



Big data analytics in paediatric research

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Acknowledgement

- Research Grant from the Food and Health Bureau, The Government of the Hong Kong Special Administrative Region (Ref. No. COVID19F01. Total:1.1million Euros)
- Colleagues from the Drug Office of the Department of Health, and Hospital Authority for providing vaccination and clinical data
- “COVID-19 Vaccine Response and Evaluation (CARE) programme” research team



COVID-19 Vaccines Adverse
Events Response and
Evaluation (CARE) Programme

Contents



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- Background and introduction to “COVID-19 Vaccine Response and Evaluation (CARE) programme”
- Examples of using big data analytics to evaluate carditis following BNT162b2 vaccination in children
- Summary

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Background

- The Prevention and Control of Disease (Use of Vaccines)
Regulation allows emergency use COVID-19 vaccine in Hong Kong.
- Pharmacovigilance programme is needed to monitor safety of COVID-19 vaccines.
 - CoronaVac from Sinovac Biotech (Hong Kong) Limited
 - BNT162b2 (Comirnaty) from BioNTech



Background

- CARE Programme is part of the enhanced pharmacovigilance plan of Department of Health and led by Department of Pharmacology and Pharmacy at the University of Hong Kong
 - A three-year research programme
 - Started with COVID-19 vaccination programme in February 2021
 - HK\$10million ~ US\$1.3million or €1.2 million

Overview

• **Part 1:** Background rates of adverse events of special interest (AESI) for monitoring COVID-19 vaccines

• **Part 2:** Active surveillance of AESI

• **Part 3:** To evaluate the safety of COVID-19 vaccines using electronic health records: record-linkage study

- Medical record

- Medical record

- Immunization record

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- **Examples of using big data analytics to evaluate carditis following BNT162b2 vaccination in children**
- Summary

Introduction

- Carditis is rare and mostly self-limiting
- Incidence rate of myocarditis: $\sim 20 / 100,000$ person-year
- Case reports of carditis following the use of BNT162b2 (Pfizer-BioNtech) are rapidly accruing worldwide
- Significant proportion of these reports described younger male individuals after receiving the 2nd dose
- Recent Israeli cohort study of nearly 1M individuals reported an elevated risk of myocarditis $RR = 3.24$ (95% CI: 1.55, 12.44)



Data collection

- Vaccination data were collected from June 14 to September 4 from the HK Department of Health of all adolescents aged 12 to 17
- Cases of myocarditis/pericarditis were identified using the Advanced Incident Reporting System (AIRS) from the Hospital Authority
- Cases were then confirmed cases using the definition Cardiovascular Injury-Coalition for Epidemic Preparedness Innovations (CEPI) and the Brighton Working Group definition
- Myocarditis/pericarditis were identified as associated with vaccination if events were within 14 days of either first or second vaccination

Data collection – Background rate comparison

- Years: 2011- 2020 yearly average
- Background rates of myocarditis/pericarditis were collected from June 14 to September 4 from the CDARS (anonymised electronic medical records system) of all adolescents aged 12 to 17
- Incidence were calculated per person per 14 days to make a fair comparison with vaccination incidence
- Denominator of incidence was using of census and statistics department for population of 12-17 year olds

Results



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- 178,163 adolescents vaccinated with BNT162b2 in Hong Kong.
- Thirty-three cases of acute myocarditis/pericarditis following vaccination
- The overall reporting rate of acute carditis was 18.52 (95% CI 11.67-29.01) per 100,000 vaccine recipients
 - First dose = 3.37 (1.12-9.51)
 - Second dose = 21.22 (13.78-32.28) (6X higher than 1st dose)

Results – Other background incidence years

- Overall incidence by gender compared to 2011-2020 average

	Incidence rate (per 100,000 person-14 days, 95% CI)	Mean background incidence rate of same age group in 2011-2020 (per 100,000 person-14 days, 95% CI)	Incidence rate difference (per 100,000 person-14 days, 95%CI)
Total	18.52 (11.67-29.01)	0.15 (0.01-14.09)	18.37 (9.90-26.84)
Male	32.29 (22.78-45.4)	0.25 (0.01-9.11)	32.04 (20.86-43.22)
Female	4.53 (1.76-11.11)	0.06 (0.01-53.73)	4.47 (0.27-8.67)

Discussion

- The reported rate is much higher than background incidence after adjusted for gender and follow-up time.
 - Using big data analytic, we identified carditis was very rare event for the last 10 years in teenagers.

Discussion

- The overall incidence of acute carditis in male adolescents in HK was 18.52 (95% CI: 11.67-29.01) per 100,000 persons vaccinated.
 - First dose = 5.57 (95% CI 2.38-12.53)
 - Second dose = 37.32 (95% CI 26.98-51.25)

Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination

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Background. Age-specific incidence of acute myocarditis/pericarditis in adolescents following Comirnaty vaccination in Asia is lacking. This study aimed to study the clinical characteristics and incidence of acute myocarditis/pericarditis among Hong Kong

Policy implications

- Hong Kong had very low infection rate during the study period
 - Relatively less direct benefit
 - Risk and benefit ratio will shift toward risk minimisation
- Joint Scientific Committee recommended single dose
 - At least 12 weeks apart



Evaluation of the effect of policy change

- The cumulative incidence of carditis declined from 43 cases in 202,315 adolescents vaccinated (21.25 per 100,000 persons 95% CI: 15.57-28.91) to zero cases in 22,245 adolescents vaccinated, upon the implementation of single-dose policy - constituting a statistically significant difference ($P = 0.0194$).
- Very effective

JAMA Pediatrics

RESEARCH LETTER

Myocarditis Following COVID-19 BNT162b2 Vaccination Among Adolescents in Hong Kong

Cases of myocarditis following the second dose of messenger RNA (mRNA) vaccine are accruing worldwide, especially in younger male adults and adolescents.¹⁻⁴ In weighing the risk of myocarditis against the benefit of preventing severe



Supplemental content

COVID-19, Norway, the UK, and Taiwan have suspended the second dose of mRNA vaccine for adolescents. Similarly, adolescents (aged 12-17 years) in Hong Kong have been recommended to receive 1 dose of BNT162b2 instead of 2 doses 21 days apart since September 15, 2021 (Figure).

15.51-30.67) per 100 000 persons for the first and second dose, respectively (Table). The number needed to harm for the first and second dose were 32 051 and 4515, respectively. The crude risk ratio of the second dose vs first dose was 7.11 (95% CI, 3.16-15.97). The cumulative incidence of myocarditis decreased from 43 cases in 202 315 adolescents vaccinated (21.25, 95% CI, 15.38-28.63) per 100 000 persons to 0 cases in 22 245 adolescents vaccinated at implementation of the single-dose policy. The 40 167 prepolicy first dose recipients did not receive the second dose because of the single-dose policy. Based on the number needed to harm of the second dose, an estimated 8.90 (95% CI, 6.23-12.32) myocarditis cases were prevented.

Discussion | In this cohort study, the single-dose regimen was found to be associated with reduction in myocarditis risk

Continuous monitoring

- However, subsequent 5th wave has changed the risk and benefit ratio:
 - The first two doses of the BioNTech vaccine were shortened from 12 weeks to 8 weeks in March.

Is the extended interval
effectiveness?

Overview

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NEWS

HEALTHCARE | STAFF REPORTER, HONG KONG

© PUBLISHED: 26 SEP 18 👁 3770 VIEW(S)



Hong Kong's healthcare system beats Singapore as the world's most efficient: Bloomberg

Absolute healthcare cost in the SAR stands at US\$2,222.

Hong Kong has once again beat Singapore, Japan and Norway for the title of the most efficient healthcare system in the world, according to the Bloomberg Health Care Efficiency Index.

Hong Kong public healthcare system

- Hong Kong Hospital Authority is the sole public-funded acute healthcare provider of Hong Kong.
- HA is serving a population of over seven million through 42 hospitals, 47 Specialist Outpatient Clinics, and 73 General Outpatient Clinics.
- Heavily subsidized system.
 - Highly popular

Hong Kong public healthcare system

- Hong Kong Hospital Authority (HA) has developed a comprehensive electronic medical record system.
 - Single unique electronic medical record for each resident
- Unified system link up data from all 42 HA hospitals, 47 Specialist Outpatient Clinics, and 73 General Outpatient Clinics.
 - All data are stored in one single system
 - It aims for clinical management
 - Transfer data to “Clinical Data Analysis and Reporting System” (CDARS) database for audit and research

Clinical Data Analysis & Reporting System database

- Diagnosis and procedures
- Drug prescribing and dispensing history
- Admission and discharge details
- Laboratory and pathology results
- Mother and baby link
- Currently contains 11 million people data

Is the extended interval effectiveness?

- A population-based nested case-control study of children and adolescents aged 5–17 years who had received two doses of BNT162b2.
- From January 1 to August 15, 2022, 5396 Covid-19 cases and 202 Covid-19 related hospitalizations were identified and matched with 21,577 and 808 controls, respectively.
- Extended dose recipients 29.2%-reduced risk of Covid-19 infection compared to those with regular intervals (21–27 days).
 - More effective, longer dosing intervals for children and adolescents should be considered.




Effectiveness of BNT162b2 after extending the primary series dosing interval in children and adolescents aged 5–17

Received: 6 January 2023

Accepted: 21 March 2023

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 Check for updates

Francisco Tsz Tsun Lai^{1,2,7}, Min Fan^{1,7}, Caige Huang¹, Celine Sze Ling Chui^{2,3,4}, Eric Yuk Fai Wan^{1,2,5}, Xue Li^{1,2,6}, Carlos King Ho Wong^{1,2,5}, Ching-Lung Cheung¹, Ian Chi Kei Wong^{1,8} ✉ & Esther Wai Yin Chan^{1,2,8} ✉

Extended intervals between the first and second doses of mRNA Covid-19 vaccines may reduce the risk of myocarditis in children and adolescents. However, vaccine effectiveness after this extension remains unclear. To examine this potential variable effectiveness, we conducted a population-based nested case-control study of children and adolescents aged 5–17 years who had received two doses of BNT162b2 in Hong Kong. From January 1 to

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COVID-19 Vaccines Adverse
Events Response and
Evaluation (CARE) Programme

Summary

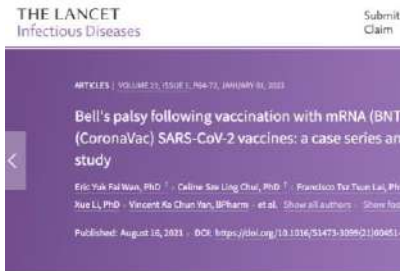
- Based on our pharmacovigilance study using big data analytic, the regulatory authority in Hong Kong assessed risk and benefit ratio of vaccination and developed evidence-based policies for child vaccination programme.

COVID vaccine Publication Highlights



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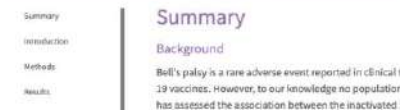
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THE LANCET INFECTIOUS DISEASES

IMPACT FACTOR = 71

Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study



NATURE COMMUNICATIONS

IMPACT FACTOR = 17.6

Multimorbidity and adverse events of special interest associated with Covid-19 vaccines in Hong Kong



JAMA Pediatrics

Myocarditis Following COVID-19 BNT162b2 Vaccination Among Adolescents in Hong Kong

Cases of myocarditis following the second dose of messenger RNA (mRNA) vaccine are accruing worldwide, especially in younger male adults and adolescents.¹⁻⁴ In weighing the risk of myocarditis against the benefit of preventing severe COVID-19, Norway, the UK, and Taiwan have suspended the second dose of mRNA vaccine for adolescents. Similarly, adolescents (aged 12-17 years) in Hong Kong have been recommended to receive 1 dose of BNT162b2 instead of 2 doses 21 days apart since September 15, 2021 (Figure).

Methods | This cohort study was conducted before the arrival of the Omicron variant. We linked vaccination records with the Hong Kong territorywide electronic health record database through government-commissioned population-based COVID-19 vaccine safety surveillance.³ Among adolescents who received at least 1 dose of BNT162b2 between March 10 and October 18, 2021, inpatient myocarditis cases were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (422.x and 429.0). Adolescents with a history of myocarditis were excluded. The study was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster and the Department of Health Ethics Committee with a waiver of informed consent because anonymized data

JAMA PEDIATRICS

IMPACT FACTOR = 26.8

Myocarditis Following COVID-19 BNT162b2 Vaccination Among Adolescents in Hong Kong

Annals of Internal Medicine

LATEST ISSUES IN THE CLINIC JOURNAL CLUB MULTIMEDIA CME/ MOC AUTHOR/ EDITOR

Carditis After COVID-19 Vaccination With Messenger RNA Vaccine and an Inactivated Vaccine

A Case-Control Study

Francisco Tsz Tsun Lai, PhD¹, Rui Li, PhD², Kuen Peng MSc, Lei Hsiang MSc, ... See More
Author, Article and Disclosure Information
<https://doi.org/10.7326/M21-3700>
#jgline for CME, JGIM, or JGIA

Background:

Case reports of carditis after BNT162b2 vaccination are accruing

ANNALS OF INTERNAL MEDICINE

IMPACT FACTOR = 51.6

Carditis following Covid-19 vaccination with messenger RNA vaccine (BNT162b2) and inactivated virus vaccine (CoronaVac): a nested case-control study



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Introduction to our research team and research themes



Children Mental Health

Lancet Psychiatry

Long-term safety of methylphenidate in children and adolescents with ADHD: 2-year outcomes of the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study



Kenneth K C Man*, Alexander Häge*, Tobias Banaschewski*, Sarah K Inglis, Jan Buitelaar, Sara Carucci, Marina Danckaerts, Ralf W Dittmann, Bruno Falissard, Peter Garas, Chris Hollis, Kerstin Konrad, Hanna Kovshoff, Elizabeth Liddle, Suzanne McCarthy, Antje Neubert, Peter Nagy, Eric Rosenthal, Edmund J S Sonuga-Barke, Alessandro Zuddas†, Ian C K Wong‡, David Coghill‡, on behalf of the ADDUCE Consortium

Summary

Background Methylphenidate is the most frequently prescribed medication for the treatment of ADHD in children and adolescents in many countries. Although many randomised controlled trials support short-term efficacy, tolerability, and safety, data on long-term safety and tolerability are scarce. The aim of this study was to investigate the safety of methylphenidate over a 2-year period in relation to growth and development, psychiatric health, neurological health, and cardiovascular function in children and adolescents.

Methods We conducted a naturalistic, longitudinal, controlled study as part of the ADDUCE research programme in 27 European child and adolescent mental health centres in the UK, Germany, Switzerland, Italy, and Hungary.

Lancet Psychiatry 2023
Published Online
March 20, 2023
[https://doi.org/10.1016/S2215-0366\(23\)00042-1](https://doi.org/10.1016/S2215-0366(23)00042-1)
See Online/Comment
[https://doi.org/10.1016/S2215-0366\(23\)00092-5](https://doi.org/10.1016/S2215-0366(23)00092-5)
*Joint first authors

Lancet Psychiatry

Psychotropic medicine consumption in 65 countries and regions, 2008–19: a longitudinal study

Ruth Brauer, Basmah Alfageh, Joseph E Blais, Esther W Chan, Celine S L Chui, Joseph F Hayes, Kenneth K C Man, Wallis C Y Lau, Vincent K C Ya Maedeh Y Beykloo, Zixuan Wang, Li Wei, Ian C K Wong

Summary

Background The WHO Comprehensive Mental Health Action Plan 2013–2030 encourages routine collection reporting of a set of essential mental health indicators, including the availability of psychotropic medicines. global monitoring of country-level psychotropic medicine consumption trends can provide information on the of the availability of psychotropic medicines. The primary objective of this study was to investigate global trend psychotropic medicines consumption from 2008 to 2019 across 65 countries and regions according to country inc level and geographical region.

Methods In this longitudinal trends study, we used pharmaceutical sales data from the IQVIA-Multinational Integri Data Analysis System (IQVIA-MIDAS). We analysed monthly sales data of psychotropic medicines betw Jan 1, 2008, and Dec 31, 2019. Total psychotropic medicine consumption included sales of antidepressants, antipsych tranquilisers, sedatives or hypnotics, and mood stabilisers. Population estimates of each country or region (eight lo middle-income countries, 19 upper-middle-income countries, and 38 high-income countries) were based on the

Lancet Child and Adolescent Health

Association between methylphenidate treatment and risk of seizure: a population-based, self-controlled case-series study



Kenneth K C Man, Wallis C Y Lau, David Coghill, Frank M C Besag, J Helen Cross, Patrick Ip, Ian C K Wong

Summary

Background Individuals with attention-deficit hyperactivity disorder (ADHD) are at increased risk of seizures. Stimulant medications such as methylphenidate are the most commonly prescribed treatment for ADHD, but the association between their therapeutic use and the risk of seizures is unclear. We aimed to investigate the association between methylphenidate treatment and the risk of seizure.

Methods For this population-based observational study, we used the electronic medical record database of the Hong Kong Clinical Data Analysis And Reporting System to identify individuals aged 6–25 years who received at least one methylphenidate prescription during the study period. Individuals with records of seizure or epilepsy before the

Lancet Child Adolesc Health
2023; 4: 435–43

See [Comment](#) page 409

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Research

JAMA Psychiatry | [Original Investigation](#)

Association of Risk of Suicide Attempts With Methylphenidate Treatment

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IMPORTANCE Patients with attention-deficit/hyperactivity disorder (ADHD) are at an increased risk of attempting suicide. Stimulants, such as methylphenidate hydrochloride, are the most common treatment for ADHD, but the association between their therapeutic use and suicide is unclear.

[+](#) Supplemental content

Maternal health and outcomes of children

nature medicine



Article

<https://doi.org/10.1038/s41591-024-02917-8>

Maternal diabetes and risk of attention-deficit/hyperactivity disorder in offspring in a multinational cohort of 3.6 million mother–child pairs

Received: 11 September 2022 | A list of authors and their affiliations appears at the end of the paper
Research

JAMA Internal Medicine | Original Investigation

Association Between Prenatal Exposure to Antipsychotics and Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, Preterm Birth, and Small for Gestational Age

Zixuan Wang, MSc; Adrienne Y. L. Chan, MPH; David Coghill, MD; Patrick Ip, MPH; Wallis C. Y. Lau, PhD; Emily Simonoff, MD; Ruth Brauer, PhD; Li Wei, PhD; Ian C. K. Wong, PhD; Kenneth K. C. Man, PhD

IMPORTANCE The risk of birth and neurodevelopmental complications with prenatal exposure to antipsychotics is unclear.

OBJECTIVE To evaluate the association between prenatal antipsychotics exposure and the risk of birth and neurodevelopmental problems.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study included children born between January 2001 and January 2015 with follow-up to December 2019 who were identified by the Hong Kong Clinical Data Analysis and Reporting System. Pregnancies with maternal antidepressant/lithium exposure were removed. Primary analyses compared gestationally exposed and gestationally nonexposed individuals with propensity score fine stratification. Additional analyses included gestationally exposed individuals vs those with past exposure and a sibling-matched analysis to evaluate the effect of confounding by indication.

EXPOSURES Prenatal antipsychotic exposure.

MAIN OUTCOMES AND MEASURES Preterm birth (<37 gestational weeks), small for gestational age (birth weight <2 standard deviations below the mean for gestational age), and first diagnosis of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in children.

RESULTS The cohorts included 333 749 mother-child pairs for ADHD (mean [SD] maternal

- Invited Commentary
- Multimedia
- Supplemental content

BMJ

RESEARCH

OPEN ACCESS

Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study

Kenneth K C Man,^{1,2,3,4} Esther W Chan,¹ Patrick Ip,² David Coghill,^{5,6} Emily Simonoff,⁷ Phyllis K L Chan,⁸ Wallis C Y Lau,¹ Martijn J Schuemie,⁹ Miriam C J M Sturkenboom,⁴ Ian C K Wong^{1,2,3}

For numbered affiliations see end of article.

Correspondence to: I C K

ABSTRACT
OBJECTIVE

To assess the potential association between prenatal

to 2.30, $P < 0.01$). The risk of ADHD in the children of mothers with psychiatric disorders was higher compared with the children of mothers without

nature human behaviour



Article

<https://doi.org/10.1038/s41562-023-01522-y>

Changes in preterm birth and stillbirth during COVID-19 lockdowns in 26 countries

Received: 29 April 2022

Accepted: 6 January 2023

Published online: 27 February 2023

Check for updates

A list of authors and their affiliations appears at the end of the paper

Preterm birth (PTB) is the leading cause of infant mortality worldwide. Changes in PTB rates, ranging from –90% to +30%, were reported in many countries following early COVID-19 pandemic response measures ('lockdowns'). It is unclear whether this variation reflects real differences in lockdown impacts, or perhaps differences in stillbirth rates and/or study designs. Here we present interrupted time series and meta-analyses using harmonized data from 52 million births in 26 countries, 18 of which had representative population-based data, with overall PTB rates ranging from 6% to 12% and stillbirth ranging from 2.5 to 10.5 per 1,000 births. We show small reductions in PTB in the first (odds ratio 0.96, 95% confidence interval 0.95–0.98, P value < 0.0001), second (0.96, 0.92–0.99, 0.03) and third (0.97, 0.94–1.00, 0.09) months of lockdown, but not in the fourth month of lockdown (0.99, 0.96–1.01, 0.34), although there were some

