as categorical variables. We used a negative binomial rather than Poisson model to allow for potential over-dispersion in the data due to clustering of cases.[20] Notifications were grouped into 18 five-year age groups, nine 5-year calendar periods, and 26 birth cohorts. A unique feature of APC models is that the three components are interrelated, specifically any two factors allow the third to be derived.[7] To overcome this identifiability problem we constrained the second and penultimate period terms to be the reference groups.[21]

We compared the full APC model with three partial models adjusting for age, age-period and age-cohort terms respectively. We further developed the APC model by including age-cohort interaction terms, to investigate potential heterogeneities in age effects in different groups of birth cohorts, as described further in the technical appendix. Alternative models were compared using the Akaike information criterion (AIC), which is a measure of goodness of fit adjusting for model parsimony where a lower value of AIC indicates a better model.[22] The AIC is derived as -2 multiplied by the fitted log-likelihood plus twice the number of parameters included in the model. In addition, three of the authors independently assessed residual plots by visual inspection to verify the goodness of fit of the regression models. The Pearson residuals for the regression model were calculated as the standardised differences between the observed and fitted values; further details are given in the technical appendix. All statistical analyses were performed using R version 2.4.1 (R Development Core Team, Vienna).

RESULTS
Figure 1 shows declining trends in age- and sex-standardized TB notification rates by sex from 1961 to 2005. Disease reporting rates have mostly leveled off in the last decade compared to the more rapid decrease in earlier years. Annual age- and sex-standardized rates fell 83% from 405 to 67 cases per 100,000 during the observation period. Notification rates have declined more rapidly in men than in women, but notification rates in men currently remain approximately 70% higher than in women. The apparent spike in 1967 is most likely an artifact due to a re-organization of TB statistics in that year.[23] Age-specific notification rates have historically been much higher in men, and particularly older males, than in women (Appendix Figure 1). In both sexes, TB notifications typically rose with age to a mode in the early adult years, then declined through adult life before increasing again with older age. However, this pattern has become less distinct, with more recent years recording far lower rates in younger individuals, but similar notification rates in those over 75 years.

We fitted age, age-period, age-cohort, age-period-cohort models to the incidence rates, and found that among these the full APC model was the most appropriate for describing the data for both sexes since it had the lowest AIC. However, examination of residual plots revealed that the full APC model was not optimal statistically; the fit was improved considerably after inclusion of age-cohort interaction terms. We investigated a variety of categorisations of the age groups and birth cohorts, and found that allowing for separate age effects in each of three groups of birth cohorts divided at 1906 and 1956 resulted in the best fitting model, that is the
model which most accurately represented the raw data according to the AIC and visual inspection of residual plots.

Figure 2 presents the age, period and cohort parameter estimates after adding the interaction term between age and cohort into the model. Figures 2a and 2d show that people born in the three birth cohort groupings had similar changes in risk of TB with age, noting that the age effects for the most recent birth cohort group were shifted upwards relative to the age effects for the other two birth cohort groups as a result of the choice of the reference groups, while the corresponding cohort effects for the birth cohorts after 1956 are shifted downwards by a similar factor. Adjusting for the effects of birth cohort and time period, the relative risk of age began to rise in both males and females from the 5-9 age group, peaked at 20-24 years old, then quickly declined to a nadir at the age group of 45-49, and finally showed an upturn during the eighth decade for women which was not apparent for men. In both sexes the risk of TB showed a turning point at approximately 1906 as the central year of birth, and another second-order change appeared in the 1991 birth cohort. Period effects in men and women yielded only one inflection during the calendar years 1971-75. The overall patterns in the APC parameter estimates were similar across the sexes. Whereas both sexes (female more so than male) showed an upward inflection as they approached their 70s, this effect was only observed for people born later (ie 1911-1956) but not earlier (1876-1906). Finally there may be an additional discontinuity or second order change in the immediate post-war period around 1950 which is more pronounced for men than women although this may be an artefact because it coincides with the birth cohort strata cut-off.

DISCUSSION
We have described a novel application of APC modelling to studying trends in TB incidence. While APC models are typically applied to study trends in chronic diseases,[8] they may also be used to analyse infectious diseases.[10-13] Given the long time scale of the TB infection process, the majority of infections being latent, and the likely huge pool of infected individuals at least among earlier generations[24] it is arguable that TB, or at least reactivation disease which forms the majority of TB notifications in Hong Kong (particularly in the elderly),[25,26] could be considered more of a chronic condition than an infectious disease. Therefore although our model does not explicitly incorporate the infection processes, or transmission dynamics, of TB in a population it can still allow us to make inferences on trends in disease incidence. While APC models are typically based on the Poisson distribution implying an underlying assumption of independence between events, we have used the negative binomial distribution to allow for the possibility of clustered events.[20] Our results will provide a useful and informative complement to more detailed future analyses with complex transmission models.

Our results have revealed important temporal shifts in the etiology of TB in Hong Kong that were decomposed into and can be explained by demographic change, intergenerational effects and historical events. One of the most vexed local public health issues is whether our currently high TB burden is mainly being driven by primary infections, re-infections, or reactivations. Since the global resurgence of TB in the 1980s, more studies have focused on the impact of recurrence (re-infection and reactivation) on TB epidemics.[27-29] We cannot directly examine the relative influences of reactivation or re-infection versus primary
infection since our dataset only describes aggregate disease notifications, and we do not have information on how many of the notifications are reactivations of previous infections. However while our crude data suggest that the risk of active TB increases with older age in the over 50s (Appendix Figure 1), the decomposition results indicate that the elevated risk may be attributed to earlier birth cohorts, rather than more advanced age per se except in the old-old and with increasing longevity (Figure 2). This implies that earlier generations of migrants were already infected in mainland China when they were young before settling in Hong Kong. Many had reactivation diseases during later adulthood which were recorded in the local notification system. Since the proportion of mainland migrants had shrunk continuously during the period of observation (Appendix Figure 2), and while TB rates have come down with economic development and population-level intervention measures in the more prosperous parts of China such as Guangdong province[30] whence most of Hong Kong’s migrants have originated, we can predict that there will be fewer reactivation cases and Hong Kong’s overall TB incidence will continue to fall.

A variety of studies have shown that migrants, specifically from developing countries with higher TB prevalence, are affecting the trends of TB incidence in developed countries.[4,5,31] Within China, migrant workers from rural areas, comprising 10% of the country’s population, joining the wage economy in towns and cities form an important vector for TB spread and the maintenance of a high burden in economically developed urban regions.[32] While only a small percentage of Hong Kong’s TB notifications are from recent migrants,[23] Hong Kong has a unique social history where the local population has historically been augmented by waves of immigrants from mainland China in the 20th century, mainly in the late 1940s, early 1950s and the late 1970s (Appendix Figure 2) who then subsequently develop reactivation disease locally.[33] About one million people migrated into Hong Kong in the late 1940s and early 1950s, largely young people looking for work, but also around 1949 some political refugees from Guangzhou and to a much lesser extent Shanghai.[34] Hong Kong birth cohorts born prior to 1945 are largely (approximately 80%) migrants from southern China, whilst birth cohorts born after 1960 are largely Hong Kong born (Appendix Figure 3).[35] Thus the turning point in the cohort effect around 1910 is likely to reflect events in southern China rather than specifically in Hong Kong. It is tempting to interpret the upstroke of the turning point as a population wide embodiment of the turmoil connected with the fall of the Qing dynasty, driven by increased population movement and exposure for the cohort of babies born around that time. However, the downstroke of the inflection might be an artefact of the major wave of migration into Hong Kong in the late 1940s of people in their 20s and 30s. Older migrants at that time from the pre-1906 birth cohorts would have been at age (40 years and more) less susceptible TB than the younger migrants, most likely progressively more strongly selected healthy migrants with age, and more likely to be political refugees who may have come from a social stratum with generally better living conditions, thus more protected against infection or recurrence.

On the other hand, given the difference in living standards between China and Hong Kong it is noteworthy that there is no obvious downward inflection in the post 1945 birth cohorts, until possibly about 1990, even though an increasingly higher proportion were born and growing up in Hong Kong with its rapidly developing economy and elements of a modern infrastructure, i.e. sanitation and public health initiatives. There are several possible
explanations for this lack of downward inflection in an earlier cohort. Firstly population mixing engendered by migration may have introduced a large pool of susceptible individuals from rural areas where TB was less prevalent than in urban areas, presumably due to the reduced exposure in such isolated, closed communities.[36] This enhanced circulation of TB may have counteracted improved living standards and public health initiatives. Secondly, living standards in China were essentially unchanged from pre-industrial levels until well into the second half of the 20th century, so older migrants (corresponding to earlier birth cohorts) would have had a cumulatively greater exposure to pre-industrial living conditions, and it may be that it is the cumulative exposure to poor living conditions rather than exposure at a critical period, e.g. during growth and development, which is important for TB, either primary infection or recurrence. Thirdly, it is possible that because of the dynamics of TB infection there is a long lag between better living conditions and reduced TB, so that several decades of improvements in living conditions are needed before the prevalence in the population drops to a level which precludes widespread infection. Certainly, given that even in the birth cohort from around 1960, about 80% were tuberculin positive at primary school, strongly suggests widespread circulation of TB in birth cohorts up to that date and such a time lag. Only by about the 1980 birth cohort did the proportion tuberculin positive fall to 20%.[37] suggesting that it took about a generation of improved living conditions and BCG vaccination for the level of TB circulation to fall dramatically. The sharp decrease for the most recent birth cohorts may be a reflection of the reduced circulation of and exposure to TB in these more recent cohorts. The implication for the future is that slowly declining levels of TB are very likely in older people in the short to medium term, after which there may be a more substantial fall.

Our data do not go back far enough in time to capture any potential period effect of newborn BCG vaccination since 1952. Nevertheless, there is substantial evidence in the literature suggesting that BCG probably does not change incidence patterns but can prevent serious complications and reduce paediatric mortality, especially in countries with high TB prevalence.[38] Empirically based on local observations, the introduction of the BCG programme has resulted in a dramatic decline in infant mortality due to TB[39] and a concomitant reduction in the risk of infection for young children.[37] but there is still no conclusive evidence on the benefit of BCG vaccination to protect adults from infection[40,41].

On the other hand, effective treatment of infected patients appears to be a much more important determinant of overall incidence. Our period inflection point centres around the 1970s, coinciding with the introduction of directly observed therapy (DOT) in 1970 which progressed to the incorporation of the short-course regimen (DOTS) in 1979.[37] This is consistent with demonstration of the benefits of DOTS elsewhere.[42] In addition to the development of effective medical interventions, societal changes could be another possible explanation for the declining TB incidence in Hong Kong. The average household size (thus density, assuming constant or increasing living space) in Hong Kong has been decreasing for decades, which might to some extent have prevented TB spread by reducing airborne dissemination.
Treating potentially infected individuals should be another focus of TB control systems in developed regions with relatively lower TB incidence. However, while treating latent TB infection is likely to speed the decline in TB incidence it might prove costly, as the effectiveness of chemoprophylaxis requires accurate diagnoses, high treatment adherence and minimisation of potential adverse drug reactions. Therefore, further study is necessary to examine the potential cost-effectiveness of such a control strategy.

The considerable gender differences in TB incidence rates in Hong Kong shown in Figure 1 is unlikely to be associated either with HIV because of low positive rate of HIV test among TB patients,[23] or sex-based inequality in accessing services given Hong Kong’s free TB clinics and universal health care more generally and that women have less serious symptoms than men at the time of diagnosis.[43] Recent studies on the association between smoking and TB in Hong Kong found that the much higher prevalence of smoking in males accounted for approximately 45% of the gender difference.[44,45]

Increasing longevity over time and survivorship to very old age (favoring women over men and later cohorts over earlier cohorts) together explain the age-specific notification patterns historically (Appendix Figure 1), and the age component results on decomposition (Figure 2). At the other age extreme, the peak risk during adolescence might have resulted from weaker immunity in the phase of growth spurts,[46] increased public activities thus mixing, or initiation of tobacco use.[47,48]
CONCLUSIONS
Our results highlight the gender differential in TB incidence and the continuing peak in disease risk for young adults. The epidemiological transition experienced by Hong Kong residents with migration from China, DOTS, and increased longevity and survivorship have likely been the most important determinants of TB notification rates in Hong Kong. Nevertheless, there remains an intermediate burden, which is most likely due both to a lead time before these public health improvements could have had a significant impact on the circulation of TB and to the re-activation of TB in people originally infected under very different circumstances. As a result it is likely that a relatively high but predictably falling burden of TB in Hong Kong will continue into the coming decades, assuming no major changes to immigration policies.
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Figure legends

Figure 1. Age- and age-sex standardized TB notification rates in Hong Kong, 1961-2005. Footnote to Figure 2: Standardised to the WHO World Standard Population.

Figure 2. Parameter estimates of age, period and cohort effects from the full APC model with age-cohort interaction term for men (above) and women (below). (a) Estimated age effects (circles for people born after 1961, triangles for people born in 1911-1956, and diamonds for people born in 1876-1906) with 95% confidence intervals for men. (b) Estimated cohort effects (circles for people born after 1961, triangles for people born in 1911-1956, and diamonds for people born in 1876-1906) with 95% confidence intervals for men. (c) Estimated period effects (circles) with 95% confidence intervals for men. (d) Estimated age effects (circles for people born after 1961, triangles for people born in 1911-1956, and diamonds for people born in 1876-1906) with 95% confidence intervals for women. (e) Estimated cohort effects (circles for people born after 1961, triangles for people born in 1911-1956, and diamonds for people born in 1876-1906) with 95% confidence intervals for women. (f) Estimated period effects (circles) with 95% confidence intervals for women.

Appendix Figure 1. Age-specific TB notification rates in Hong Kong in 10-year intervals since 1965 for (a) men and (b) women.

Appendix Figure 2. Number of new immigrants (‘000s) to Hong Kong, 1942-96 (bars) and proportion of immigrants to total population (line). Footnote to Appendix Figure 2. Sources: Hong Kong Annual Report [34] and Hong Kong census and by-census from 1961 to 1996.

Appendix Figure 3. Proportion of population born in Hong Kong by sex, 1961, 1981 and 2001.
REFERENCES


