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Research Fund for the Control of Infectious Diseases

Research Dissemination Reports

衛生及醫護服務研究基金

控制傳染病研究基金

研究成果報告

Health Services Research
醫療服務研究

Severe Acute Respiratory Syndrome
嚴重急性呼吸系統綜合症

Sexually Transmitted Infections
性傳播感染

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Research Dissemination Reports

EDITORIAL

Dissemination reports are concise informative reports of health-related research supported by funds administered by the Food and Health Bureau, namely the *Research Fund for the Control of Infectious Diseases* (RFCID) and the *Health and Health Services Research Fund* (HHSRF). In this edition, 11 dissemination reports of projects related to health services research, severe acute respiratory syndrome, and sexually transmitted infections are presented. In particular, three projects are highlighted due to their potentially significant findings, impact on health care delivery and practice, and/or contribution to health policy formulation in Hong Kong.

Chronic pain, insomnia, and fatigue are important public health problems but are poorly documented in Chinese populations. Fielding and Wong[1] conducted a cross-sectional, population-based, observational study via structured telephone interviews on more than 5000 randomly selected ethnic Chinese adults. This study aimed to determine the prevalence and severity of chronic pain, fatigue, and insomnia in the general adult population of Hong Kong, identify associated factors, and quantify the health care utilisation associated with these conditions during the preceding 3 months. The authors found that these chronic symptoms affected a substantial proportion of the general population, with as many as a quarter of the adult population experiencing at least one of them. There is a considerable burden to society in terms of individual suffering and to the health care system. Risk factors for the development of these chronic symptoms included older age, female gender, higher levels of education, and other health problems.

The severe acute respiratory syndrome (SARS) epidemic struck Hong Kong in 2003. Mental health morbidity of patients was reported during the acute and early discharge period. However, the impact of SARS did not end with the resolution of the infection. During rehabilitation, many patients faced psychosocial difficulties including stigmatisation, grief, unemployment, functional impairment, and medical co-morbidities. Despite improvements in their physical condition, their stress and psychiatric symptoms persisted for up to 12 months. Among SARS survivors, chronic fatigue was common. Wing and Leung[2] investigated *inter alia* the prevalence and associated risk factors for psychiatric disorders and chronic fatigue syndrome in SARS survivors. Nearly half of the SARS survivors had one or more psychiatric disorders in their lifetime—most of whom still had the disorder 3 years after the SARS epidemic. Chronic fatigue was common among SARS survivors, and SARS was not simply an infection but a disastrous experience for these patients.

Sexually transmitted infections (STIs) remain a major public health problem in Hong Kong. Sex workers are reservoirs and vectors for the transmission of STIs in the community. To formulate prevention strategies, the prevalence and risk factors of STIs among asymptomatic female sex workers (FSW) should be determined. Wong et al[3] recruited 511 FSWs aged 18 to 55 years from the well woman clinic of a non-governmental organisation. The prevalence of hepatitis B surface antigen positivity, syphilis, gonorrhoea, chlamydia, and HIV were 8.5%, 1.8%, 1.8%, 4.6%, and 0.2%, respectively. Risk factors for STIs included alcohol consumption, place of origin, a history of termination of pregnancy, higher education level, having multiple partners, and being a non-smoker. Importantly, the reported inconsistent use of condoms when having sex with regular partners among FSWs may have a bridging effect in the spread of STIs to other population groups. The authors note that continued surveillance of STIs in FSWs in Hong Kong is important and suggest that a coherent policy and holistic approach is necessary to control the spread of STIs in the community.

We hope you will enjoy this selection of research dissemination reports. Electronic copies of these dissemination reports and the corresponding full reports can be downloaded individually from the Research Fund Secretariat website (http://www.fhb.gov.hk/grants). Researchers interested in the funds administered by the Food and Health Bureau may visit the website for detailed information about application procedures.

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Smoking reduction intervention for smokers ot willing to quit smoking: a randomised controlled trialn

Introduction

China has the largest smoking population in the world, but most smokers are not willing to quit smoking. In Hong Kong, the prevalence of smoking was 11.8% in 2008, according to a household survey.[1] Although smoking cessation decreases the health risks associated with tobacco use, many smokers were unmotivated to quit, and 67% of Hong Kong Chinese smokers had never tried to give up smoking.[1] Smoking reduction may provide an intermediate step for complete cessation, especially for those who are unready or unwilling to quit. Although nicotine replacement therapy (NRT) increases the quit rate, few smokers undergoing NRT adhere to the recommended regimen.[2]

There has been no randomised controlled trial on intervention to increase NRT adherence. The present study aimed to evaluate the effectiveness of smoking reduction therapy and adherence intervention for 6 months among Chinese smokers in Hong Kong who were unmotivated to quit smoking. We hypothesised that the smoking reduction and adherence counselling would lead to a higher rate of abstinence, reduction, and adherence to NRT, compared to controls.

Methods

A single-blinded randomised controlled trial was conducted from October 2004 to April 2007. Subjects were eligible for inclusion if they were ethnic Chinese, aged 18 years or above, smoked at least two cigarettes daily, had no intention to quit in the near future or had failed in previous attempts to quit using NRT, intended to reduce smoking within the next 7 days using NRT, had no contraindication to NRT, and were not following other smoking cessation or reduction interventions. People who were psychologically or physically unable to communicate, pregnant or intending to become pregnant within the next 6 months, on regular psychotropic medications, or with any serious health problems such as stroke, palpitations or other life-threatening conditions were excluded.

After informed consent, the subjects were randomised into the control group or one of the two intervention groups. In the control group, subjects received simple advice on smoking cessation and a self-help quitting pamphlet only. In the reduction and adherence intervention group, subjects received 15-minute face-to-face smoking reduction counselling and 3-minute adherence counselling for NRT by a trained smoking cessation counsellor. Information on health consequences of smoking and benefits of quitting was provided. Smokers were encouraged to reduce consumption before quitting. Using the '5R' approach (relevance, risk, rewards, roadblocks, and repetition), the counselling focused on the importance and function of smoking reduction when complete cessation is difficult. In addition, the importance of adherence to the prescribed NRT dosage and the advantages of adherence were emphasised. Ways to overcome barriers were discussed. Problem-orientated interventions to improve adherence were delivered. Strict adherence to the prescribed dosage for at least 4 weeks was advised. In the reduction intervention group, subjects received smoking reduction counselling only.

Key Messages

1. This smoking reduction study examined the effectiveness of smoking reduction counselling together with free nicotine replacement therapy (NRT) for smoking cessation and tested the effectiveness of brief counselling on adherence to NRT among Chinese smokers who were not willing to quit but intended to reduce cigarette consumption.
2. The smoking reduction intervention was effective in helping the unmotivated smokers in quitting (intervention: 17.0% vs control: 10.2%, P=0.012) and in reducing their daily cigarette consumption by 50% or more (intervention: 50.9% vs control: 25.7%, P<0.001) at 6-month follow-up.
3. Our results provided evidence for the effectiveness of smoking reduction intervention, which is important for planning smoking cessation services.
4. Free NRT was widely accepted by participants (8-week NRT adherence rate: 54.5%). Free NRT together with smoking reduction counselling was a feasible and cost-effective approach to help unmotivated smokers to reduce and quit smoking, especially in developing countries like China where NRT is expensive and not used extensively.
5. The motivation to quit smoking was not undermined by smoking reduction intervention. To the contrary, offering assistance to reduce smoking could attract smokers who were not willing or ready to quit.

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For both intervention groups, 1 week of NRT was provided at the first contact. Further smoking reduction counselling and free NRT were provided at the 1-week and 4-week follow-ups. For the reduction and adherence intervention group, NRT usage was checked by counting the amount of NRT left, and additional adherence counselling was provided. At month 3, information on NRT use in the intervention groups up to 4 and 8 weeks was collected. At month 6, all subjects (including controls) were interviewed via telephone using a standard questionnaire. All self-reported quitters (with 7-day abstinence) and reducers (reducing daily consumption by ≥50%) were invited for biochemical validation of exhaled carbon monoxide and urinary cotinine levels.

The primary outcome measures were: (1) self-reported 7-day point-prevalence tobacco abstinence at month 6, (2) self-reported reduction rate (≥50%) of cigarette consumption at month 6 between the intervention and control groups, and (3) rate of continuous NRT use for 4 weeks (4-week adherence rate) at month 3 between the two intervention groups. Secondary outcome measures were: (1) validated quit rate at month 6, (2) self-reported quit rate at month 1, (3) self-reported continuous use of NRT for at least 8 weeks, and (4) the number of quit attempts up to month 6.

The required sample size was calculated based on primary outcome measures to provide at least 90% power with a significance level of 5%. We estimated that there would be (1) a 4% difference in the self-reported quit rate between the intervention and control groups, (2) a 12% difference in the self-reported reduction rate between the intervention and control groups, and (3) a 10% difference in the adherence rate between the intervention groups. Thus, 3246 subjects (1229 in the reduction and adherence intervention group, 1229 in the reduction intervention group, and 788 in the control group) were needed.
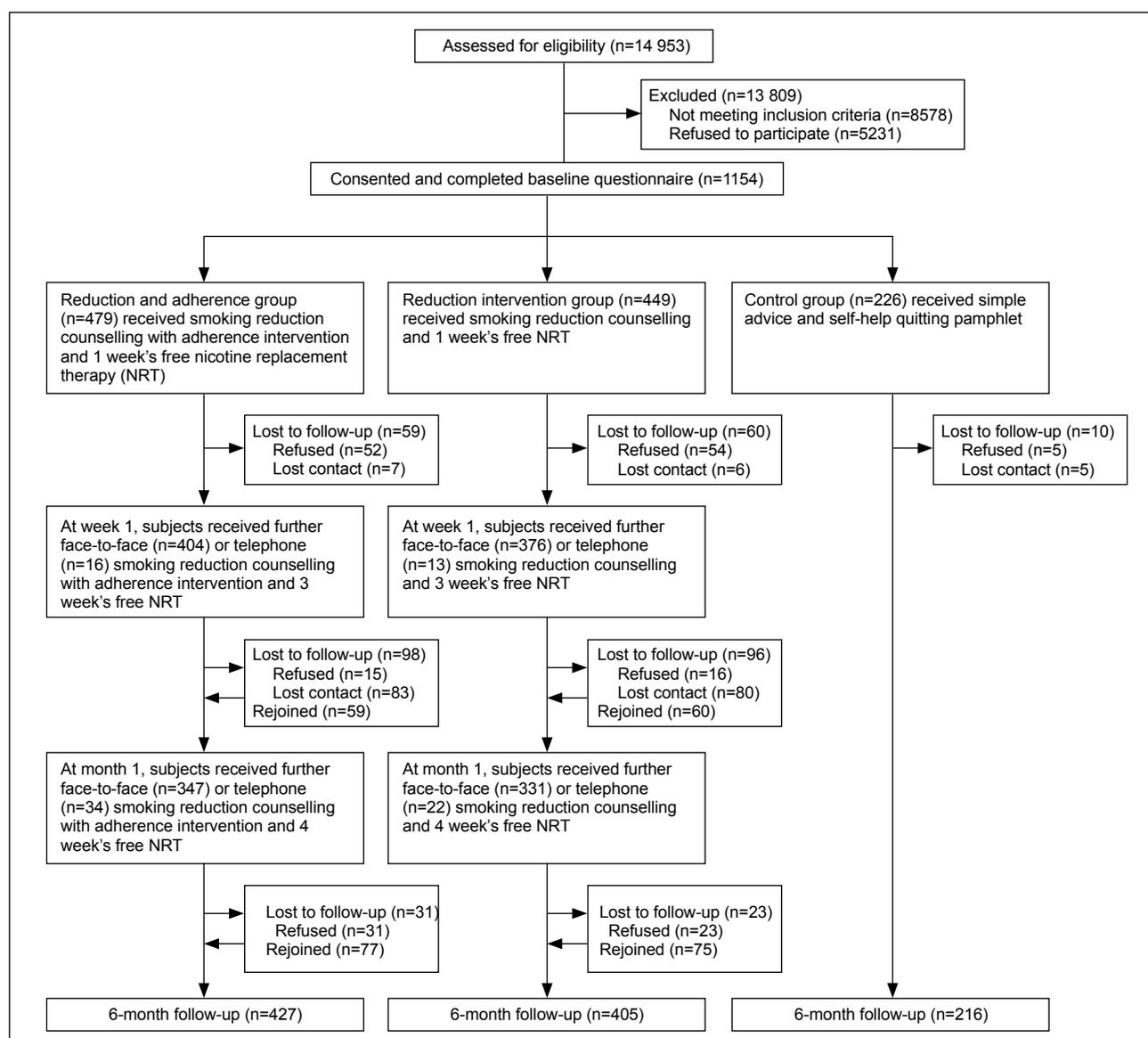

Fig. Consolidated standards of reporting trials flow chart of the study

All analyses were based on the intention-to-treat principle. To test the effectiveness of the smoking reduction counselling and NRT, the two intervention groups were combined and compared with the control group. To test the effectiveness of the adherence intervention to NRT, the two intervention groups were compared. Recruitment of subjects was stopped upon advice from the Independent Data Monitoring Committee after the interim analysis showed that the self-reported quit rate at month 6 was significantly different between the intervention and control groups, and that the adherence rates to NRT between the two intervention groups were almost identical. Tobacco abstinence rates, reduction rates, and the adherence rates between groups were compared using the Pearson Chi-squared test, odds ratios, and 95% confidence intervals.

Results

From October 2004 to April 2007, 1154 participants were randomised into the smoking reduction and NRT adherence intervention group (n=479), the smoking reduction group (n=449), and the control group (n=226). A consolidated standards of reporting trials flow chart detailing the enrolment, allocation and follow-up of participants is shown in the Figure. Table 1 outlines characteristics of participants and results of baseline measurements. No significant difference was noted in baseline variables across the three groups, except that there were more females in

the reduction and adherence intervention group (22.1% vs 16.5% vs 12.4% respectively, Table 1). The follow-up rates of the combined intervention group at the 1-week, 1-month, and 3-month follow-up were 87.2%, 79.1%, and 85.9%, respectively. At 6 months, 89.7% of the combined intervention group and 95.6% of the control group were followed up.

Cigarette consumption and abstinence
Smoking status of all subjects was assessed by research assistants at the 6-month follow-up by telephone interview. The mean daily cigarette consumption of the intervention groups was significantly lower than that of the controls (9.5 vs 13.1 cigarettes, P<0.001, Table 2). The quit rate was significantly higher in the intervention groups than the controls (17.0% vs 10.2%, P=0.012, Table 2). Subjects who reported complete abstinence were invited for biochemical validation, and the participation rate was 56.4% (102/181); 74 (quit rate of 8.0%) of the intervention group subjects passed the validation test, with urinary cotinine concentrations of <115 ng/ml and expired carbon monoxide levels of <9 ppm, compared to 10 (quit rate of 4.4%) of the controls (P=0.066).

Smoking reduction and quit attempts
Successful smoking reduction was defined as a self-reported reduction in daily cigarettes by ≥50% at the 6-month follow-up. The smoking reduction rates were significantly

Table 1. Patients' demographics, smoking profiles, quitting history, and self-efficacy to resist smoking at aseline*

Parameter	Reduction and adherence intervention (n=479)	Reduction intervention (n=449)	Control (n=226)
Male	373 (77.9)	375 (83.5)	198 (87.6)
Female	106 (22.1)	74 (16.5)	28 (12.4)
Patient age (years)	41.5±10.3	42.4±10.3	42.5±11.2
Marital status			
Married/cohabiting	323 (67.4)	335 (74.8)	153 (67.7)
Others	156 (32.6)	113 (25.2)	73 (32.3)
Education level			
Primary or below	53 (11.1)	48 (10.7)	27 (11.9)
Secondary	331 (69.1)	329 (73.4)	156 (69.1)
Tertiary or above	95 (19.8)	71 (15.8)	43 (19.0)
Smoking profiles			
Age started smoking (years)	18.0±4.6	17.5±4.8	17.8±4.8
Years of regular smoking	23.5±10.8	24.8±9.9	24.5±11.1
Daily cigarette consumption	19.8±9.4	20.1±10.1	19.2±8.9
Fagerstrom test			
Mild	102 (21.3)	109 (24.3)	56 (24.8)
Moderate	151 (31.5)	134 (29.9)	76 (33.6)
Severe	226 (47.2)	205 (45.8)	94 (41.6)
Quit attempt			
0	104 (21.8)	100 (22.4)	43 (19.1)
1	144 (30.1)	122 (27.4)	55 (24.4)
2-5	178 (37.2)	192 (43.0)	109 (48.4)
6-10	21 (4.4)	11 (2.5)	8 (3.6)
>10	31 (6.5)	21 (4.7)	10 (4.4)
Previous use of nicotine replacement therapy	193 (40.3)	166 (37.1)	84 (37.2)
Self-efficacy to resist smoking†			
Importance of reducing smoking	82.8±17.3	82.5±17.2	79.7±18.8
Difficulty in reducing smoking	69.0±22.7	69.8±21.7	68.1±22.1
Confidence in reducing smoking	64.9±20.1	63.3±20.5	61.6±20.2
Confidence in quitting smoking (years)	76.3±21.0	75.0±21.7	76.4±20.3

* Data are presented as No. (%) or mean±SD
† Range from 0 indicating not important, not difficult, or not confident at all to 100 indicating very important, very difficult, or very confident

Table 2. Abstinence, reduction, quit attempts and adherence rates of the intervention and control groups

Abstinence and reduction rate	No. (%) of subjects		P value	Odds ratio (95% CI)
	Combined intervention (n=928)	Control (n=226)		
Self-reported 7-day point prevalence quit rate	158 (17.0)	23 (10.2)	0.012	1.81 (1.14-2.88)
Biochemical validated quit rate*	74 (8.0)	10 (4.4)	0.066	1.87 (0.95-3.70)
Self-reported reduction in daily cigarette consumption by ≥50%	472 (50.9)	58 (25.7)	<0.001	3.0 (2.16-4.15)
Tried to quit smoking for at least 24 hours within last 30 days (excluding the quitters)	172 (22.9) of 770	42 (20.7) of 203	0.05	0.88 (0.6-1.3)
	Reduction and adherence intervention (n=479)	Reduction intervention (n=449)		
Self-reported 7-day point prevalence quit rate at month 3	67 (14.0)	58 (12.9)	0.91	1.1 (0.75-1.60)
Self-reported 7-day point prevalence quit rate at month 6	100 (20.9)	58 (12.9)	0.001	1.78 (1.25-2.53)
Biochemical validated quit rate*	48 (10.0)	26 (5.8)	0.02	1.81 (1.10-2.98)
4-week adherence rate to nicotine replacement therapy at month 3	334 (69.7)	304 (67.7)	0.51	1.1 (0.83-1.45)
8-week adherence rate to nicotine replacement therapy at month 3	270 (56.4)	236 (52.6)	0.25	1.2 (0.90-1.51)

* Quitting is confirmed by an expired carbon monoxide level of <9 ppm and a urinary cotinine level of <115 ng/ml

higher in the intervention groups than in the control group, including and excluding the quitters (50.9% vs 25.7%, P<0.001; 41.2% vs 17.2%, P<0.001, respectively). Those who had an expired carbon monoxide level reduced by ≥1 ppm were classified as validated reducers. The participation rate was 48.9% (171/350). There were more validated reducers in the intervention groups than the control group (11.2% [104/928] vs 5.3% [12/226], P=0.008). Excluding the quitters, more smokers in the intervention groups tried to stop smoking for at least 24 hours within the previous 30 days than controls did (22.9% vs 20.7%, P>0.05).

Adherence to nicotine replacement therapy
Comparing the two intervention groups, there was no significant difference in the adherence rates to NRT at week 4 (69.7% vs 67.7%, P=0.51) and week 8 (56.4% vs 52.6%, P=0.25), as well as the self-reported 7-day quit rate (14.0% vs 12.9%, P=0.91) at month 3. Nonetheless, the quit rate was significantly higher in the reduction and adherence intervention group (20.9% vs 12.9%, P=0.001).

Discussion

Smoking reduction counselling, with or without NRT adherence counselling, was effective in helping 'pre-contemplators' to quit or reduce their daily cigarette consumption by ≥50%. This is important for planning local smoking cessation services (when most smokers are unmotivated to quit) and making smoking reduction an intermediate step toward complete cessation.

In our study, the effectiveness of the 3-minute adherence counselling on NRT was examined. Although there was no significant difference in the 4-week and 8-week adherence rates between the two intervention groups at the 3-month

follow up, NRT was widely accepted (54.5%), compared to previous studies that have reported rates of 16 to 46%.[2-4] This was likely to be due to provision of free NRT. Cost is the main reason for NRT discontinuation; offering free NRT with smoking reduction counselling is feasible and cost-effective in helping unmotivated smokers to reduce and quit smoking, especially for those in developing countries like China where NRT is expensive and not widely used.

Reduction counselling may undermine smoking cessation and smokers' motivation to quit, as smokers may rationalise that reducing consumption is what they can accomplish and perceive reduction as an alternative to complete cessation.[5] Our study does not support this notion. Compared with the controls at month 6, smoking reduction intervention plus nicotine treatment achieved significantly higher abstinence rates, reduction rates, and quit attempts. No evidence of undermined motivation for quitting smoking was noted. To the contrary, offering assistance to reduce smoking may attract the smokers who are unwilling or unready to quit.

The main limitation of our study was the difficulty in subject recruitment despite vigorous promotional campaigns, and thus stopping recruitment before reaching our planned number of participants. From our previous experience, 60% of the current smokers were not intending to quit or join a cessation programme. This percentage was much lower when the smokers were sought from our database. Further studies on new adherence intervention are needed. Our study provided multi-session counselling (baseline, 1-week and 1-month) with telephone follow-up, but 20% of the participants were lost to follow-up and hence did not receive the complete intervention, possibly weakening effectiveness.

Conclusion

Smoking reduction counselling together with NRT was effective in achieving smoking reduction and complete cessation for smokers who were not ready to quit. Although there was no significant difference in the 4-week and 8-week adherence rates to NRT between the two intervention groups, the group receiving the adherence intervention achieved a significantly higher quit rate.

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Prevalence of chronic pain, insomnia, and fatigue in Hong Kongn

Key Messages

1. Chronic pain, insomnia and fatigue affect a substantial proportion of the Hong Kong general population; as much as a quarter of the adult population experience one of these chronic symptoms. The prevalence of comorbidity is also high, impacting nearly one-third of the adult population. This is a considerable burden to society in terms of individual suffering and disability and to the health care system.

2. Those who are older, female, more educated, married or divorced, or with other health problems are more likely to develop these chronic symptoms.

Introduction

Chronic pain, insomnia, and fatigue are important public health problems but are poorly documented in Chinese populations. About 11% of Hong Kong's adult population are affected by chronic pain and insomnia. The prevalence of fatigue among women has been reported to be as high as 71%. There may be considerable overlapping among these three symptoms, but the extent of comorbidity is uncertain. These chronic symptoms pose significant burdens on the health care system, social security, and quality of life of those affected. This study aimed to: (1) determine the prevalence and severity of chronic pain, fatigue, and insomnia in the general adult population of Hong Kong; (2) identify associated factors; and (3) quantify the health care utilisation associated with these conditions over the preceding 3 months.

Subjects and methods

This cross-sectional, population-based, observational study was conducted from February 2007 to September 2008. A random sample of 5001 Chinese adults aged ≥18 years was recruited to complete a structured telephone interview.

Chronic pain was first identified using two questions: "Are you currently troubled by physical pain or discomfort, either all the time or on and off?" and "Have you had this pain or discomfort for more than 3 months?"[1] Subjects answering yes to both questions were then asked about the severity, site, and duration of their pain. The severity of current pain and pain over the previous 6 months was assessed using the Chronic Pain Grade questionnaire[2] and was classified into five grades: grade zero (pain free), grade I (low disability, low intensity), grade II (low disability, high intensity), grade III (high disability, moderately limiting), and grade IV (high disability, severely limiting). According to the International Association for the Study of Pain in 1986,[1] chronic pain is defined as pain that has persisted for at least 3 months. We therefore changed the time frame of the questionnaire items to 3 months.

The Pittsburgh Sleep Quality Index[3] was used to assess chronic insomnia. It evaluates multiple dimensions of sleep over a 1-month period.[4,5] There are 19 items generating seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of the seven component scores yields one global score of subjective sleep quality ranging from 0 to 21; higher scores indicate poorer subjective sleep quality. A global score of >5 is defined as having chronic insomnia.[3-5]

Chronic fatigue (defined as fatigue for more than 6 months) was assessed using the Chalder Fatigue Scale,[6] which consists of 11 items measuring severity of physical and mental fatigue in the past 6 months using two subscales. Responses 1 and 2 are dichotomised as a score of 0, whereas responses 3 and 4 are dichotomised as a score of 1. The highest total fatigue score is 11, a cut-off score of ≥8 is defined as having chronic fatigue.[6,7]

Mental health was evaluated with the Hospital Anxiety and Depression Scale,[8] which assesses emotional well-being in people with physical illness, minimising contamination by physical symptoms. It comprises two subscales,

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one measuring anxiety and another measuring depression.

Quality of life (QoL) was measured using the 12-item Short-Form Health Survey (SF-12) that consists of a physical component score and a mental component score.[9,10]

Health care utilisation was assessed using the Thematic Household Survey 2002,[11] which comprises a series of household surveys conducted by the Census and Statistics Department to collect statistics on the health status of local residents and patterns of doctor consultation, hospitalisation, dental consultation, the provision of medical benefits by employers/companies, and the coverage of medical insurance purchased by individuals. In the present study, questions pertaining to doctor consultation, whether having chronic or long-term disease, and types of diseases were enquired.

Sociodemographic data was gathered using questions on gender, age, education, marital status, religious affiliations, income, and employment status. Questions pertaining to lifestyle (tobacco use, alcohol consumption, and physical activity) were modified from the Thematic Household Survey to suit the needs of telephone interviewing. Questions on smoking status, drinking, and exercise habits were also included.

Results

Of the 5001 respondents, 55% were women; 70.2% had no religious affiliation; and 65% reported a monthly household income below HK$25 000. In terms of marital status, education, and employment, 34.1% had never married whereas 59.9% were married/cohabited; 19% had completed tertiary education whereas 45% had attained secondary education; and 47.2% were in full-time employment. Those aged 40 to 49 years constituted the largest proportion of respondents (24.1%).

For chronic pain, the prevalence was 34.2% and it was most common in the age-group of 40 to 49 years (41.7%). For chronic insomnia, the prevalence was 39.4% and it was least common in the youngest and oldest age-groups (18-29

years, 34.0%; ≥60 years, 46.9%). For chronic fatigue, the prevalence was 10.7% and it was most common in the age-group of ≥60 years (14.1%) [Table].

The prevalence of these chronic symptoms was higher among women, with chronic insomnia being the most common (43.1%), followed by chronic pain (39.9%), and chronic fatigue (13.1%). The prevalence of only one of the chronic symptoms was 13.3% and was similar between males (13.6%) and females (13.0%). The prevalence of any two of the chronic symptoms (comorbidity) was 13.8% and was most common in the middle-aged groups (40-49 years, 15.7%; 50-59 years, 16.1%) and among females (15.8%). The prevalence of all three chronic symptoms (multiple comorbidities) was 4.3% and was more common in females (5.7%) than males (2.6%), and most common in the age-group of 40 to 49 years (5.0%).

Factors associated with increased odds of chronic pain included female gender, older age, being divorced/separated, higher education level, working part-time, having had chronic health problems, poor mental health, and lower QoL score. Students and those taking regular exercise had lower odds of chronic pain. Those having chronic insomnia were more likely to be female, practising Buddhism/Daoism/ancestor worship, having had chronic health problems, poor mental health, and lower mental QoL score. Compared to those with no religion, respondents who were Catholic were less likely to report chronic insomnia. Factors associated with increased odds of chronic fatigue included younger age, being retirees or housewives, having had chronic health problems, poor mental health, and lower QoL score. Compared to those who did not exercise, those who exercised three to five times a week were less likely to report chronic fatigue.

Factors significantly associated with increased odds of having any of the two chronic symptoms included female gender, older age, Christian, higher education level, having had chronic health problems, poor mental health, and lower QoL score. Compared to those who did not exercise, those who exercised one to two times per week had lower odds of having any of the two symptoms. Females, older age,

Table. Prevalence of chronic pain, insomnia, and fatigue   y age and gender*

Group	Chronic pain	Chronic insomnia	Chronic fatigue	Only one symptom	Any of two symptoms	All three symptoms
Entire sample	34.19 (33.26-35.13)	39.42 (38.34-40.50)	10.72 (10.43-11.00)	13.30 (12.94-13.65)	13.84 (13.47-14.21)	4.30 (4.19-4.40)
Age- roup (years)						
18-29	22.68 (22.07-23.29)	34.0 (33.07-34.93)	9.52 (9.27-9.77)	11.62 (11.31-11.93)	11.04 (10.75-11.33)	3.17 (3.10-3.24)
30-39	33.84 (32.91-34.76)	73.49 (71.47-75.51)	8.90 (8.67-9.14)	12.33 (12.00-12.66)	14.52 (14.13-14.91)	3.84 (3.74-3.93)
40-49	41.66 (40.52-42.80)	72.12 (70.14-74.11)	10.90 (10.61 -11.18)	14.67 (14.28-15.06)	15.67 (15.25-16.10)	5.03 (4.90-5.15)
50-59	39.98 (38.88-41.07)	68.46 (70.34-66.58)	10.79 (10.50-11.07)	15.36 (14.95-15.77)	16.06 (15.63-16.49)	4.81 (4.69-4.93)
≥60	37.11 (36.09-38.12)	46.92 (45.63-48.21)	14.13 (13.75-14.51)	13.05 (12.71-13.40)	13.48 (13.12-13.84)	4.75 (4.63-4.86)
Gender						
Male	28.26 (27.49-29.02)	35.12 (34.16-36.08)	8.10 (7.89-8.31)	13.64 (13.28-14.00)	11.43 (11.12-11.73)	2.61 (2.56-2.67)
Female	39.85 (38.76-40.94)	43.08 (41.90-44.26)	13.09 (12.74-13.44)	13.01 (12.67-13.36)	15.82 (15.40-16.25)	5.69 (5.54-5.83)

* Data are presented as % (95% CI)

being married, divorced or separated, having had chronic health problems, poor mental health, and lower QoL score were more factors conferring increased odds of having all three chronic symptoms. Compared to those with a monthly household income below HK$15 000, those with monthly household incomes ranging from HK$40 000 to HK$59 999 had lower odds of having all three chronic symptoms.

Regarding health care utilisation for those with chronic pain, insomnia, and fatigue, 47%, 49%, and 55.5%, respectively, had visited at least one type of western medicine practitioner, and 31%, 30.2%, and 32.6%, respectively, had consulted at least one type of therapist, with Chinese herbal medicine practitioner being the most common (17.6%, 17.6%, and 19.8%, respectively). The use of self-medication was high (49.5%, 43.4%, and 45.2%, respectively), whereas 25.4%, 24.6%, and 24.4%, respectively, had consumed over-the-counter western medication.

Older age and having had chronic health problems were significantly associated with one, two, and all levels of health care utilisation (all P<0.05). Higher pain score was significantly associated with all three levels of health care utilisation (all P<0.001). Higher insomnia and fatigues scores were associated with two and all levels of health care utilisation (P<0.05). The number of symptoms, lifestyle, mental health, and QoL score were not associated with levels of health care utilisation.

Discussion

Based on our sample, the estimated point prevalence of chronic pain, insomnia, and fatigue in the Hong Kong general population are 28.6%, 32.5%, and 8.8%, respectively, which corresponds to 0.6 to 1.8 million middle-aged women. Our estimates for chronic pain and insomnia are comparable to those reported in western populations (2-45% for chronic pain, 10-48% for chronic insomnia),[3,8-10] whereas our estimate for chronic fatigue is much lower than that reported in western populations (23.6%).[12-16]

In our sample, the prevalence of multiple chronic symptoms was high. The estimated point prevalence of comorbidity in the Hong Kong general population is 11.4%, which represents about 0.6 million adults. The prevalence of comorbidity was higher in the middle-aged group and among women. Our estimate for comorbidity is higher than that in a UK study reporting 6% for only one symptom and 2% for comorbidity.[7]

In our sample, the presence of chronic or long-term health problems was associated with the three chronic symptoms, suggesting involvement of other physical illnesses. There was also an age-related trend. Lack of regular exercise was associated with chronic pain and fatigue, reflecting both reverse causality and inadequacy of the activity assessment questions for pain. Women, older age-groups, those having

had chronic health problems, and those who lacked regular exercise had higher odds of comorbidities. These findings were in agreement with those in the UK study.[7] In addition, poor mental health and lower QoL score were associated with the presence of multiple chronic symptoms.

After controlling for gender, age, and chronic health problems, more severity in chronic pain, insomnia, and fatigue was associated with greater use of health care services, which is consistent with previous studies in the West.[2,14,17-19] Lower utilisation rates in the public sector by those with chronic pain or fatigue may be due to difficulties in accessing public services and the lack of pain clinics in Hong Kong. Chinese herbal medicine was the most popular type of alternative therapy for those with chronic symptoms, and about 25% of the respondents had consumed over-the-counter western preparations. Self-medication is cheaper and is the first resort for those who do not view their problems as life-threatening.

Acknowledgement

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Key Messages

1. The prevalence of neck pain in the past 12 months in our sample was 64.6%. Of those with neck pain, 37.8% had moderate to severe pain; 13.7% had to limit their social activities; and 18.9% had to limit their work.
2. Managers, professionals, and administrators were at significantly higher risk of having neck pain, compared with housewives or those who were unemployed or retired.
3. Of the neck pain sufferers, 25.2% consulted health service practitioners: medical consultation in a public or private clinic was most common (9.2%), followed by physiotherapy (4.9%). For self-care treatment, massage was most preferred (83.3%).
4. Physiotherapy was regarded as the most effective treatment; 60.7% of those receiving physiotherapy achieved complete improvement. Self-massage was less effective; 59.5% of those who self-massaged had an improvement of half or less.

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Neck pain in Hong Kong: a telephone survey on consequences and health service utilisation

Introduction

Neck pain is common among Hong Kong people.[1] Nonetheless, information on the health service utilisation by people with neck pain, and the consequences and cost of neck pain management is lacking. Without objective population data, patient-centred clinical studies on the efficacy of various therapeutic or rehabilitation programmes and planning of budgets and resources allocation for management of neck pain are based on estimates of impact.

This study aimed to (1) investigate the consequences of neck pain in terms of disability and rate of absenteeism from work, (2) describe the health service utilisation pattern of neck pain sufferers in Hong Kong, and (3) analyse factors associated with neck pain and health services utilisation in neck pain sufferers.

Methods

This study was conducted from October 2007 to September 2009. A regionally representative telephone survey using a two-stage randomisation process (of the telephone numbers and the respondents in the households) was carried out. The inclusion criteria were Hong Kong residents older than 15 years and ability to communicate in Cantonese. Verbal consent was obtained before starting the interviews.

Results

Of 6754 telephone numbers dialled, 4640 subjects were selected and successfully interviewed. The response rate was 68.7%. The mean duration of the interviews (for respondents who met the definition of neck pain) was 15.7 (standard deviation, 3.4; range, 7-39) minutes.

Of the 4640 respondents, 2997 (64.6%) reported having neck pain in the previous 12 months. In 166 (5.5%) neck pain sufferers, the neck pain was confirmed by a physician as being work-related. The most common cause (as speculated by the respondents) was poor sleeping posture (25.6%), followed by work (22.3%) and others (18.4%) [Table 1]. The pain was mild in 59.1% and moderate to severe in 37.8%; 13.7% had to reduce their social activities; 18.9% had to limit their work; 11.6% reported that neck pain disturbed their daily activities; and 3.6% applied for sick leave owing to neck pain during the past 12 months. The mean duration of disturbance in 271 subjects was 65.5 days, whereas the mean total sick leave duration for 100 subjects was 19.4 days.

Females had a significantly higher prevalence than males (68.1% vs 59.5%, P<0.001). Managers, professionals, and administrators had the highest prevalence (81.6%), whereas 65.1% of those who were unemployed and retired had neck pain.

Regarding utilisation of health services in the past 12 months, 25.2% of those with neck pain consulted health service practitioners in the past 12 months: medical consultation in a public or private clinic was most common (9.2%), followed by physiotherapy (4.9%). For self-care treatment, massage was most preferred (83.3%) [Table 2].

Table 1. Cause of neck pain and severity

Parameter	No. (%) of subjects with neck pain (n=2997)
Cause of neck pain (as speculated by respondents)	
Degeneration	169 (5.6)
Household work	50 (1.7)
Exercises	62 (2.1)
Entertainment	69 (2.3)
Academics	81 (2.7)
Not enough rest	182 (6.1)
Mentally unstable	39 (1.3)
Work	667 (22.3)
Poor sleeping posture	768 (25.6)
Height of pillow not appropriate	149 (5.0)
Others	551 (18.4)
Not sure	210 (7.0)
Severity of recent episode	
Almost no pain	37 (1.2)
Mild pain	1771 (59.1)
Moderate pain	996 (33.2)
Severe pain	138 (4.6)
Intolerable pain	55 (1.8)
Social activities	
Normal, without extra pain	2209 (73.7)
Normal, but with extra pain	257 (8.6)
Reduced	412 (13.7)
Staying at home	92 (3.1)
Completely stopped	26 (0.9)
No response	1 (0.0)
Job or household work	
No problem	1474 (49.2)
Able to perform normal tasks with pain	952 (31.8)
Shorten the normal work/job by <50%	286 (9.5)
Shorten the normal work/job by >50%	217 (7.2)
Can't work at all	66 (2.2)
No response/refused to answer	2 (0.1)

A total of 2431 subjects with neck pain identified the treatment they considered most effective for neck pain alleviation; 86.6% believed that their neck pain improved following treatment; 50.1% considered that the neck pain reduced completely or by more than half (Table 2). Physiotherapy was regarded as the most effective treatment; 60.7% of those receiving physiotherapy achieved complete improvement. Massage was the most preferred self-care treatment, but 59.5% of those who self-massaged had an improvement of half or less.

Discussion

For the worldwide adult population (age 17-70 years), the 12-month prevalence of neck pain ranges from 16.7% to 75.1% (mean, 37.2%).[2] In this study, the prevalence was 64.6%, which is higher than the 53.6% reported in our previous study in 2006.[1] The percentage of neck pain sufferers having moderate-to-severe neck pain was also higher (37.8% vs 15%[1]); 13.7% (compared to 4.8% in 2006[1]) had to reduce their social activities; and 4% (compared to 0.3% in 2006[1]) had to stay at home or stop their social activities. Neck pain caused a mean disturbance of 65.5 days in the past year; 18.9% of neck pain sufferers (compared to 3.1% in 2006[1]) had to limit their work; and 3.6% had to apply for sick leave (mean, 19.4 days). These results suggest that the severity and impact of neck pain in the general adult population in Hong Kong is higher than that in 2006.

Table 2. Pattern of health services utilisation and self-care, choice of most effective treatment, and degree of improvement

Parameter	No. (%) of subjects with neck pain (n=2997)	No. of subjects identifying the most effective treatment (n=2431)	Self-rated improvement in neck pain after treatment (% of subjects)			
			Less than half	Half	More than half	Complete
Health service provider						
Public clinic	124 (4.1)	19	15.8	5.3	57.9	21.1
Private clinic	152 (5.1)	54	3.7	11.1	35.2	50.0
Physiotherapy	147 (4.9)	54	13.0	11.1	25.3	60.7
Chinese massage therapy	106 (3.5)	50	10.0	30.0	50.0	10.0
Acupuncture	82 (2.7)	32	25.0	3.1	50.0	21.9
Bone setting	59 (2)	28	10.7	7.1	46.4	35.7
Herbal medicine	34 (1.1)	15	20.0	13.3	33.3	33.3
Chiropractic	27 (0.9)	3	0.0	20.6	33.3	46.1
Reflexology	24 (0.8)	1	0	100	0	0
Total	755 (25.2)					
Self-care treatment*						
Massage	2497 (83.3)	931	30.9	28.6	28.4	12.1
General exercise	1576 (52.6)	252	24.6	25.0	33.7	16.7
Ointment and medicine plaster	1550 (51.7)	477	22.2	27.3	27.3	23.3
Hot pack	736 (24.6)	94	20.2	30.9	38.3	10.6
Western medicine	262 (8.7)	67	10.4	14.9	34.3	40.3
Cold pack	196 (6.5)	11	9.1	45.5	36.4	9.1
Traction	156 (5.2)	193	28.0	33.2	26.9	11.9
Chinese medicine	129 (4.3)	8	12.5	12.5	37.5	37.5
Electrotherapy	123 (4.1)	8	37.5	25.0	25.0	12.5
Others	320 (10.7)	134	14.9	13.4	42.5	29.1

* More than one item may be chosen; items may not be exclusively for treating neck pain

Managers, professionals and administrators were at significantly higher risk of having neck pain, likely owing to highly competitive working environments, excessive stress at work, and long working hours. High levels of stress and physical and psychological workplace factors are predictors of neck pain among workers in industrial and service sectors.[3]

In our study, 25.2% of neck pain sufferers (compared to 16.9% in 2006[1]) consulted medical or health professionals. Of them, 9.2% (compared to 15.7% in 2006[1]) visited a medical doctor and 4.9% (compared to 1.7% in 2006[1]) sought help from physiotherapists. There is a increasing trend for complementary methods such as Chinese massage therapy (3.5%) or acupuncture (2.7%), compared to the study in 2006.[1] This is comparable to a survey in the United States[4] reporting that one in three Americans with back or neck pain consulted complementary health professionals. Utilisation of health care resources for neck pain has increased. In our study, 60.7% and 50.0% of neck pain sufferers reported complete improvement of neck pain following physiotherapy and medical consultation in private clinics, respectively. This is contrary to the survey in the United States[4] that reported low perceived effectiveness of conventional therapies.

Massage (83.3%) and general exercises (52.6%) were the two most preferred modes of self-care treatment for neck pain, but their effectiveness was low. Self-medication with western or Chinese medicine achieved a high percentage of complete improvement, and their use increased to 13% from 2.8% in 2006.[1] Nonetheless, it is inappropriate to use the results of this observational study to assess the efficacy of various treatments for neck pain. Randomised controlled trials are warranted.

Limitations

Despite the high telephone coverage rate in Hong Kong, non-coverage bias may still occur. Application of visual aids to depict the topographical location of neck pain was not feasible. The self-reporting nature of this survey may have recall bias.

Acknowledgement

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Impact of SARS-coronavirus-encoded proteins on cellular signalling pathways and cytokine/chemokine gene expression

Key Messages

1. Although GFP-tagged ORF8 and ORF3 potently activate the JNK and p38 MAPK pathways, expression of non-tagged SARS-CoV-encoded ORF8 or ORF3 has no obvious effect.

2. Although both GFP-tagged ORF8 and ORF3 induce cell death, expression of non-tagged ORF8 or ORF3 has no obvious effect on cell survival.

3. Addition of an epitope tag to a protein of interest, a common way to study novel proteins in the absence of suitable antibodies, may generate unexpected artefacts. Caution should be taken with any results derived from epitope-tagged proteins.

4. When studying a novel protein, it is essential to prepare suitable antibodies to facilitate detection and purification (eg by immunoprecipitation) of the native or endogenous proteins.

Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV) was responsible for the global SARS pandemic in 2003.[1,2] Although all CoVs have similar microscopic appearance, gene products, and genomic organisation, SARS-CoV is unique in that it is associated with high mortality rates in humans. Spike, membrane, envelope, and nucleocapsid proteins as well as replicase are commonly conserved among all CoVs. The genome of SARS-CoV also encodes nine other novel open-reading frames (ORFs) with unknown functions (Fig 1).[1,2]

Various viruses exert their pathogenic effects through interaction of their viral proteins with distinct cellular targets. We hypothesised that the severe inflammation and high mortality caused by SARS-CoV are contributed in part by these novel ORFs. Therefore, we aimed to evaluate the functions of these novel ORFs by overexpressing them in human cell lines.

Mitogen-activated protein kinases (MAPK) are important cellular signalling molecules involved in cell growth, differentiation, and apoptosis under both normal and pathological conditions. Three major classes of MAPKs, namely extracellular signal-regulated kinases, cJun N-terminal kinases (JNKs), and p38 MAPKs, have been extensively characterised in the past 15 years. Many viral proteins are known to activate these MAPKs to exert their cytotoxic effects and trigger host inflammatory responses. For example, the Tax protein of human T-cell leukaemia virus type 1 and the latent membrane protein 1 (LMP1) of the Epstein-Barr virus potently activate the JNK pathway. We hypothesised that the novel ORFs of SARS-CoV may trigger inflammation and promote apoptosis of host cells through activation of MAPKs, especially the JNK and p38 MAPKs, which are known to be activated by pro-inflammatory and apoptotic stimuli.

Methods

This study was conducted from September 2004 to December 2006. To amplify the novel SARS ORFs from the SARS-CoV genome and to insert them into two sets of expression vectors (Flag-tagged pcDNA3 and eGFP-tagged pEGFP-C1), two sets of polymerase chain reaction primers were respectively designed: one containing the Nhe I (or Xba I for ORFs3 and 14)/Not I sites and another containing the Bgl II/Sal I sites. All constructs were verified by restriction enzyme digestion and sequencing.

All DNA constructs were transiently transfected into HEK293 cells using Lipofectamine Plus reagents (Invitrogen) following the manufacturer's instructions. Fluorescent images of live HEK293 cells containing green fluorescence protein (GFP) fusion proteins were acquired by an Olympus IX70 fluorescent microscope linked to a charge-coupled device digital camera (Spot RT, Diagnostic Instruments Inc, MI, USA).

HEK293 cells were co-transfected with HA-JNK2 together with individual viral ORFs. After 24 hours of transfection, cells were harvested, lysed, and

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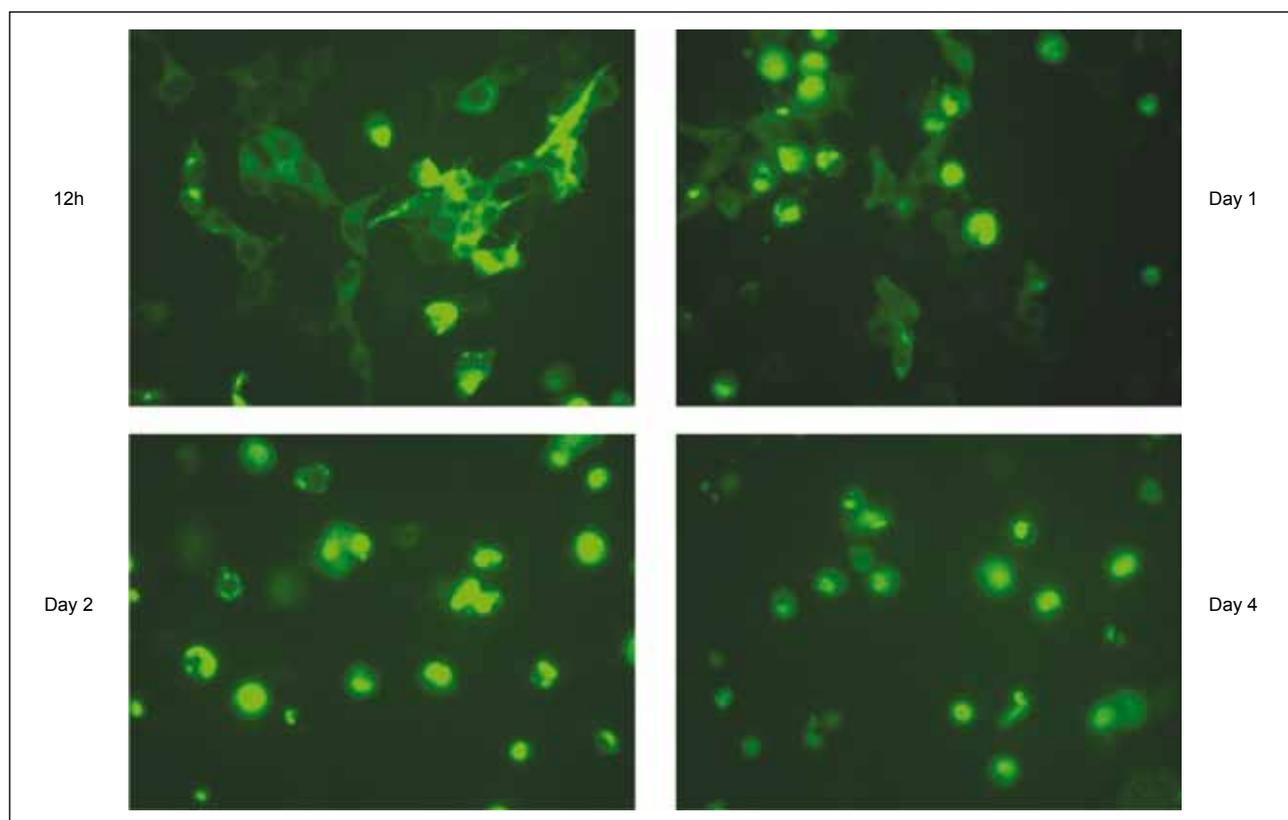Fax: (852) 2358 1552
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Fig 1. Expression of GFP-ORF8 in HEK293 cells results in significant cell death
HEK293 cells are transiently transfected with a construct encoding GFP-ORF8. At different time points after transfection, fluorescent images are taken using an Olympus IX70 fluorescent microscope linked to a charge-coupled device digital camera

the soluble whole cell lysates were prepared. After normalisation by Western blotting, an equal amount of HA-JNK was immunoprecipitated from cell lysates using anti-HA antibodies. The immunoprecipitates were then subjected to kinase assays using either GST-cJun(1-79) or GST-ATF2 (1-92) as substrates.

A segment of ORF8 gene encoding aa17-94 was subcloned into pET32M expression vector to generate the recombinant His-thioredoxin-ORF8 fusion protein in bacteria. The proteins were injected into rabbits to generate polyclonal antibodies according to standard procedures.

Results

Subcellular localisation of novel ORFs from SARS-CoV

As antibodies against the novel ORFs from SARS-CoV were not available, an enhanced GFP inframe was first fused to the N-terminus of all nine ORFs. After transfecting individual fusion constructs into HEK293 cells, the subcellular localisation patterns of these nine ORFs were classified using live cell imaging into three categories: GFP-ORFs3, 7, 8, 9, and 14 (which were mainly cytoplasmic); GFP-ORFs10, 11, and 13 (which were evenly distributed in both the cytoplasm and nucleus); and GFP-ORF4 (which was mainly nuclear).

Effect of GFP-ORFs on cell survival

After transfecting GFP-ORFs into HEK293 cells, the behaviour of the GFP-positive cells was monitored by fluorescent microscopy every 12 to 24 hours for up to 4 days. Several GFP-ORFs, especially GFP-ORF8, caused obvious cell death. After 24 hours of transfection into HEK293 cells, GFP-ORF8-positive cells started to round up and then detached from culture plates (Fig 1). By 48 hours, most of the GFP-positive cells had died. This was consistent with other reports.[3,4] Similarly, GFP-ORF3, GFP-ORF9, and ORF14 also promoted cell death.

GFP-tagged ORF8 activates both JNK and p38 MAPK

Based on the finding that GFP-ORF8 promoted cell death, we tested whether GFP-ORF8 could activate JNK and p38 MAPK (both of which are often activated by pro-apoptotic stimuli). The HEK293 cells were co-transfected with GFP-ORF8 together with either HA-JNK2 or HA-p38α. EBV-encoded LMP1 was used as a positive control. In immune-complex kinase assays, GFP-ORF8 potently activated both JNK and p38 as well as LMP1 (Fig 2).

There is a 15-aa leader peptide at the N-terminus of ORF8, which might correct targeting of the viral protein to the endoplasmic reticulum and Golgi networks.[5] To make sure that the effects seen above were not due to inappropriate
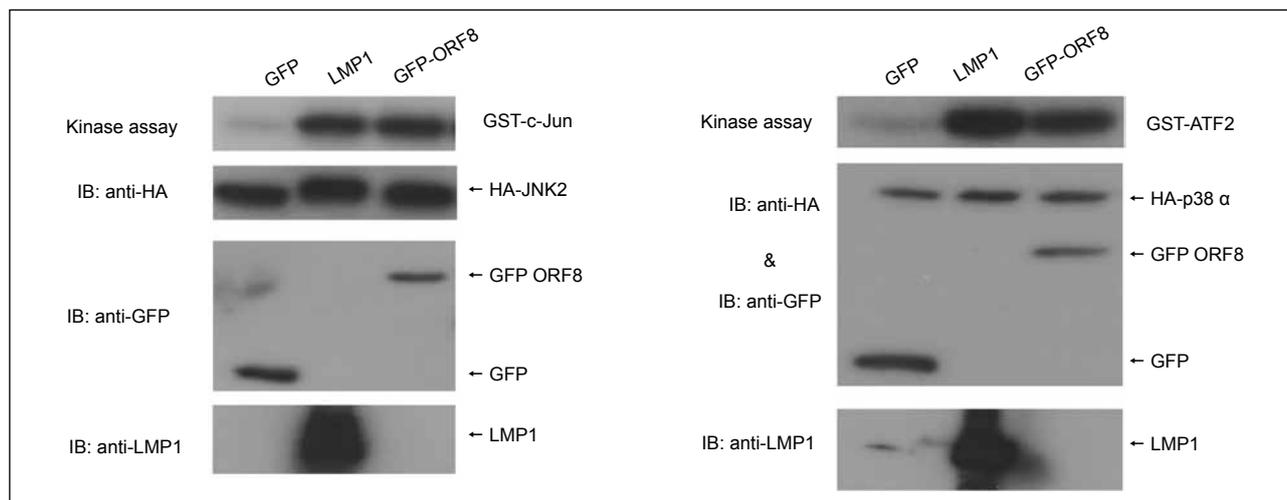
Fig 2. Activation of JNK and p38 MAPK by GFP-ORF8
HEK293 cells are co-transfected with GFP-ORF8 together with either HA-JNK2 or HA-p38 . HA-tagged kinases are immunoprecipitated from cell lysates and subjected to kinase assays

positioning of the GFP tag in the fusion protein, another expression construct (ORF8-GFP) was generated with GFP-fused inframe to the C-terminus of ORF8. When the construct encoding ORF8-GFP was introduced into HEK293 cells, ORF8-GFP was as efficient as GFP-ORF8 (ie the N-terminally tagged ORF8) in promoting cell death. Furthermore, when co-transfected together with HA-JNK2 or HA-p38α into HEK293 cells, ORF8-GFP potently activated both JNK and p38 as well as GFP-ORF8.

Non-tagged ORF8 did not cause cell death and activate JNK and p38

To further exclude the possibility that the effects of ORF8 fusion proteins seen above were caused by inappropriate fusion of the GFP tag, an expression construct encoding the native ORF8 was generated, without any additional tag at either end of ORF8. To ensure that the ORF8 protein was actually expressed from the construct, polyclonal antibodies against ORF8 were generated using recombinant ORF8 protein spanning aa 17-84. The antibodies we used were able to detect ORF8 either as a GFP-ORF8 fusion protein or a non-tagged protein (Fig 3). When transfected into HEK293 cells, the non-tagged ORF8 did not cause obvious cell death. In addition, although GFP-ORF8 potently activated JNK, the non-tagged ORF8 failed to do so (Fig 3). Similarly, the non-tagged ORF8 also failed to activate p38.

Discussion

To study the cellular function of novel proteins in the absence of suitable antibodies, it has been a widely adopted practice to fuse a unique tag (eg HA, FLAG, Myc, etc) to either end of the protein of interest. This facilitates detection of the protein in cells and cell lysates and in isolation of the protein of interest by immunoprecipitation. In recent years, GFP has become a very popular tag, as it enables imaging
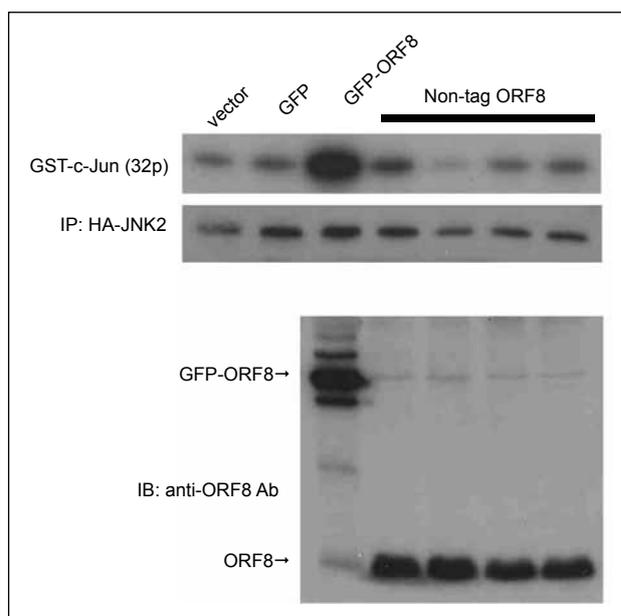
Fig 3. ORF8 without tag does not activate JNK
HEK293 cells are co-transfected with constructs encoding HA-JNK2 and non-tagged ORF8. HA-JNK is immunoprecipitated from cell lysates and subjected to protein kinase assays. The expression of ORF is detected by our locally produced antibodies

of live cells, instant knowledge of subcellular localisation patterns, and tracking of the fate of GFP-positive cells over a long period of time. Although protein tagging is a fast and useful technique (especially for proteins without suitable antibodies), addition of a tag to a protein can create artefacts due to changes in protein localisation and folding, interference or disruption of interaction of the protein with other partners, etc. Therefore, caution is necessary for findings derived from tagged proteins.

Owing to the high mortality rate caused by SARS-CoV, it is essential to understand the molecular mechanisms underlying the pathogenesis. We undertook the project at a time when many key reagents (including the antibodies againt ORF8) were not available. GFP-tagged ORF8 was found to potently induce cell death, which was consistent with other reports.[3,4] In addition, GFP-tagged ORF8 strongly activated the JNK and p38 MAPK pathways in host cells. Non-tagged ORF failed to induce these changes; this suggested that artefacts were generated in the GFP fusion proteins. Before obtaining the ORF8 antibody, a segment of ORF8 gene encoding aa 17-94 was used as the bait in the yeast two-hybrid screening. Several interesting clones were found. Owing to the lack of a suitable biological assay for the native ORF8, these clones were not further characterised.

In addition to ORF8, ORF3 (also known as ORF3a), another novel ORF that was found to be expressed in SARS-CoV-infected cells was also extensively studied. Similarly, GFP-ORF3 induced cell death and activated both JNK and p38 in host cells. In contrast, the non-tagged ORF3 failed to induce cell death and activate JNK and p38 as well as IkB kinase.

Conclusions

The native (non-tagged) ORF8 and ORF3 did not significantly induce cell death, nor did they activate JNK and p38 MAPK pathways. We believe that results in several reports on ORF8 and ORF3 were most likely due to artefacts generated by inappropriate fusion of an epitope tag at either end of the viral proteins.[3,4] Therefore, caution should be exercised in interpreting results derived from epitope-tagged proteins. Suitable antibodies to the protein of interest should be prepared to facilitate the study of the native proteins.

Acknowledgement

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Neuroprotection in steroid therapy: a rodent modeln

Key Messages

1. Chronic steroid therapy causes disturbance in cell proliferation of the hippocampus and the subventricular zone. This may be the underlying cause of altered memory and cognitive function.
2. Co-administration of paroxetine (a class of antidepressants) during steroid therapy could counteract the destruction. Modification of the current steroid therapy regimen may be required.

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Introduction

Corticosteroid decreases neural cell production in the hippocampus,[1] whereas antidepressants induce neurogenesis.[2] The hippocampus is a brain region for memory formation. Decreased production of neurons in this region has a negative impact on cognitive function. We assessed the hypothesis that the neuro-damaging effect of high-dose corticosteroid on the hippocampus and subventricular zone (SVZ) could be reversed by administration of paroxetine—a selective serotonin reuptake inhibitor for treatment of depressive disorders. A rodent model was used to test the effect of paroxetine, corticosterone, and co-treatment of these two drugs on neurogenesis of the hippocampus and SVZ. In patients receiving steroid therapy, the neuroprotective effect of paroxetine suggests that administration of antidepressant could prevent deterioration of neuron production. This study aimed to investigate drug interactions of paroxetine, lithium, and corticosterone on the hippocampus and SVZ in terms of cell proliferation, dendritic morphology, neuronal survival, and molecular mechanisms, and whether selective serotonin reuptake inhibitor and lithium could exert protection against corticosterone-induced neuron damage on the hippocampus and SVZ.

Methods

This study was conducted from January 2005 to December 2006. Six groups of rats (n=4-5 for each group) were divided into: (1) 14 days of corticosterone injections (40 mg/kg, subcutaneously), (2) 14 days of paroxetine injections (10 mg/kg, intraperitoneally), (3) 14 days of both corticosterone and paroxetine injections (same dosage as above), and (4) 14 days of vehicle injections.

To study the effect of lithium and corticosterone on dendritic morphology, the rats were divided into: (1) 14 days of lithium treatment (85 µg/kg, n=6), and (2) 14 days of lithium and corticosterone treatment (same dosage as above, n=6).

Proliferative cells in the hippocampus and SVZ were labelled by bromodeoxyuridine (BrdU) injection (50 mg/kg) during the final 3 days of treatment. After 14 days of treatment, rats were sacrificed by decapitation, and their brains were processed for BrdU immunohistochemistry or Golgi staining. During the treatment period, another set of experimental rats was sacrificed and their hippocampi were dissected for quantitative polymerase chain reaction.

For the differentiation and neurogenesis study, the rats were divided into 4 groups as described above, with each group containing 6 rats. The rats were allowed to survive for 3 weeks after completion of the 14 days' treatment. The total number of rats used was 135.

BrdU immunohistochemistry
Frozen slices of the hippocampus and SVZ were slide-mounted and boiled in citric acid (pH=6.0) for 10 mins, followed by PBS rinses. The brain sections were incubated in 1M HCI (37ºC, 30 mins) and then boric acid buffer (pH=8.5, 10 mins). After blocking with 5% normal goat serum in 0.01% Triton X-100, sections were incubated overnight with anti-mouse BrdU (1:400, Roche) at 4ºC. Sections were then incubated for 1 hr with secondary antibody (biotinylated goat

anti-mouse; Vector Laboratories), followed by amplification with an avidin-biotin complex (Vector Laboratories). Cells were then visualised with diaminobenzidine. For the neurogenesis study, co-immunostaining with rat anti-BrdU antibody (1:1000, abcam) and mouse anti-NeuN (1:1000, Chemicon) were used as primary antibody. Secondary antibodies were goat anti-mouse and rat (Alexor fluor 488 and 563, Molecular Probes). The chemical supplier was Sigma-Aldrich unless otherwise indicated.

Golgi staining
Golgi staining was carried out using the FD Rapid GolgiStain Kit according to the manufacturer's protocol. In brief, the brains of the treated rats were immersed in the impregnation solution for 2 weeks, after which the tissue was cut into 50-micron-thick sections and stained.

Quantitative polymerase chain reaction
Hippocampi of the rats in the three treatment groups (corticosterone, paroxetine, and co-treatment) were taken out at different time points: 4 hours, 2 days, 4 days, 7 days, and 14 days after treatment. Hippocampal tissues were dissected and stored at -70ºC until use. Hippocampal RNA was extracted with Trizol reagent (Invitrogen) according to the manufacturer's protocol. Gene expression of brain-derived neurotrophic factor (BDNF) and cAMP response element-binding protein (CREB) among different groups of rats at different time points were measured by the iCycler iQ™ Multi-Color RT-PCR System. The primer sequences and probe for amplification of BDNF were: 5'-CTGACACTTTTGAGCACGTGATC-3' (forward), 5'-CGTTGGGCCGAACCTTCT-3' (reverse), and 5'-CATCCAGCAGCTCTTC-3' (probe). The primer sequences of GAPDH (as internal controls) were: 5'-CAGAACATCATCCCTGCATCCA-3' (forward), 5'-CCGTTCAGCTCTGGGATGAC-3' (reverse), and 5'-CTTGCCCACAGCCTTG-3' (probe).

Data quantification and statistical analysis
BrdU-positive cells on every 12th unilateral section through the whole dentate gyrus were counted at ×1000 magnification, with the aid of the Stereo Investigator software. BrdU-positive cells in the dentate gyrus were counted from 2400 to 3600 μm posterior to Bregma. In SVZ, BrdU cells were counted from 1800 to 0 μm anterior to Bregma. The number of BrdU-labelled cells per dentate gyrus was then multiplied by 24 to estimate the total number of BrdU-positive cells through the dentate gyrus. The number of BrdU-positive cells in the hippocampal subgranular zone in each group was defined as a percentage of control (vehicle). For SVZ sections, the cell number was expressed as the number of cells per section.

Brain-derived neurotrophic factor enzyme-linked immunosorbent assay
BDNF enzyme-linked immunosorbent assay (ELISA) kits (Chemicon) were used to assess hippocampal BDNF protein level after 14 days of treatment. Protein extracts were prepared from snap-frozen rat hippocampi. For each rat, 50 μg of protein extract was used for assay. ELISA was carried out according to the manufacturer's protocol.

Results

Adrenal gland atrophy caused by subchronic corticosterone treatment
After 14 days of treatment, the adrenal glands were dissected and weighed. Respectively in the control, corticosterone, co-treatment, and paroxetine groups, the mean adrenal weights (in g) were 27.63±4.85, 6.20±2.78, 10.633±1.46, and 45.47±14.15. Adrenal weights of the rats in the corticosterone and co-treatment groups decreased, which indicated hypercortisolaemia induction and chemically induced lesions. This confirmed that the rats were subjected to chronic exposure of high-dose corticosterone during the treatment period.

Hippocampal neurogenesis after corticosterone and paroxetine treatment
In the cell proliferation assay, the number of proliferating cells was identified by immunohistochemical detection of BrdU within the nuclei of actively dividing cells. The BrdU-positive nuclei were clustered in the subgranular layer and hilus and exhibited irregular shape. In the experiment, only subgranular layer cells were counted. Compared to the controls, corticosterone significantly decreased the number of BrdU-labelled cells in the dentate gyrus (2470.00±31.56 vs 1677.38±146.97, P<0.05). Chronic treatment with paroxetine significantly increased BrdU-labelled cells (13255.71±83.98, P<0.001) in the subgranular and granule cell layer, compared to the corticosterone or vehicle-alone group. The number of BrdU-positive cells in the co-treatment group (2204.48±90.40) was not significantly different from the vehicle-treated controls. For neuronal differentiation, no difference in the percentage of BrdU-labelled cells showing NeuN expression was noted among the four groups. This indicated that subchronic corticosterone treatment decreased hippocampal neurogenesis, whereas co-treatment with paroxetine increased the effect to a level similar to controls. In short, antidepressant therapy may be effective in preventing neurological damage caused by subchronic or chronic steroid therapy.

Morphological analysis by Golgi staining
Brain tissues were subjected to Golgi staining to study morphological changes (dendritic trees and spines) of hippocampal neurons after treatment. In the corticosterone, lithium, and co-treatment groups, at least five neurons were traced using the Neurolucida software, and the data were analysed using the NeuroExplorer software. The number of neuronal nodes (ie the number of dendritic tree branches) in the corticosterone group was significantly lower than in the lithium and co-treatment groups (13.5±4.36 vs 32±6.00 vs 33.63±12.00, P<0.05). The mean dendritic length of each neuron (in μm) in the corticosterone group was significantly smaller than in the other two groups (410.0±49.7 vs

1762.6±182.4 vs 2068.6±782.9, P<0.05). This indicated that corticosterone decreased dendritic length and the number of dendrite branches, whereas corticosterone plus lithium could reverse the changes.

Effect of drug treatment on hippocampal cell death

Cell death in the hippocampus was assessed by Nissl staining. No cells with pyknotic appearance (ie undergoing apoptotic cell death) were detected with cresyl-violet staining in any treatment group. This indicated that subchronic corticosteroid treatment was unlikely to cause neurological damage by increasing hippocampal cell death, and that antidepressants may not exert their therapeutic effect by protecting neurons from apoptosis.

Quantification of change of brain-derived neurotrophic factor and cAMP response to element-binding protein after drug treatments

The quantitative polymerase chain reaction was used for detecting alteration of BDNF and CREB levels in the hippocampus. In contrast to expectation, BDNF gene expression levels in all treatment groups decreased but not significantly across the treatment period when compared to day 0.

Brain-derived neurotrophic factor protein expression by enzyme-linked immunosorbent assay

The BDNF level in the hippocampus decreased significantly in corticosterone-treated rats than in vehicle-treated rats (66.88±4.22 vs 90.2±6.63 ng/mL, P<0.05, ANOVA with LSD post-hoc test). Co-treatment with corticosterone and paroxetine (87.73±6.65 ng/mL, P>0.05) prevented the effect of decreased BDNF expression, compared to controls. No significant difference was noted between the vehicle group and paroxetine-treated group (90.2±6.63 vs 99.07±8.42 ng/mL, P>0.05).

Effect of corticosteroid and paroxetine on subventricular zone neurogenesis

Similar to the findings for hippocampus cell proliferation, corticosterone treatment significantly reduced the number of BrdU-positive cells in SVZ, whereas paroxetine treatment significantly increased the number. Respectively in the control, corticosterone, paroxetine, and co-treatment groups, the numbers of BrdU-positive cells in SVZ were 324.0±33.3, 264.1±28.1, 434.9±36.2, and 330.9±23.2 cells/section (P<0.05 for control vs corticosterone and control vs paroxetine).

Discussion

Using the cell birth-dating technique (BrdU labelling), the numbers of proliferative cells in the hippocampus and SVZ were noted to increase with paroxetine treatment. However, no pyknotic cells were observed in the hippocampus in any of the treatment groups, indicating that the drugs had no significant effect on cell survival in our treatment paradigm. The neurogenesis-promoting effect of antidepressants may be due to their influence on the serotonergic system and thus the serotonergic pathways.[3] Lithium could reverse the adverse effect of corticosterone on the dendritic complexity of the hippocampal CA3 region. Administration of lithium during steroid therapy may prevent the undesirable effect of high-dose steroid, but further investigation is needed to determine its behavioural consequence. The intracellular mechanisms responsible for the neurogenic effect remain unclear, but are likely to involve more than one intracellular pathway. Previous studies have suggested a major role of the cAMP-CREB cascade[4] in the process, and that BDNF may be essential for neurogenesis. In our study, the ELISA data showed increased levels of BDNF in paroxetine-treated rats.

Conclusions

Paroxetine, a potent selective serotonin reuptake inhibitor, could reverse the adverse effect of corticosteroid on hippocampal and SVZ neurons. Paroxetine could induce cell proliferation in both neurogenic regions and restore the number of hippocampal proliferative cells in corticosteroid-treated rats. Dendritic morphology study revealed that lithium may be beneficial for dendritic arborisation under the stress condition created by corticosterone treatment. Future studies may investigate the behavioural consequence of altered neurogenesis and dendritic morphology. Also, the molecular interaction between BDNF and CREB is worth studying. Understanding the molecular mechanisms in the neuroprotection of antidepressants may help patients undergoing steroid therapy in preventing cognitive deterioration.

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Mental health impact of severe acute respiratory syndrome: a prospective studyn

Key Messages

1. Psychiatric disorders and chronic fatigue were common among severe acute respiratory syndrome (SARS) survivors even after 3 years, and were associated with various functional impairments.

2. Factors associated with the post-SARS experience and dysfunctions (including perceived stigmatisation, frequent recall, medicolegal issues, and working status) were likely to be related to long-term psychiatric disorders and fatigue.

3. A proportion of SARS survivors may have partial insufficient adrenal responses, but the hypothalamo-pituitary-adrenal status was not related to the psychiatric and fatigue status.

Introduction

The severe acute respiratory syndrome (SARS) epidemic struck Hong Kong in 2003. Varying rates of mental health morbidity were reported during the acute and early discharge period.[1] The impact of SARS did not end with the resolution of the infection. During the rehabilitation period, many patients had to face psychosocial difficulties including stigmatisation, grief reactions, unemployment, functional impairment, and medical co-morbidities. Despite improvements in physical condition, the stress and psychiatric symptoms persisted even after 1 year.[2-4] Chronic fatigue was common among SARS survivors.[5] There seemed to be a reciprocal association between fatigue problems and psychiatric disorders. Dysregulation in endocrine functions, especially of the hypothalamo-pituitary-adrenal (HPA) axis, was common in those with psychiatric disorders and chronic fatigue syndrome (CFS).[6] This study aimed to investigate the prevalence and associated risk factors for psychiatric disorders and CFS in SARS survivors, and the association between HPA status and CFS.

Methods

Data were collected from December 2005 to July 2007 in the Prince of Wales Hospital. A total of 369 Chinese SARS survivors in the New Territories East Cluster hospitals were invited to participate. Patients who were not of Chinese ethnicity and those who had medical illnesses unrelated to SARS were excluded. Personalised letters introducing the research aim and method were sent, followed by invitation by telephone. For those who could not be contacted or who declined to participate in face-to-face interviews, questionnaires were sent out to them.

Subjects were assessed by psychiatrists using the Chinese bilingual version of the Semi-Structured Clinical Interview (SCID-II). They also completed a series of psychometric inventories, including the Chinese versions of the Hospital Anxiety and Depression Scale, revised version of the Impact of Event Scale, the Global Assessment of Functioning Scale, the Quality of Life Scale, and a self-reported questionnaire enquiring demographics and subjective experiences of patients after the SARS infection. In addition, the length of hospitalisation, history of hypoxia and oxygen supplementation, intensive care unit admission, duration and dosage of steroid and ribavirin treatment, and presence of physical comorbidity were collected after a case-note review supplemented by the computerised medical information system.

For the second part of the case-control study, a proportion of the SARS survivors were invited to undergo endocrine assessment of HPA axis function. Three consecutive morning salivary cortisol levels and a low-dose short synacthen test (LDSST) were measured. Controls were recruited from the community; they had no major physical, sleep, or psychiatric disorders. Their fatigue status and 3 days of morning salivary cortisol levels were also assessed.

Results

Of the 369 eligible subjects, 233 (63.1%) responded after a mean post-SARS duration of 39 months. Among these subjects, 181 underwent interviews with

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SCID-II for assessment of any psychiatric morbidity. Of whom, 90 were diagnosed with psychiatric illnesses and 77 were having active psychiatric illnesses at the time of interview (Table). The commonest disorders were major depressive disorder, post-traumatic stress disorder, somatoform pain disorder, and panic disorder. Although fatigue was a common symptom, only 24 to 40% of the patients fulfilled various CFS criteria. Those with psychiatric disorders and/or CFS had poorer quality of life, more subjective impairments in various functional aspects, and scored more poorly on all psychometric scales (Table).

In the multivariate analysis, the perception of stigmatisation and recall of SARS memories were associated with both lifetime and current psychiatric disorder. In addition, chronic fatigue and working status also predisposed to the risk of lifetime psychiatric disorder. In contrast, the presence of physical illness at baseline seemed to protect against the development of psychiatric problems. The presence of CFS was influenced by medicolegal issues (application for SARS fund and involvement in litigation process), perceived stigmatisation, worries over avian flu, and background of psychiatric disorder. The HPA axis function (both LDSST and morning salivary cortisol level) was similar in those with and without psychiatric disorders and/or CFS.

Discussion

Nearly half of the SARS survivors had one or more psychiatric disorders in their lifetime; most still had the disorder, despite more than 3 years since the SARS epidemic. Chronic fatigue was common among SARS survivors. Although both psychiatric disorders and CFS were closely associated, a proportion of patients developed CFS in the absence of co-morbid psychiatric disorders. Both CFS and psychiatric disorders were associated with a variety of functional impairments.

SARS was not simply an infection but a disastrous experience for these patients. Indeed, SARS survivors shared similar psychopathologies with other disaster survivors who reported varying rates of posttraumatic stress disorder (30-40%), depression (25%), and fatigue symptoms (50%).[7]

Table. Comparison of SARS survivors with or without psychiatric disorder

Parameter	No psychiatric illness (n=91)	Psychiatric illness (lifetime or current) (n=90)	Current psychiatric disorder (n=77)
Mean±SD age (years)	44.9±15.6	44.5±12.0	45.6±12.0
% of male:female	39.6:60.4	23.3:76.7*	24.7:75.3*
Health care worker at 2003 (% of subjects)	33.0	52.2*	54.5*
Working at follow-up (% of subjects)	77.4	56.5*	53.8*
Self-reported questionnaire (% of subjects)			
Marital status			
Single/divorced/widowed	33.9	33.9	30.8
Married	66.1	66.1	69.2
SARS fund			
Not applied	73.8	41.9*	42.3*
Applied	26.2	58.1	57.7
Involvement in lawsuit	3.2	19.4*	21.2*
Stigmatisation			
No/a little bit	87.1	47.5*	43.1*
Sometimes/always	12.9	52.5	56.9
Worry about avian flu			
Never/a little bit	75.8	39.3*	35.3*
Sometimes/always	24.2	60.7	63.7
Recall of SARS memories			
Never/seldom	69.4	20.0*	14.0*
Sometimes/always	30.6	80.0	86.0
Impairment			
Mean±SD total Hospital Anxiety and Depression Scale score	9.8±5.7	20.7±7.3*	21.6±7.4*
Mean±SD total revised Impact of Event Scale score	24.3±16.9	56.0±22.9*	59.0±22.7*
Chronic fatigue (% of subjects)	45.2	75.0*	76.5*
Chronic fatigue syndrome (% of subjects)	17.7	55.1*	59.3*
Mean±SD Global Assessment of Functioning Scale score	76.9±9.2	55.7±12.1*	53.6±11.2*
Mean±SD World Health Organization Quality of Life Scale			
Physical score	54.2±26.1	34.6±19.0*	33.0±18.3*
Psychological score	64.7±12.2	41.6±16.7*	40.0±16.5*
Social score	57.9±13.2	44.1±16.7*	43.6±16.6*
Environmental score	63.4±13.0	46.9±13.6*	45.4±12.7*
Working ability†	43.4	82.9*	89.5*
Housework ability†	44.1	82.2*	87.7*
Social activities†	43.0	83.3*	88.1*
Leisure activities†	43.0	83.3*	88.2*
Intimate relationship†	41.6	83.5*	87.8*

* P<0.05, non-parametric Mann-Whitney U test
† Higher scores indicate more subjective impairment; non-case was compared separately with lifetime or current psychiatric case

Owing to the infectious nature of SARS, the survivors and their family members may have been stigmatised as hazardous with potential for cross-infection.[8] The disabling symptoms (such as fatigue and non-specific pain), functional decline, and lengthy litigation processes may have further increased others' scepticism and stigmatisation. The perception of stigmatisation was the most consistent aetiological factor for the development of psychiatric disorders and CFS. It may also be amplified by the negative cognitive distortion and interpersonal sensitivity commonly seen in psychiatric disorders.

The SARS epidemic has heightened the perception of the risk posed by other potential infectious epidemics (such as avian flu). Constant alertness to the potential threats of novel infections may have perpetuated SARS survivors' traumatic experience. Recall of SARS memories and concern about avian flu were predictors of psychiatric disorders and CFS.

The protective role of physical illness (at baseline) against the development of psychiatric disorders in this SARS cohort was intriguing. In most studies, the presence of underlying physical illness usually predisposes to the risk of psychiatric disorder. However, in our SARS cohort, most of the psychiatric disorders occurred after SARS attacks and in healthy subjects, including health care workers. Those with physical illness may have had better mental preparation for handling deterioration in health, but there was a selection bias, in which those with serious and multiple medical illnesses may have died from the SARS infection.[1]

Working status seemed to be associated with the presence of psychiatric disorder. The relationship could be bidirectional in that unemployment or retirement may have resulted in or from psychiatric disorder. Being a health care worker was associated with a higher risk of posttraumatic stress disorder.[9] Ongoing adverse experiences during the SARS epidemic, the sudden change of status from being a health care worker to patient, and the proximity and similarity between their usual working area and ward environment may have increased their risk of re-experiencing the trauma.

The association of SARS fund application and litigation with chronic fatigue needs careful interpretation. Patients with more functional impairments (which may reflect long-term dysfunction) are more likely to succeed in applying to the SARS fund. A large proportion of SARS patients reported litigation against the health authority and/or employers. Those with more fatigue and prominent mental dysfunction might have negative attitude toward the health authority. In addition, the lengthy litigation process might perpetuate their mental anguish. The phenomenon known as 'compensation neurosis' remains a controversial issue.[10] As the litigation process was still ongoing at the time of this study, longer-term studies are required to delineate the role of compensation and litigation in the psychopathology of SARS survivors.

The SARS group was not significantly different from the controls in terms of the morning salivary cortisol level; subgroup analysis of SARS survivors in terms of the presence of CFS and psychiatric disorders did not yield any significant difference. Similarly, the LDSST could not differentiate the SARS survivors with or without psychiatric and/or fatigue disorders, albeit there was a proportion of patients who might be considered to have partially insufficient adrenal response to LDSST. Most of mentally ill SARS survivors declined further psychiatric management, as they worried about 'double stigmatisation'.

The response rate of 63% was modest, but it was achieved after intensive recruitment strategy and careful explanation and reassurance of confidentiality. The participants could be regarded as representative of the SARS population of the New Territories East Cluster hospitals. Not all participants completed a full set of assessments. Nonetheless, over 80% of them consented to a face-to-face psychiatric interview. In addition, a number of subjects agreed to undergo endocrine measurement. Future study should integrate both mental and physical complications in assessing the long-term outcome of SARS survivors.

Conclusions

Psychiatric disorders and chronic fatigue were highly prevalent among SARS survivors even after 3 years. They further impaired SARS survivors in various psychosocial areas. Although relative adrenal insufficiency was noted in some patients, this did not appear to influence the emergence of psychiatric disorders or chronic fatigue.

Acknowledgements

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Role of dendritic cells in SARS coronavirus infection

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Key Messages

1. Severe acute respiratory syndrome coronavirus (SARS-CoV) entered and replicated in monocyte-derived dendritic cells (DCs), but virus replication was incomplete. In addition, SARS-CoV did not induce apoptosis or maturation of infected DCs.
2. SARS-CoV infected DCs showed low expression of antiviral cytokines (IFN-α, IFN-β, IFN-γ, and IL-12p40), moderate up-regulation of proinflammatory cytokines (TNF-α and IL-6), and significant up-regulation of inflammatory chemokines (MIP-1α, RANTES, IP-10, and MCP-1).
3. SARS-CoV did not modulate gene expression of Toll-like receptors (TLR-1 to 10) but induced significant up-regulation of chemokine receptors (CCR-1, CCR-3, CCR-5).
4. SARS-CoV induced high expression of TRAIL but not FasL gene expression in DCs.
5. The characteristic phenotype of SARS-CoV infected DCs suggested some possible mechanisms of immune escape and amplification of immunopathology in SARS.

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Introduction

In 2003, the severe acute respiratory syndrome coronavirus (SARS-CoV) caused severe, rapidly progressive atypical pneumonia with fever, myalgia, and diarrhoea.[1,2] Viruses were detected in the respiratory tract, stool, and urine of patients indicating that SARS was a systemic disease. White pulp atrophy was noted in the spleen, and lymphoid depletion was noted in lymph nodes. Lymphopaenia and increasing viral load in the first 10 days of disease strongly suggested an evasion of the immune system by SARS-CoV.[3,4]

Based on the function of dendritic cells (DCs) in immune surveillance, priming, and tolerance, DCs play an important role in the immunopathology of SARS. These cells are professional antigen-presenting cells linking innate and adaptive immunity. Immature DCs reside in the respiratory tract for immune surveillance and respond dynamically to local tissue inflammation in the airways and the distal lung. They express a wide range of c-type lectin receptors and Toll-like receptors (TLRs) for recognition of conserved pathogen patterns and induction of subsequent immune responses.

Some TLRs are expressed on the cell surface (TLR-1, TLR-2, TLR-4, TLR-5, TLR-6, TLR-10), whereas others are expressed in intracellular compartments (TLR-3, TLR-7, TLR-8, TLR-9). They are differentially expressed in different DC subsets and are modulated in response to a variety of stimuli. Viral proteins bind to TLR-2 or TLR-4; single stranded RNA binds to TLR-7 and TLR-8; double stranded RNA binds to TLR-3; and viral DNA binds to TLR-9. The binding of ligands to TLRs triggers the downstream signalling pathways that are involved in the cytokine release during primary induction of inflammation and secondary activation of anti-inflammatory mechanisms. Cross talks between TLRs are common, and the formation of TLR heterodimers allows a higher level of complexity in ligand-receptor binding and subsequent signalling.

Migration of DCs from peripheral tissues to lymph nodes is essential for antigen presentation and triggering of adaptive immune responses. The trafficking of DCs is regulated by chemokines in their microenvironment and their expression of chemokine receptors (CCRs). Differential expressions of CCRs are observed during DC maturation, and some viruses (such as herpes simplex virus) can block CCR expressions on DCs to alter their migratory properties.

Chemokines can be classified as homeostatic (constitutively expressed) or inflammatory (induced/augmented) according to their immune functions. Respiratory viruses commonly induce inflammatory chemokines (such as MIP-1α/CCL3, RANTES/CCL-5, IP-10/CXCL10, and MCP-1/CCL2) in local tissues and DCs. There are redundancies in the interactions between chemokines and CCRs, as many different ligands bind the same receptor and many receptors bind the same ligand. For example, RANTES binds to CCR-1, CCR-3 and CCR-5, whereas MIP-1α binds to CCR-1 and CCR-5.

Death receptors and their ligands also play important roles in innate and adaptive immune responses by regulating cell death and survival. Well-characterised death receptor ligands include TNF-α, FasL, and TRAIL/Apo2L. Several viruses (including measles virus, human immunodeficiency virus,

cytomegalovirus, and herpes simplex virus) have been shown to induce TRAIL expression on DCs. These 'killer DCs' may be involved in the killing of virus-infected cells or bystander lymphocytes and natural killer cells. Therefore, we aimed to determine if the expression of death receptor ligands on DCs can also be modulated by SARS-CoV.

Clinically, manifestation of SARS was less severe in children than adults. We hypothesised that the developmental status of the host immune system may affect the severity of acute respiratory diseases. We compared the effect of SARS-CoV on adult and cord blood DCs. SARS-CoV could enter DCs and alter their expression of cytokines, chemokines, TLRs, CCRs, and DLRs. There were possible mechanisms of immune escape and amplification of immunopathology in SARS.

Methods

This study was conducted from August 2005 to July 2007. We studied the effects of SARS-CoV on human monocyte-derived DC maturation, apoptosis, cytokines/chemokines expression, receptors expression, and death receptor ligands expression by flow cytometry and real time quantitative polymerase chain reaction (PCR).[5,6]

Real-time quantitative PCR was used to analyse some immune-related genes based on the advantages that:

(1) Less DCs are needed for total RNA extraction (0.25-0.5x10^6 DCs per sample for real-time quantitative PCR versus 2-5x10^6 DCs per sample for microarray analysis).

(2) Point 1 above translated to the requirement of less SARS-CoV for infection. This is important for the researchers' safety when performing the experiments.

(3) Even with the microarray data, the findings need to be substantiated by increasing the sample size and comparing the gene expression by real-time quantitative PCR.

Results

As evident by electron microscopy and immunofluorescence staining, SARS-CoV could enter both immature and mature human monocyte-derived DCs. Viral replication in DCs was suggested by the detection of negative strands of SARS-CoV RNA. However, there was no increase in viral RNA over time. Using cytopathic assays, SARS-CoV was not detected in DCs and cell culture supernatant. This confirmed that virus replication was incomplete. SARS-CoV did not induce apoptosis or maturation of DCs. SARS-CoV-infected DCs showed low expression of antiviral cytokines (IFN-α, IFN-β, IFN-γ, and IL-12p40), moderate up-regulation of proinflammatory cytokines (TNF-α and IL-6), and significant up-regulation of inflammatory chemokines (MIP-1α, RANTES, IP-10, and MCP-1).[5] SARS-CoV did not modulate Toll-like receptors (TLR-1 to 10) gene expression, but induced significant up-regulation of chemokine receptors (CCR-1, CCR-3, CCR-5). There was strong induction of TRAIL but not FasL gene expressions in SARS-CoV-infected DCs.

Discussion

The role of immune evasion in the severity and immunopathology of SARS has been supported.[2-4] In this study, DCs, which are the key antigen-presenting cells, played crucial roles in anti-viral immune responses and may have involved in some immune escape mechanisms specific for SARS-CoV (Table). Particularly, up-regulation of chemokines and death receptor ligands may have contributed to infiltration of cells into the lungs

Table. Possible mechanism of immune evasion in SARS patients

Parameter	Observations from this study[5,6]	Possible mechanism of immune evasion[3,4]	Reported pathology in SARS patient[1,2]
Permissiveness	SARS-CoV can enter DCs	Use DCs as vehicle or 'Trojan horse'	Dissemination of virus to multiple organs
Viral replication	SARS-CoV replication is incomplete	-	-
Dendritic cell (DC) survival	SARS-CoV did not induce DCs apoptosis	-	-
DC maturation	SARS-CoV did not induce maturation	Escape from adaptive immune response; induction of regulatory DC and regulatory T cells	Low antibody production in the first 10 days
Anti-viral cytokines	Low interferons and IL-12	Block anti-viral responses	Low antibody production in the first 10 days of SARS
Proinflammatory cytokines	Moderate expression of TNF-α and IL-6	-	-
Inflammatory chemokines	↑↑↑MIP-1α, RANTES, IP-10, and MCP-1	Increased cell trafficking and DC trafficking	↑↑ mononuclear inflammatory cell infiltration in lungs
Toll-like receptors	No induction	-	-
Chemokine receptors	↑CCR-1 & CCR-5; ↑↑ CCR-3; no change in CCR-7	Increase DC trafficking; suppress activated T cells or induce regulatory T cells	Reduced immune responses
Death receptor ligands	Low FasL; strongly up-regulated TRAIL	Killing cells at the site of infection and in lymphoid organs	Lymphopaenia; white pulp atrophy in spleen and lymphoid depletion in lymph nodes

and lymphopaenia, respectively. Further studies into the mechanisms of newly emerged viruses to evade the innate immune responses are necessary.

There was significant induction of RANTES and its expression of corresponding receptors CCR-1, CCR-3, and CCR-5 mRNA in SARS-CoV-infected DCs. Our previous gene association study has shown a higher death rate in SARS patients who have inherited the high-production gene allele of RANTES.[7] Further investigations into the therapeutic strategies that can reduce RANTES production are warranted.

The up-regulation of TRAIL gene expression in both adult and cord blood DCs after SARS-CoV infection represented a killer DC phenotype. This up-regulation is similar to our observation in macrophages infected by avian influenza virus. Further investigation is needed to confirm the cytotoxic function of SARS-CoV-infected DCs on immune cells, and to help design therapeutic strategies that reduce TRAIL gene expression, neutralise TRAIL, or block signalling of TRAIL receptors, so as to reduce lymphopaenia.

Comparing adult and cord blood DCs, both the basal and SAR-CoV-induced gene expression levels of chemokines and CCR genes were significantly higher in the latter. Based on the function of chemokines on cell trafficking, more severe infiltration of cells into the lungs was expected in children. On the contrary, SARS was less severe in children than adults. The age-dependency of SARS severity merits further studies to elucidate the underlying mechanisms. As the information on the chemokine and CCR expression and function in children is scanty, further studies are warranted.

Conclusions

Dendritic cells played an important role in the pathogenesis of SARS. The lack of antiviral cytokine response, intense chemokine up-regulation, induction of CCR expression and strong expression of TRAIL observed in SARS-CoV-infected DCs suggested possible mechanisms of immune escape and amplification of immunopathology in SARS.[3]

Acknowledgements

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Detection of body temperature with infrared thermography: accuracy in detection of fevern

Key Messages

1. Infrared thermography (IRT) for detecting body temperature is less accurate in women, elderly people, and those with fever.
2. The core temperature significantly but weakly correlates to the IRT temperatures obtained from frontal and lateral of the face, and the forehead.
3. Among the three areas, the forehead IRT temperature showed the largest discrepancy and poorest correlation with the core temperature.
4. If IRT is used, the lateral maximum temperature of the face should be used. A cut-off temperature of 36°C gives 77% sensitivity and 74% specificity.
5. Owing to its weak correlation with the core temperature, IRT should not replace direct body temperature measurement in clinical situations.

Introduction

Since the outbreak of severe acute respiratory syndrome, infrared thermography (IRT) systems have been deployed at the airport and border crossings in Hong Kong for screening travellers. However, its use to identify people with elevated body temperature is limited. In a pilot study of 176 subjects,[1] temperatures measured by IRT might be used as a proxy for core temperature, but they are affected by a variety of factors, such as the part of the face measured. We aimed to investigate the effectiveness of IRT to identify people with fever.

Methods

This study was conducted from September 2005 to August 2006. The protocol was approved by the Institutional Review Board of the Hong Kong West Cluster of hospitals. Unselected patients attending the accident and emergency department of the Queen Mary Hospital were invited to participate. Patients on stretchers or needing immediate emergency treatment were excluded. Verbal informed consent was obtained from each subject.

The core temperature was defined as either the oral or aural temperature, or whichever was higher if both were available. At ports and border crossings, the maximum IRT temperatures obtained from the frontal (Areamax) or lateral (Latmax) of the face or the forehead temperature were used as proxies for the core temperature. Ambient temperature, barometric pressure, and humidity were also recorded. The degree of clothing and the time of measurement were noted.

For the study of the effect of distance on IRT readings, temperatures of 31 healthy (afebrile) volunteers were measured in a controlled laboratory setting with the subjects standing at 1, 2, 3, 4 and 5 m from the IRT camera.

The software program ThermaCAM Researcher was used to extract from the IRT temperatures of designated parts of the face. Data analysis was stratified by age and gender. Pearson correlation coefficients between IRT temperatures and oral/tympanic temperature were determined. The 95% confidence limits of agreement of IRT measurements with the reference method were calculated according to the method of Bland and Altman.[2] The standard error of the 95% limit of agreement is approximately $\sqrt{(3s^2/n)}$, where s is the standard deviation of the differences between measurements by the two methods, and n is the sample size.[2] The receiver operator characteristics were determined by plotting the sensitivity against 1-specificity. The sensitivity, specificity, false-positive, and false-negative rates of IRT were calculated. Likelihood ratios, which describe the odds of getting a positive or negative test result, were calculated from the sensitivity and specificity.

Results

A total of 747 men and 770 women consented to participate; 215 of them had a core temperature of ≥37.5°C and were considered to have fever. The forehead IRT temperature showed the largest discrepancy from the core temperature and was on average 3.1°C lower. The Latmax yielded the best correlation with the

core temperature (*r*=0.441), whereas the forehead IRT temperature yielded the poorest correlation (*r*=0.361) [Table 1].

In all subgroups examined, forehead IRT temperature was consistently lower than Latmax or Areamax (Fig 1). The difference between core and IRT temperature was greatest in febrile subjects; the forehead IRT temperature was on average 3.0°C and 3.7°C lower than the core temperature in afebrile and febrile subjects, respectively (Fig 1).

In the Bland-Altman plots of the difference between the IRT and core temperatures against the mean of the IRT and core temperature, IRT temperatures were on average lower than the core temperature. The difference between IRT and core temperatures increased as core temperature decreased (Fig 2).

The subjects were divided into nine age groups (1-2, 3-6, 7-10, 11-19, 20-29, 30-39, 40-49, 50-65, 66-100

years). The best correlation of IRT temperatures with core temperature was seen in children (aged 3-18 years), followed by infants (aged 1-2 years). Male subjects showed better correlation between IRT and core temperatures. The respective correlation coefficients for the three variables of Areamax, Latmax, and Forehead were 0.496, 0.5, and 0.404 for males, and 0.369, 0.385, and 0.323 for females (Table 1). A better correlation was observed in subjects with a core temperature of ≥37.5°C. For subjects with a normal body temperature, the correlation coefficients between the IRT and core temperatures tended to be <0.25.

Ambient temperature had a minor effect on IRT values. Each 1°C change in ambient temperature changed the IRT values by 0.196°C on average.

The sensitivity, specificity, type-I error, and type-II error at different IRT temperatures are tabulated in Table 2. At 36°C, the positive and negative likelihood ratios were 3.97 and 0.39 for the Latmax, respectively.

Table 1. Mean infrared thermographic (IRT) temperatures for the frontal (Areamax) and lateral (Latmax) of the face and the forehead, and correlation coefficients (*r*) etween IRT and core temperatures

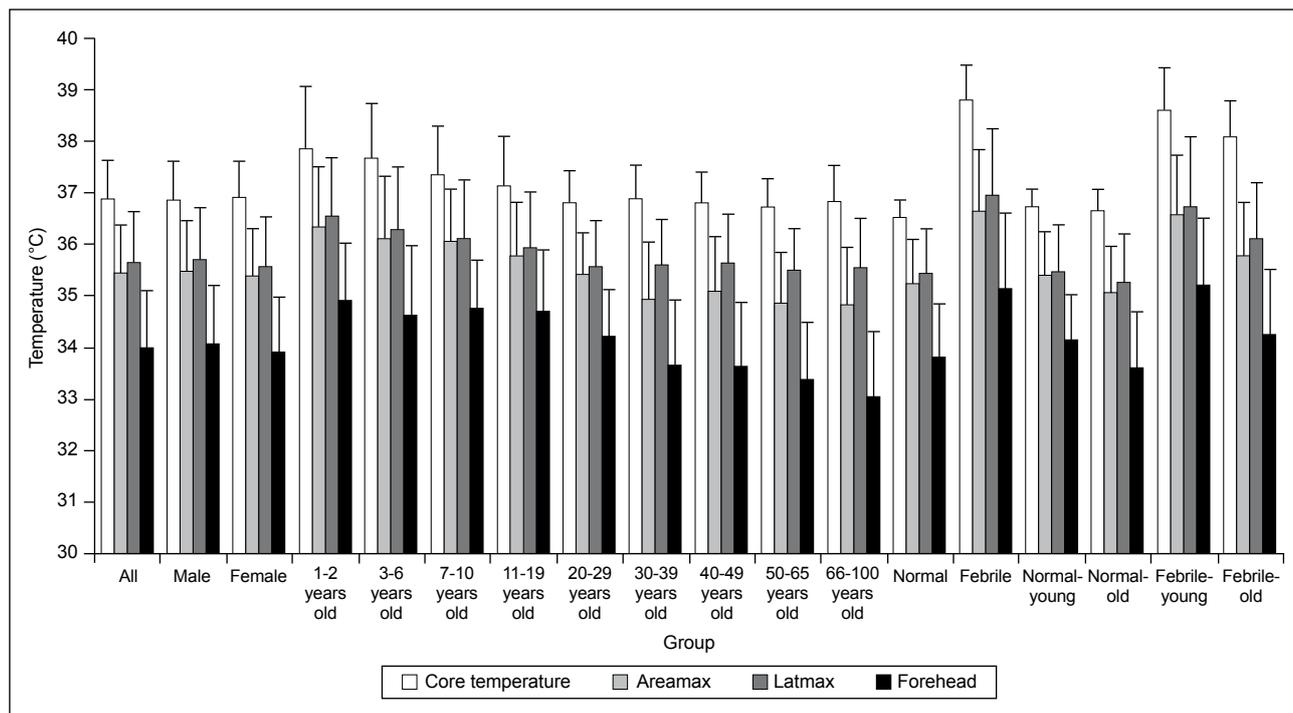| Parameter	Areamax (n=1511)	Latmax (n=1513)	Forehead (n=1509)
Mean±SD IRT temperature (°C)	35.23±0.99	35.43±1.03	33.79±1.15
Mean±SD difference from core temperature (°C)	-1.67±0.93	-1.46±0.96	-3.10±1.11
Mean±SE lower limit of agreement	-3.49±0.04	-3.34±0.04	-5.28±0.04
Mean±SE upper limit of agreement	0.15±0.04	0.42±0.04	-0.92±0.04
r for all	0.434	0.441	0.361
r for males	0.496	0.500	0.404
r for females	0.369	0.385	0.323

Fig 1. Mean and standard deviation of core and infrared thermography temperatures in different subgroups
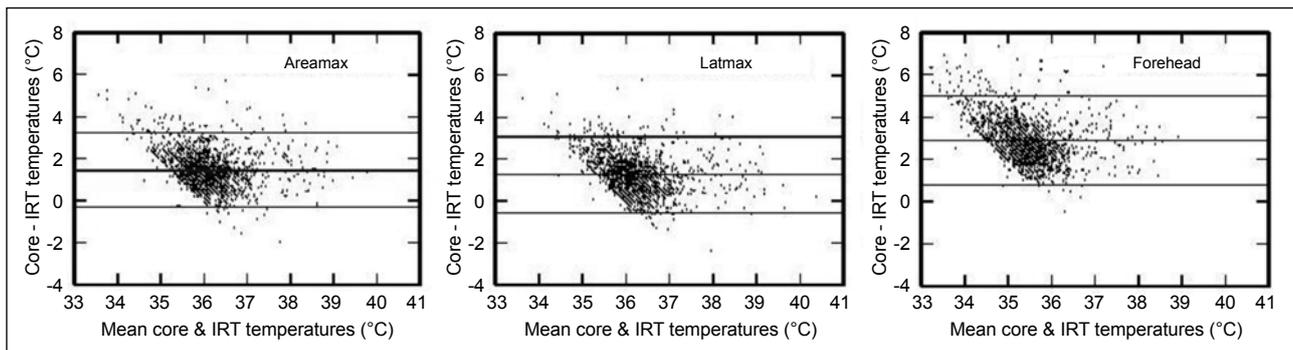
Fig 2. Bland-Altman plots of the difference between core and infrared thermography (IRT) temperatures of the frontal (Areamax) or lateral (Latmax) of the face or the forehead against the means of core and IRT temperatures

Table 2. Sensitivity and specificity of maximum frontal and lateral infrared thermographic (IRT) temperatures

Parameter	Cut-off temperature							
	34°C	34.5°C	35°C	35.5°C	36°C	36.5°C	37°C	37.5°C
Maximum frontal IRT temperature								
Sensitivity	0.97	0.94	0.88	0.79	0.68	0.52	0.40	0.21
Specificity	0.08	0.20	0.39	0.60	0.83	0.96	0.99	1.00
Type-II error, β	0.03	0.06	0.12	0.21	0.32	0.48	0.60	0.79
Type-I error, α	0.92	0.80	0.61	0.40	0.17	0.04	0.01	0.00
False negative rate	0.02	0.02	0.02	0.03	0.03	0.04	0.05	0.06
False positive rate	0.92	0.91	0.90	0.86	0.76	0.51	0.21	0.08
Failing %*	92.0	80.9	63.3	42.8	20.7	7.9	3.7	1.7
Maximum lateral IRT temperature								
Sensitivity	0.97	0.96	0.89	0.85	0.77	0.61	0.46	0.21
Specificity	0.07	0.17	0.31	0.52	0.74	0.90	0.97	1.00
Type-II error, β	0.03	0.04	0.11	0.15	0.23	0.39	0.54	0.79
Type-I error, α	0.93	0.83	0.69	0.48	0.26	0.10	0.03	0.00
False negative rate	0.03	0.02	0.03	0.02	0.02	0.03	0.04	0.06
False positive rate	0.92	0.92	0.91	0.88	0.81	0.67	0.43	0.23
Failing %*	92.9	84.0	70.9	51.0	29.4	13.5	6.1	2.0

* Total percentage of subjects tested positive

Distance between subject and IRT had a significant effect on IRT readings; IRT temperature decreased linearly with distance (p=0.001). Using 1 m as the reference, the IRT temperature was 0.35°C lower at 2 m and 1.1°C lower at 5 m. The IRT temperature decreased on average by 0.26°C per meter of distance.

Discussion

The correlation of IRT temperatures with the core temperature was significant but weak (r<0.45). Gender, age, and core temperature influenced the accuracy of IRT temperature as a proxy for body temperature. Females showed a poorer correlation between IRT and core temperatures. It is not possible to rule out if this was due to cosmetics, as such data were only available on three subjects.

The IRT system seems more accurate in younger age groups, especially children and teenagers.[3-5] The core temperatures were higher in children than adults, perhaps because children with fever were more likely to attend hospital. The core temperatures in the elderly were lower, and their febrile response to infection could be attenuated.

The Bland-Altman analysis showed that IRT temperatures were lower than the core temperature, especially when the core temperature was low. This finding may be useful as it reduces the number of people with a normal core temperature being mistaken for having fever.

The use of forehead IRT temperature as a proxy for the body temperature is questionable.[6] The forehead IRT temperature was lowest among the three IRT temperatures of the face. Its correlation with the core temperature was also lowest. Based on the forehead IRT readings, if 37°C was used as the cut-off temperature for screening, the sensitivity was exceedingly low (4%). Reducing the cut-off temperature to 36°C and 35°C increased the sensitivity to 25% and 52%, respectively. To achieve a sensitivity of about 79%, the cut-off temperature should be lowered to 34°C. This, however, would yield a specificity of 55% and a false positive rate of 88% (88% of those tested positive would actually be afebrile). This would require an unacceptably high percentage (47.8%) of subjects to be retested. Thus, the forehead IRT temperatures are not effective in screening passengers with fever. This casts doubt on the efficacy of using a single-point IRT probe to detect passengers with fever.

When the maximum frontal IRT temperature was used as the screening temperature, a cut-off temperature of 36ºC would yield a sensitivity of 68% and would result in 22.4% of all subjects to fail the screening. This is much better than the forehead IRT temperature in terms of sensitivity and retesting rate. Reducing the cut-off temperature to 35.5ºC would yield a sensitivity of 79% and a specificity of 60%. However, 86% of those tested positive would actually be afebrile and the percentage of subjects failing the screening would increase to 51%.

When the maximum lateral IRT temperature was used as the screening temperature, the same cut-off temperature of 36ºC would yield a sensitivity of 77%, a specificity of 74%, and a false negative rate of 23%. This would be a reasonable setting in terms of sensitivity and false negative rate. However, it would require 29.4% of the subjects to be retested. If the percentage of subjects requiring retesting is a constraining factor, raising the cut-off temperature to 36.5ºC would reduce the percentage of subjects failing the screening to 13.5%. However, the sensitivity would be reduced to 61% and the false negative rate increased to 39%. This may be unacceptable during an epidemic.

The distance between the IRT camera and the subject is a limiting factor on the efficiency. Although the camera can be calibrated for different distances, it is impractical at border crossings and airports to do so. One particular mode of operation compares the maximum detected temperature of travellers passing in front of the camera with the temperature inside a control box kept at a constant temperature. Errors can arise if the subject and the control box are at different distances from the camera.

Conclusions

For the application of IRT in screening for travellers with elevated body temperature at airports and border crossings, the forehead IRT temperature differed substantially from the core temperature, and the maximum lateral IRT temperature should be used. The reading should also be taken at a defined distance from the camera. Overall the sensitivity of IRT in detecting fever is low unless the cut-off temperature is low. When the risk of an epidemic is high and high sensitivity is required, a low cut-off temperature (≤35.5ºC) should be chosen, although a large number of people will require a confirmatory temperature measurement. As IRT is relatively less accurate on women and older people, more sampling for aural measurement should be done on these individuals.

Acknowledgements

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Characterisation of animal angiotensin-converting enzyme 2 receptors and use of pseudotyped virus to correlate receptor binding with susceptibility of SARS-CoV infection

Key Messages

1. Comprehensive surveillance of civets, mice, cats, Golden Syrian hamsters, and horseshoe bats is suggested when SARS or SARS-like CoVs re-emerge in the human population in the future.
2. Rabbits and horseshoe bats are animal carriers of SARS-CoV.
3. Investigation of the genetic diversity of CoV in two bat species (*Rhinolophus sinicus* and *Rhinolophus pearsonii*) should provide insights into the direct ancestor of human SARS-CoV.

Introduction

Civets (*Paguma larvata*) and raccoon dogs (*Nyctereutes procyonoides*) were thought to be the direct zoonotic sources of the severe acute respiratory syndrome (SARS) epidemic in 2003, because the coronaviruses (CoVs) isolated from these mammals were almost identical to the human SARS-CoV.[1] However, these mammals might not be the natural reservoir of SARS-CoV owing to the lack of widespread infections. A diverse group of CoVs were identified in various species of horseshoe bats, which were thus proposed to be the natural reservoir of SARS-CoV.

In experimental infection, a broad range of animals was demonstrated to support *in vivo* replication of SARS-CoV to different extents. Some of these species showed observable pathological signs after inoculation, whereas others showed rapid viral clearance. Based on their ability to support SARS-CoV replication, they may have potential roles in the transmission of SARS-CoV. Susceptibility of host cells to CoVs is mainly determined by spike (S) protein–induced receptor binding and internalisation. Angiotensin I-converting enzyme 2 (ACE2) is a functional receptor for SARS-CoV, acting as a major determinant that restricts the tropism and host range.[2] In particular, the differences among the susceptibility of humans, mice, and rats to SARS-CoV have been correlated to the differential efficiency of interaction between their ACE2 and S protein.[3]

Methods

This study was conducted from January 2007 to December 2008. The ACE2s of 15 different species were prepared. Bagg Albino mouse, Dunkin-Hartley guinea pig, Sprague-Dawley rat, and New Zealand White rabbit were obtained from the Laboratory Animal Unit of the University of Hong Kong. Common domestic cat (*Felis domesticus*), dog (*Canis lupus familiaris*), pig (*Sus scrofa domestica*), and chicken (*Gallus gallus domesticus*) were obtained from the Agriculture, Fisheries and Conservation Department of Hong Kong. Tissues from the small intestines of these animals were harvested after terminal anaesthetisation. Fresh small intestine tissues of the Chinese rufous horseshoe bat (*Rhinolophus sinicus*) and Japanese house bat (*Pipistrellus abramus*) were provided by Dr Susanna PK Lau from the Department of Microbiology of the University of Hong Kong. Fresh small intestine tissues of masked palm civet (*Paguma larvata*), Golden Syrian hamster (*Mesocricetus auratus*), Russian dwarf hamster (*Phodopus campbelli*), and long-tailed chinchilla (*Chinchilla lanigera*) were provided by Prof JD Chen from the South China Agricultural University in Guangzhou, China. Human intestine cDNA was provided from the Department of Medicine, The University of Hong Kong.

The ACE2 of these species was expressed on the surface of the AD293 cell line, which is non-susceptible to SARS-CoV. ACE2-expressing cells were infected by vesicular stomatitis virus (VSV) pseudotyped with the S protein of

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SARS-CoV (VSV-Sh). The relative expression level of ACE2 and the relative susceptibility of ACE2 to VSV-Sh were determined by flow cytometry.

Full-length ACE2-coding sequences were cloned into a mammalian expression vector pCI with a C-terminal V5 epitope-6×His (V5H) tag. These plasmids were transfected and expressed in AD293 cells. Human ACE1 was also cloned and expressed as a negative control.

After transfection, ACE2-expressing cells were harvested and the membrane fraction in 1% Triton X-100 was separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The relative molecular sizes of the ACE2s were revealed in Western blot using AP-anti-V5 antibody after deglycosylation. The percentage of cells expressing ACE2 was quantified using flow cytometry with anti-V5–fluorescein isothiocyanate antibody after fixation and permeabilisation.

The full-length codon-optimised S gene, excluding its cytoplasmic tail (S_{XCT}) derived from HKU-39849, was cloned into a mammalian expression vector pCAGGS. VSV-Sh carrying a green-fluorescent protein (GFP) gene was prepared using the pCAGGS-S_{XCT} and VSV-ΔG*-G. The transfected cells were infected by an equal infectious unit of VSV-Sh after transfection. The percentage of GFP-positive cells was determined using flow cytometry.

Results

The nucleotide sequence similarities of the ACE2s of the 15 species towards human and Chinese rufous horseshoe bat ACE2s are shown in the Table. The ACE2s among the mammalian species were generally conserved with at least 85% identity.

The ACE2 of the 15 species was expressed as demonstrated by their relative molecular sizes shown in Western blot (Fig 1a). The expression level of each ACE2 was determined by flow cytometry and was adjusted by modifying the DNA amount in transfection until a comparable expression level was obtained (Figs 1a & 1b). The surface localisation of the recombinant human ACE2 was demonstrated by flow cytometry analysis on the transfected cell without permeabilisation (Fig 1c).

Efficiencies of the ACE2s as receptors for VSV-Sh were compared based on their relative susceptibility, which is defined as the percentage of VSV-Sh infected cells normalised by the percentage of ACE2-expressing cells calculated from three independent experiments (Fig 2). The 15 ACE2s were categorised into groups I to IV according to their relative susceptibility. Group IV was designated as the unsusceptible group with relative susceptibilities not significantly higher ($P>0.05$) than that of the negative control, ie human ACE1 (Fig 2). Group I included the host species of SARS-CoV, human, and civet. Group II included mouse, Golden Syrian hamster, cat, and Chinese rufous horseshoe bat, showing comparable ($P>0.05$) relative susceptibilities, but these were substantially lower than those of the group I species. Group III included all other species showing relative susceptibilities that were significantly lower ($P<0.05$) than those of group II, but significantly higher ($P<0.05$) than those of group IV.

Discussion

From the results of the infection assay, four groups of ACE2s with differentiated susceptibilities were categorised. Species from the first 2 groups (including human, civet, mouse, cat, Golden Syrian hamster, and horseshoe bat) are expected to support the infection of SARS-CoV. These findings correspond with an *in vivo* infection study, implying that the ACE2 receptor is one of the determining factors for *in vivo* susceptibility that can be extended to other animal studies in the future. Moreover, the potentially susceptible animal species should be under comprehensive

Table. Nucleotide sequence similarity of various angiotensin I-converting enzyme 2 (ACE2) compared with human and *Rhinolophus sinicus* ACE2, respectively

| ACE2 (ranked by relative susceptibility to VSV-Sh)	Length of coding sequence (bp)	DNA similarity to human ACE2 (%)	DNA similarity to horseshoe bat (*R sinicus*) ACE2 (%)	GenBank Accession number
Human	2418	100	88.0	GQ262784
Civet	2418	89.0	89.3	GQ262789
Mouse	2418	90.2	85.7	GQ262785
Golden Syrian hamster	2418	89.8	85.6	GQ262794
Cat	2415	90.3	90.0	GQ262792
Horseshoe bat (*Rhinolophus sinicus*)	2418	88.0	100	GQ262791
Rabbit	2418	91.7	87.5	GQ262787
Guinea pig	2418	86.8	90.0	GQ262786
Dog	2415	90.4	89.7	GQ262793
Japanese house bat	2412	85.6	85.7	GQ262782
Pig	2418	89.4	86.9	GQ262781
Chinchilla	2415	90.2	87.2	GQ262783
Russian dwarf hamster	2418	89.5	85.9	GQ262790
Rat	2418	89.7	85.8	GQ262788
Chicken	2442	71.9	72.5	GQ262780
Rhinolophus pearsonii[4]	2418	88.0	96.7	EF569964
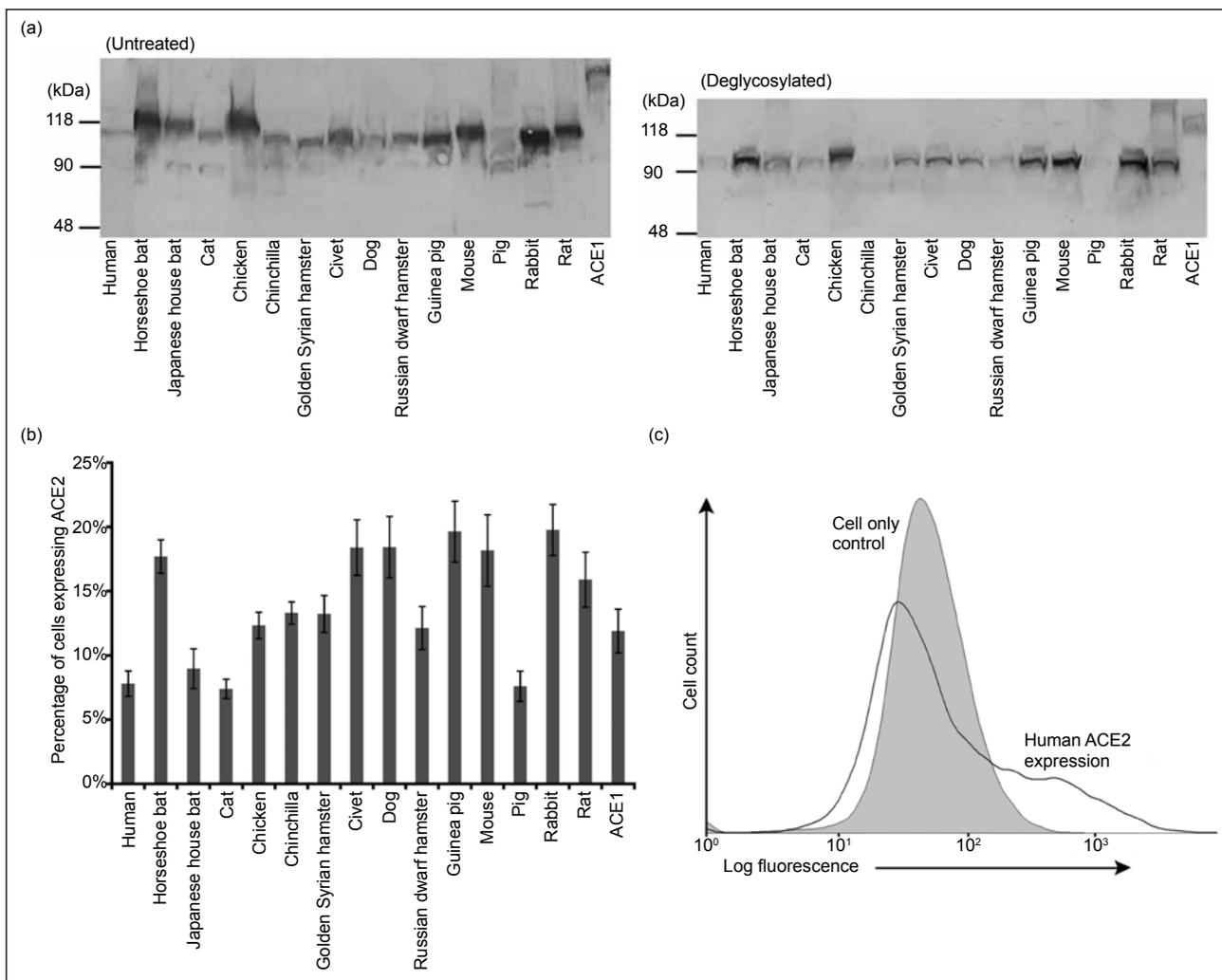
Fig 1. Expression of various angiotensin I-converting enzyme 2 (ACE2) in AD293
(a) Membrane fraction of ACE2-expressing cells analysed in Western blot. (b) Percentage of cells expressing various ACE2s detected in flow cytometry analyses. (c) Cell surface transient expression of human ACE2
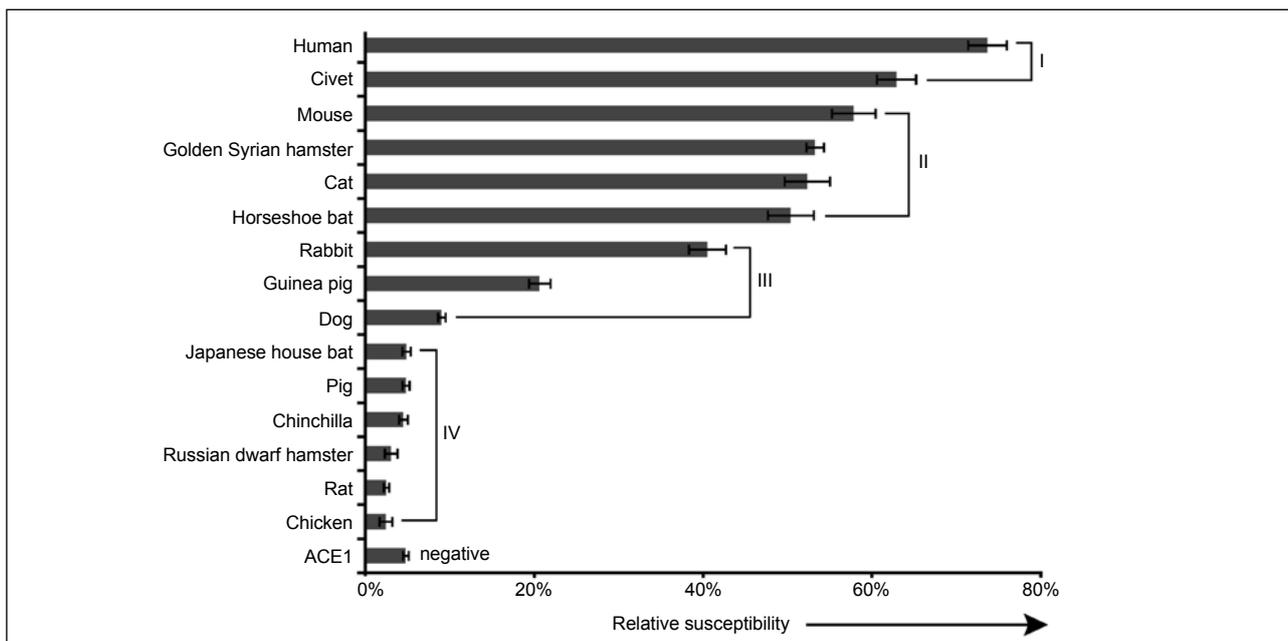

Fig 2. Percentage of VSV-Sh infected cells normalised by the percentage of cells expressing the corresponding angiotensin I-converting enzyme 2 (ACE2) to 100% expression, ie (% of green-fluorescent protein-positive) / (% of ACE2 expression) × 100%

surveillance when SARS or SARS-like CoVs appear in the human population again.

Most species investigated were common consumption and companion animals that intensively interact with humans. It is crucial to assess their potential for being animal vectors for SARS-CoV transmission. Rodents have been proposed as a possible vector for SARS-CoV transmission. The *in vivo* susceptibility of group III animals (chinchilla, Russian dwarf hamster, dog, and rabbit) has not been investigated. Based on the results, the ACE2s of these animals did not seem to support entry of VSV-Sh as efficiently as groups I and II species. Nonetheless, the relative susceptibility of rabbit ACE2 was significantly higher than that of the guinea pig, which was found to inefficiently support *in vivo* replication of SARS-CoV. Thus, SARS-CoV might replicate more efficiently in rabbits than in guinea pigs. The risk that group IV species transmit SARS-CoV may be remote, as none of these species has been shown to efficiently shed virus after experimental inculcation. Although further *in vivo* experiments are needed to confirm such speculations, this study should provide a better scope of investigation for animal vectors of SARS-CoV, particularly of rabbit and Chinese rufous horseshoe bat.

The relative susceptibility of the ACE2 of *R sinicus* was comparable to that of cat, mouse, and Golden Syrian hamster, whereas the ACE2 of Japanese house bat (in this study) and *Rhinolophus pearsonii* (in a previous study[4]) did not seem to support the entry of SARS-CoV S-pseudotyped viruses. These findings imply that the susceptibility of ACE2 towards human SARS-CoV may be species-specific in bats. Further investigations of the ACE2s of different bat species are needed to extend this observation. The susceptibility of *R sinicus* ACE2 towards VSV-Sh implies the potential existence of a bat SARS-like-CoV, which may carry an S protein that shares significant structural homologies with the human SARS-CoV S protein, and may be the direct progenitor of human SARS-CoV. Although the S protein of all currently sampled bat SARS-like-CoV in *R sinicus* is highly divergent from that of human SARS-CoV, the presence of an uncharacterised lineage in *R sinicus* is possible based on the relatively high genetic diversity of bat SARS-like-CoV. Our previous study speculated that the direct progenitor of human SARS-CoV may exist in *R pearsonii* based on the ORF1 phylogeny.[5] Interspecies transmission of CoVs between *Rhinolophus* spp appears to be a common process, suggesting the possibility of coinfection and thus recombination between bat SARS-like-CoVs.

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Voluntary counselling and testing plus information distribution to reduce HIV-related risk behaviours among Hong Kong male cross-border truck drivers: a randomised controlled studyn

Key Messages

1. A randomised controlled trial was conducted to compare the efficacy of voluntary counselling and testing (VCT) plus information distribution versus information distribution alone in 300 Chinese male cross-border truck drivers.

2. Two months after the intervention, participants of the VCT intervention group were more likely to be consistent condom users when having sex with female sex workers and non-regular sex partners, were more knowledgeable about HIV, and were less likely to have contracted a sexually transmitted disease in the past 2 months, compared to the controls.

3. Almost all participants of the intervention group were satisfied with the VCT service, and almost 90% agreed that it would increase their chance of using condoms in the future.

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Introduction

Mobility is a risk factor for the spread of HIV across geographic locations.[1-3] Travellers are more likely to practice HIV-related risk behaviours when they are away from home[4,5] and may become a bridge population transmitting HIV to other populations.[1-3] It is hence warranted to provide HIV intervention services to frequent travellers. Cross-border truck drivers are one of the target groups, as they tend to have HIV-related risk behaviours.[6]

In 2010, there were 4832 reported HIV cases in Hong Kong and about 400 new cases per year, 29% of which were attributed to heterosexual transmission,[7] many of which were suspected to be related to cross-border sexual activities.[7] Respectively, 9-12% and 11-13% of Hong Kong adult men travelling to mainland China had had sex with a female sex worker (FSW) and a female non-regular sex partner (NRP) during the most recent trip.[8] A high prevalence of unprotected sex and sexually transmitted diseases have also been reported in this group.[8] In addition, there are 919 reported HIV/AIDS cases per year in Shenzhen in 2010.[9] Cross-border HIV prevention needs to be strengthened to keep HIV prevalence low in Hong Kong.

With the advancement of rapid HIV testing tools, voluntary counselling and testing (VCT) becomes an important means of HIV prevention.[10] It can be used for case detection and for reducing risk behaviours.[10] Its effectiveness has been mixed, and there have been few randomised controlled trials.[11,12] Evidence-based HIV interventions are lacking. Evidence-based randomised controlled trials are important, as is translation of research results into practice. Collaboration with non-governmental organisations and the Department of Health is necessary for HIV prevention.

Methods

This study was conducted from November 2004 to March 2006. During 2005 and 2006, a randomised controlled trial was carried out to compare the efficacy of VCT plus information distribution versus information distribution alone.

With informed consent, more than 2000 cross-border truck drivers were screened in a cafe (rest area) of the checkpoint while waiting for custom clearance. Of them, 320 were eligible to join the study. They were 18+ years old, self-reported to have had sexual intercourse with either a FSW or a NRP (who was not a FSW, spouse, or girlfriend) in mainland China in the past 12 months. A total of 300 participants were randomised into the intervention group (VCT plus information distribution) or the control group (information distribution alone). The intervention group was given a 30-45 minute VCT intervention, which included the HIV rapid screening test and pre- and post-test counselling. None of the participants tested HIV positive. The primary outcome measures were consistent (every time) condom use during sexual activity with FSW and NRP

in mainland China over a 2-month post-intervention period. Anonymous surveys were conducted before randomisation (baseline) and at month 2, using a computer-assisted interviewing method to reduce bias.[8,13] Absolute and relative risk reduction statistics and their 95% confidence intervals were used to assess treatment effects.[14]

Results

The results have been published in full in AIDS Care.[15] Baseline statistics were not significantly different between the intervention and control groups. At baseline, only about two-thirds of the participants of both groups consistently used condoms during sexual activity with a FSW in mainland China in the past 2 months, and about 30% did so with their NRP.[15] At month 2, participants of the intervention group were more likely to be consistent condom users when having sex with a FSW and NRP, were more knowledgeable about HIV, and were less likely to have contracted sexually transmitted diseases in the past 2 months.[15] Almost all participants of the intervention group were satisfied with the VCT service, and about 90% agreed that it would increase their chance of using condoms in the future.[15]

Discussion

Our target population was at high risk of HIV/STD infection as the prevalence of consistent condom use was low (especially when having sex with a NRP), and the incidence of self-reported sexually transmitted diseases among the controls and within the 2-month post-intervention period was quite high. The results of this study were disseminated to HIV workers and funders in Hong Kong, and one non-governmental organisation successfully applied funding using our findings and implemented an up-scaled VCT service.

This study exemplifies how public health research can be translated into real intervention programmes. Our role as academics is to provide feasible, innovative, and evidence-based models, which can be implemented in a sustainable manner by health organisations or the government. During the research process, it was important to involve non-governmental organisations, the truck drivers' associations and their community leaders, the checkpoint officials, the owner of the cafe (rest area), and the laboratory of the Department of Health in order to provide diagnostic services for positively screened results, if any. We used the healthy setting approach[16] to access the target group at a place that they gather and have time to take up the VCT.

HIV detection is very important for its treatment and control. Some health authorities suggest that HIV antibody testing should be simplified and the counselling component should be reduced or even removed on the grounds that VCT is ineffective in changing risk behaviours.[17] Our studies showed that VCT is effective in reducing risk behaviours,

although the follow-up period was short and the sample size was moderate. Further large-scale studies are warranted.

Acknowledgements

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Prevalence and risk factors of sexually transmitted infections in female sex workers in Hong Kongn

Key Messages

1. The prevalence of hepatitis B surface antigen, syphilis, gonorrhoea, chlamydia, and HIV among the participating female sex workers (FSW) accounted for 8.5%, 1.8%, 1.8%, 4.6%, and 0.2%, respectively.
2. Alcohol consumption, place of origin, a history of termination of pregnancy, higher education level, having multiple partners, and being a non-smoker were risk factors of sexually transmitted infections (STIs) among asymptomatic FSWs.
3. Inconsistent use of condom when having sex with regular partners among FSWs may have a bridging effect in the spread of STIs to other population groups.
4. Continue surveillance of STIs in FSWs in Hong Kong is important. A coherent policy and holistic approach is required to control the spread of STIs in the community.

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Introduction

Sexually transmitted infections (STIs) remain a major public health problem in Hong Kong. Sex workers are reservoirs and vectors for the transmission of STIs in the community. To formulate prevention strategies, the prevalence and risk factors of STIs among asymptomatic female sex workers (FSW) should be determined.

In Hong Kong, STI (including HIV) testing, treatment, and other medical services are available for free to local residents, but non-Hong Kong residents are charged a minimum fee of HK$1400. These high fees deter many non-local FSWs from seeking proper treatment, and may result in the potential spread of STIs to their clients and families.[1] An outreach well-women clinic for FSWs in Hong Kong was established by the non-governmental organisation—Ziteng—in February 2004. In the clinic, Pap smears, STI (including HIV) screening, and basic physical examinations were provided for free to all FSWs. We aimed to report on the prevalence and risk factors of STIs (including HIV) among FSWs in Hong Kong.

Methods

This study was conducted from October 2005 to September 2007. A total of 511 FSWs aged 18 to 55 years were recruited in the clinic of Ziteng between December 2005 and April 2007. It coordinated the screening service including Pap smears and venipunctures for STI (including HIV) testing, provided health education and ensured continuity of care through re-tests and follow-up interviews, conducted outreach and screening services at places where FSWs work. A team of two to three volunteer doctors worked in the clinic to provide medical counselling and care 2 to 3 hours a day, twice monthly.

The subjects remained anonymous and their identification documents were not checked to ensure privacy and confidentiality. They had a face-to-face interview with a doctor or nurse, and HIV pre-test counselling and an opportunistic health education were given. They also underwent a physical examination, Pap smear, and blood tests for detection of gonorrhoea, chlamydia, hepatitis B, syphilis, and HIV infections. Demographics (age, place of origin, and marital status), lifestyle (smoking, drinking, and exercise habits), and sexual behaviour (use of condoms, number of sexual partners, and vaginal douching) were recorded using a multifaceted self-report questionnaire.

After 2 to 4 weeks, the results of these examinations were explained to the patients. If the results were positive, follow-up medical care was arranged and treatment was given based on the Department of Health's STI management guidelines (except for HIV). Follow-up services (prescriptions and referrals) were provided.

Results

A total of 503 FSWs were classified into three groups according to their place of origin: 97 (19.3%) were local; 361 (71.8%) were new immigrants; and 45 (8.9%)

were non-local illegal migrants on a temporary visitor visa (Table 1). Non-local FSWs were younger and less likely to be smoker, whereas local FSWs were less likely to be married and more likely to be smokers. New immigrant and non-local FSWs were more likely to have single child. The prevalence of STI among these FSWs was 43 (8.5%) for hepatitis B surface antigens, 9 (1.8%) for syphilis, 9 (1.8%) for gonorrhoea, 23 (4.6%) for chlamydia, and 1 (0.2%) for HIV infection.

Of these FSWs, 55 (10.9%) worked on the street, 361 (71.8%) in a single-woman brothel, 81 (16.1%) in a sauna or massage parlour, and 6 (1.2%) in a karaoke club or for an agency (Table 2). The street was the most popular place for non-local FSWs (91.1%), whereas single-woman brothels were the most popular place for locals (72.2% of FSWs born in HK and 79.8% of new immigrants). About 57.6% of the FSWs had worked for <1 year. The average number of clients per day was 5.0; new immigrant FSWs received most clients per day.

Twenty (4.0%) of the FSWs had ≥2 regular sexual partners (Table 2); 97.5% and 77.0% of the FSWs reported to have always used condoms when they had vaginal sex and oral sex with their clients, respectively. However, only 23.0% insisted on using condoms when they had sex with their partners. In addition, 56.1% of them performed regular vaginal douching with over-the-counter medicines or water. About 89.5% of FSWs had gynaecological examinations in the past and 70.6% had undergone a cervical smear, with non-local FSWs being significantly less likely to do so. Around 13.1% of FSWs had a history of STIs; new immigrant FSWs were least likely to contract STIs.

Table 1. Demographic and family characteristics of female sex workers

Characteristics	No. (%) of female sex workers				P value
	Total	Local (born in Hong Kong, n=97)	Local (new immigrants, n=361)	Non-local (n=45)	
Age group (years)					<0.01‡
≤25	14 (2.8)	8 (8.2)	1 (0.3)	5 (11.1)	
26-30	57 (11.3)	9 (9.3)	38 (10.5)	10 (22.2)	
31-35	190 (37.8)	30 (30.9)	149 (41.3)	11 (24.4)	
36-40	102 (30.2)	26 (26.8)	115 (31.9)	11 (24.4)	
≥41	90 (17.9)	24 (24.7)	58 (16.1)	8 (17.8)	
Education level					0.32‡
Primary school or below	46 (9.1)	9 (9.3)	32 (8.9)	5 (11.1)	
Low secondary school	344 (68.4)	75 (77.3)	240 (66.5)	29 (64.4)	
High secondary school	94 (18.7)	10 (10.3)	73 (20.2)	11 (24.4)	
University or above	19 (3.8)	3 (3.1)	16 (4.4)	0 (0.0)	
Marital status					<0.01†
Married	265 (52.7)	38 (39.2)	201 (55.7)	26 (57.8)	
Co-habited	3 (0.6)	1 (1.0)	1 (0.3)	1 (2.2)	
Divorced	168 (33.4)	28 (28.9)	131 (36.3)	9 (20.0)	
Single	60 (11.9)	29 (29.9)	23 (6.4)	8 (17.8)	
Widow	7 (1.4)	1 (1.0)	5 (1.4)	1 (2.2)	
No. of children in family					<0.01†
0	110 (21.9)	32 (31.4)	66 (18.5)	12 (26.7)	
1	276 (54.9)	37 (36.3)	216 (60.7)	23 (51.1)	
2	97 (19.3)	26 (25.5)	62 (17.4)	9 (20.0)	
>2	20 (4.0)	7 (6.9)	12 (3.4)	1 (2.2)	
Alcohol drinking					0.05†
Yes	20 (4.0)	8 (9.2)	10 (2.8)	2 (4.4)	
No	483 (96.0)	89 (90.8)	351 (97.2)	43 (95.6)	
Smoking					<0.01*
Yes	167 (33.2)	51 (52.6)	109 (30.2)	7 (15.6)	
No	336 (66.8)	46 (47.4)	252 (69.8)	38 (84.4)	
Hepatitis B					0.19†
Yes	43 (8.5)	5 (5.2)	36 (10.0)	2 (4.4)	
No	460 (91.5)	92 (94.8)	325 (90.0)	43 (95.6)	
Syphilis					0.01†
Yes	9 (1.8)	1 (1.0)	4 (1.1)	4 (8.9)	
No	494 (98.2)	96 (99.0)	357 (98.9)	41 (91.1)	
Gonorrhoea					0.02†
Yes	9 (1.8)	3 (3.1)	3 (0.8)	3 (6.7)	
No	494 (98.2)	94 (96.9)	358 (99.2)	42 (93.3)	
Chlamydia infection					0.10†
Yes	23 (4.6)	8 (8.2)	12 (3.3)	3 (6.7)	
No	480 (55.4)	89 (91.8)	349 (96.7)	42 (93.3)	
HIV infection					0.10†
Yes	1 (0.2)	0 (0.0)	0 (0.0)	1 (2.2)g	
No	502 (99.8)	97 (100.0)	361 (100.0)	44 (97.8)	

* Chi squared test
† Chi square computed by Monte Carlo method for non-2x2 table, in which at least one cell has expected cell count of <5
‡ Chi squared linear-by-linear association test computed by Monte Carlo method, in which at least one cell has expected cell count of <5

Table 2. Sexual ehaviour and working conditions of female sex workers

Characteristics	No. (%) of female sex workers				P value
	Total	Local (born in Hong Kong, n=97)	Local (new immigrants, n=361)	Non-local (n=45)	
Working place					<0.01†
Street	55 (10.9)	4 (4.1)	10 (2.8)	41 (91.1)	
Single woman brothel	361 (71.8)	70 (72.2)	288 (79.8)	3 (6.7)	
Karaoke club	5 (1.0)	2 (2.1)	3 (0.8)	0 (0.0)	
Sauna or massage	1 (0.2)	21 (21.6)	60 (16.6)	0 (0.0)	
Call or hotel	81 (16.1)	0 (0.0)	0 (0.0)	1 (2.2)	
Time in sex work					<0.01‡
≤3 months	93 (18.5)	5 (5.2)	77 (21.3)	11 (24.4)	
3 months to <1 year	197 (39.1)	41 (42.3)	135 (37.4)	21 (46.7)	
1 to <2 years	122 (24.3)	19 (19.6)	94 (26.0)	9 (20.0)	
2 to <3 years	37 (7.4)	7 (7.2)	28 (7.8)	2 (4.4)	
≥3 years	54 (10.7)	25 (25.8)	27 (7.5)	2 (4.4)	
Average no. of clients per day	5.0	4.6	5.1	4.1	0.01§
No. of sexual partners					0.02‡
0	122 (24.2)	30 (30.9)	87 (24.1)	5 (11.1)	
1	361 (71.8)	61 (62.9)	264 (73.1)	36 (81.8)	
≥2	20 (4.0)	6 (6.2)	10 (2.8)	4 (9.1)	
Condom use (vaginal sex)					0.13†
Always	474 (97.5)	91 (97.8)	343 (98.0)	40 (93.0)	
Not always	12 (2.5)	2 (2.2)	7 (2.0)	3 (7.0)	
Condom use (oral sex)					<0.01†
Always	362 (77.0)	61 (66.3)	266 (78.2)	35 (92.1)	
Not always	108 (23.0)	31 (33.7)	74 (21.8)	3 (7.9)	
Condom use with partner					0.25*
Always	88 (23.0)	17 (25.4)	66 (17.6)	5 (12.5)	
Not always	294 (77.0)	50 (74.6)	208 (82.4)	35 (87.5)	
Vaginal douching					0.38‡
Everyday	72 (14.3)	11 (11.3)	52 (14.4)	9 (20.0)	
Weekly	76 (15.1)	10 (10.3)	57 (15.8)	9 (20.0)	
Monthly	129 (25.6)	28 (28.9)	94 (26.0)	7 (15.6)	
Occasionally	5 (1.1)	0 (0.0)	5 (1.4)	0 (0.0)	
No	221 (43.9)	48 (49.5)	153 (42.4)	20 (44.4)	
Knowledge on human papillomavirus and cervical cancer					0.75†
Known	16 (3.2)	2 (2.1)	12 (3.3)	2 (4.4)	
Unknown	487 (96.8)	95 (97.9)	349 (96.7)	43 (95.6)	
Human papillomavirus vaccine					0.22†
Income of one day	461 (91.7)	86 (88.7)	331 (91.7)	44 (97.8)	
Income of a week	42 (8.3)	11 (11.3)	30 (8.3)	1 (2.2)	
Previous gynaecological examination					<0.01*
Yes	450 (89.5)	87 (89.7)	331 (91.7)	32 (71.1)	
No	53 (10.5)	10 (10.3)	30 (8.3)	13 (28.9)	
Previous Pap smear					<0.01*
Yes	355 (70.6)	75 (77.3)	266 (73.7)	14 (31.1)	
No	148 (29.4)	22 (22.7)	95 (26.3)	31 (68.9)	
Previous sexually transmitted infection					0.01*
Yes	66 (13.1)	21 (21.6)	37 (10.2)	5 (11.9)	
No	437 (86.9)	76 (78.4)	324 (89.8)	37 (88.1)	
Previous sexually transmitted infection in those with previous gynaecological examination					0.01†
Yes	59 (13.1)	19 (21.8)	33 (10.0)	7 (21.9)	
No	391 (86.9)	68 (78.2)	298 (90.0)	25 (78.1)	
Age of first sex (years)					0.03‡
12-14	4 (0.8)	3 (3.1)	0 (0.0)	1 (2.2)	
15-17	130 (25.8)	34 (35.1)	82 (22.7)	14 (31.1)	
18-20	278 (55.3)	48 (49.5)	209 (57.9)	21 (46.7)	
21-23	69 (13.7)	9 (9.3)	53 (14.7)	7 (15.6)	
24-26	20 (4.0)	3 (3.1)	15 (4.2)	2 (4.4)	
>26	2 (0.4)	0 (0.0)	2 (0.6)	0 (0.0)	

* Chi squared test
† Chi square computed by Monte Carlo method for non-2x2 table, in which at least one cell has expected cell count of <5
‡ Chi squared linear-by-linear association test computed by Monte Carlo method, in which at least one cell has expected cell count of <5
§ Kruskal Wallis test

Regarding risk factors for STIs, syphilis and gonorrhoea were more common in non-local FSWs (Table 3). The FSWs who had ≥2 sexual partners were more likely to have gonorrhoea infection, whereas those who had a higher level of education had a higher risk of contracting chlamydia. Previous termination of pregnancy was associated with contracting syphilis. Hepatitis B infection was associated with being a non-smoker.

Table 3. Demographic features significantly associated with specific sexually transmitted infections

Demographic feature	Sexually transmitted infection		P value
	No	Yes	
Hepatitis B			
Smoking			0.02*
Yes	160 (95.8)	7 (4.2)	
No	300 (89.3)	36 (10.7)	
Syphilis			
No. of abortion			0.02†
0	91 (97.8)	2 (2.2)	
1	90 (94.7)	5 (5.3)	
2	139 (98.6)	2 (1.4)	
>2	174 (100.0)	0 (0.0)	
Gonorrhoea			
No. of sexual partners			<0.01†
0	121 (99.2)	1 (0.8)	
1	357 (98.9)	4 (1.1)	
≥2	16 (80.0)	4 (20.0)	
Place of origin			0.02*
Local	94 (96.9)	3 (3.1)	
Local (new immigrants)	358 (99.2)	3 (0.8)	
Non-local	42 (93.3)	3 (6.7)	
Chlamydia Infection			
Education level			0.04‡
Primary or below	46 (100.0)	0 (0.0)	
Low secondary	328 (95.3)	16 (4.7)	
High secondary	90 (95.7)	4 (4.3)	
University or above	16 (84.2)	3 (15.8)	

* Fisher's exact test for 2x2 table
† Chi squared linear-by-linear association test computed by Monte Carlo method, in which at least one cell has expected cell count of <5
‡ Chi square computed by Monte Carlo method for non-2x2 table, in which at least one cell has expected cell count of <5

Discussion

Of 503 FSWs, 71.8% were from single-woman brothels. Only 19.3% were born in Hong Kong, whereas most street FSWs were non-local illegal migrants. They received an average of five clients per day; of whom 97.5% claimed to have used condoms consistently. Nonetheless, condom use with regular sexual partners remained low at 23.0%. Hepatitis B surface antigen, syphilis, gonorrhoea, chlamydia, and HIV infections were present in 8.5%, 1.8%, 1.8%, 4.6%, and 0.2% of our sample, respectively. The risk factors for STIs among asymptomatic FSWs were place of origin, a history of termination of pregnancy, higher education level, having multiple partners, and being a non-smoker.

One limitation of this study was that our sample included only those who were willing to engage with Ziteng and was not representative of all FSWs in Hong Kong. This group of FSWs was no doubt more health conscious; the actual STI rate in the general population FSWs is likely to be higher. Moreover, this cross-sectional study was unable to identify the specific timing and relationships of our participants' responses and their STIs. Causal relationships between STIs and various risk factors should be inferred carefully.

In comparison with FSWs who had attended the Social Hygiene Service from 1999 to 2000,[2] the rate of chlamydia was significantly lower in our cohorts (41.7% vs 4.6% had non-specific urethritis). The rates of gonorrhoea were consistent (1.5% vs 1.8%), but those of HIV (0.1% vs 0.2%) and syphilis (0.1% vs 1.8%) were significantly higher in our sample. These increases could be due to the time gap between the two studies. Currently, hepatitis B and HIV are the only STIs that have to be reported according to the Quarantine and Prevention of Disease Ordinance. It is of public health interest to consider the inclusion of other STIs or to conduct a continuous serial surveillance other than the sentinel surveillance.

Condom use with regular sexual partners was infrequent (23.0%) among FSWs. This was consistent with a recent systematic review reporting a proportion of 8% to 30%.[3] The concept of a partner appeared rather unclear in this group. It could refer to a husband in a formal marriage, co-inhabitants, frequent customers, or whoever they feel attached to. In our sample, 4% of FSWs reported having ≥2 partners, but this figure may be an under-estimate. This may have a bridging effect for the spread of STI to other population groups, especially clients and their families.

Alcohol consumption and multiple partners are known risk factors. Unexpectedly, higher education level and not smoking were correlates of chlamydia and Hepatitis B infections, respectively. These may be due to an unrealistic optimism regarding their physical well being, and thus less concern about adopting various health protection measures. More research is necessary to explore this argument.

Medical professionals and public health specialists should address these misconceptions through education and prevention activities, which should focus on the promotion of consistent condom use and awareness of the risks of STIs. Nonetheless, education alone may not be sufficient, as FSWs already have good awareness and appropriate attitudes towards protective behaviours, but have difficulty translating them into action. Therefore, the World Health Organization's holistic approach to sexual health (the integration of the somatic, emotional, intellectual, and social aspects of sexual well-being in ways that are positively enriching and that enhance personality, communication, and love) should be adopted.[4]

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AUTHOR INDEX