

From Influenza to COVID-19 vaccinations: counselling anxious parents about deaths following influenza immunizations in Korea

Kam Lun Hon, Karen KY Leung

Department of Paediatrics and Adolescent Medicine,
The Hong Kong Children's Hospital

Correspondence to: Kam Lun Ellis Hon, Department of Paediatrics and Adolescent Medicine, The Hong Kong Children's Hospital, Hong Kong SAR, China.

Tel: (852) 57413085. Fax: (852) 35127598. E-mail: ehon@hotmail.com.

Hong Kong citizens and anxious parents are astonished by the news that over 80 deaths have been reported following influenza immunizations in Korea, while some adverse events were also brought to the public's attention in Taiwan.(1) In Korea, the vaccine providers are believed to include domestic firms such as GC Pharma, SK Bioscience, Korea Vaccine and Boryung Biopharma Co Ltd, a unit of Boryung Pharm Co Ltd, along with Sanofi which is headquartered in France.(2) The reports raised yet further concerns amongst the general public after the Singapore Ministry of Health advised temporary cessation for the use of two vaccines, one of which is used in Hong Kong. This episode could become an international crisis as the annual winter surge of influenza is just around the corner and raise serious public concerns. We analyse and search the literature to provide some facts which can help address these questions and further discuss the role of vaccination in combating influenza and COVID-19 from a public health perspective.

Influenza vaccines are one of the most well-studied pharmaceutical products in use with a very good safety profile established over many decades. Mortality associated with influenza vaccines have not been reported in recent years, and plausible theoretical explanations of death following influenza vaccination could potentially include anaphylaxis, Guillain-Barre syndrome, fall-related injuries associated with syncope, post-vaccinal encephalitis and myocarditis.(3) The Korean Disease Control and Prevention (KDCCP) Agency has thoroughly examined the reported deaths and concluded that causality with influenza vaccination cannot be established. According to the KDCCP, more than 11.5 million South Koreans received their influenza vaccination this year, which is 61% of South Korean's population of 19 million.(1) Further, 85.5% of the death cases were in the >70 years-old population, and there was no evidence in the autopsy results and medical records to suggest anaphylaxis or adverse reactions to the vaccine at the time of death.(1) These death cases are co-incidental with

influenza vaccination, and are most likely attributable to underlying conditions.(1) The 'number' of death cases might possibly be artefact of reporting bias, given the vast number of vaccine doses distributed was high at 11.5 millions which covers a high proportion of the total population especially in the >62 age group who are more likely to have co-morbidities.(1)

Influenza vaccination

Vaccination against influenza began in the 1930s.(4)(5)(6) Influenza vaccines provide modest to high protection against influenza, and new versions are developed twice a year, as the influenza virus changes due to antigenic drift/shift.(7)(8) Every year, the World Health Organisation (WHO) holds Consultation and Information Meeting on the Composition of Influenza Virus Vaccines yearly to recommend the influenza strains that should be selected for the vaccines. Influenza vaccination is recommended for those at higher risk of serious complications, hospitalizations, and deaths.(9)(10) Despite the wide adoption of annual flu vaccination, the winter surge of influenza continue to recur every year, which shows that vaccination alone cannot fully eliminate the annual toll of this respiratory virus which causes significant mortality and morbidity around the World.

The vaccine comes in either inactive or weakened viral forms.(7) The live, attenuated vaccine is generally not recommended in pregnant women, children less than two years old, adults older than 50, or immunocompromised people.(7) They can be injected intramuscular, sprayed into the nose, or injected intradermal.(7) The inactivated flu vaccine is widely used and are largely produced using egg-based techniques. They are nonetheless still recommended for people with egg allergies, as studies examining the safety of influenza vaccines in people with severe egg allergies found that anaphylaxis is very rare, occurring in 1.3 cases per million doses given.(11) A study of nearly 800 children with egg allergies, including over 250

with previous anaphylactic reactions, resulted in zero systemic allergic reactions when given the live attenuated flu vaccine.(12)(13) However, influenza vaccines are not recommended in those who have had a severe allergy to previous versions of the vaccine itself.(7)(11)

Physicians are obligated to counselling anxious parents that influenza vaccines are generally safe.(7) Minor side effects that are relatively common include soreness, redness, temporary muscle pain, tiredness, swelling around the point of injection, headache, fever, nausea or fatigue.(7)(4)(5)(6)(14) Side effects of a nasal spray vaccine may include runny nose, wheezing, sore throat, cough, or vomiting.(14) Fever occurs in five to ten percent of vaccinated children.(7) Influenza vaccine has been linked to an increase in Guillain–Barré syndrome among older people at a rate of about one case per million doses.(7) However, most studies on modern influenza vaccines have seen no link with Guillain–Barré.(15)(16) A separate review estimated an incidence of about one case of Guillain–Barré per million vaccinations.(17) A large study in China, covering close to 100 million doses of vaccine against the 2009 H1N1 flu found only eleven cases of Guillain–Barré syndrome, (0.1 per million doses). Separately, there are also reports of an increased incidence of autoimmune narcolepsy among recipients of the pandemic H1N1 influenza ASO3-adjuvanted vaccine.(18) (19)

Will COVID-19 vaccines be the holy grail to bring an end to the pandemic?

In the case of influenza, the usual hygiene recommendations of hand-hygiene, mask wearing and social distancing may help but are unlikely to eradicate the winter surge of the flu virus. In the same line of reasoning, the probability that human can completely eradicate SARS-CoV-2 through modern medicine (i.e. pharmacological treatments, vaccination and non-pharmacological interventions) is rather low in the foreseeable future. A few relatively small

cities and countries like Hong Kong, Taiwan, Macau, Singapore and New Zealand, have managed to avoid the brunt of COVID-19 but at the expense of complete socio-economic lock-down. The USA, UK, France, Italy and India and the South Americas have failed to bring the virus under control, and the majority of the global population are currently living with the risk of contracting the virus.

Strict public health measures including social distancing, school closing, lock-down of international travel, strict isolation in Airborne Infection Isolation Rooms (AIIR) even for the “asymptomatic” or mild disease are all ideal from a medical perspective, but clearly not practical for this transmissible respiratory disease with an R_0 of 2-3 and the majority being asymptomatic or mildly symptomatic. Just like vaccination is not the ultimate solution for flu, vaccination alone will not be sufficient to bring an end to the COVID-19 pandemic. Furthermore, a large UK population surveillance study found that the proportion of people who tested positive for COVID-19 antibodies in the study population fell by 26.5% over 3 months.(20) Although it is unclear how the level of antibodies correlates with the effective level of immunity, lasting immunity from vaccination and herd immunity may be difficult to achieve for COVID-19. In conjunction with vaccination, a combination of low cost rapid COVID-19 testing which can be widely deployed, vigilant contact tracing and isolation might be exit strategies that could bring the COVID-19 pandemic under control, allowing the resumption of ‘normal’ social and economical activities.

Conclusion

Until the development and availability of novel vaccines and therapeutics options with good efficacy and safety profile, we will need to learn from our vast experience in the management of influenza epidemics and other past pandemics in the history of mankind. With the

alertness in personal hygiene and mass mask-wearing behaviour due to SARS, the incidence of influenza and respiratory viral diseases was much reduced in 2003.⁽²¹⁾ Out of all public health policies available today, influenza vaccination is a low-hanging fruit and should be actively encouraged. Given the relatively low influenza vaccination rate in Hong Kong (Table), healthcare professionals should continue to promote the importances of this safe and reliable interventions, and dismiss the misinformation and fallacies in the general public. An influenza epidemic occurring alongside a COVID-19 pandemic would inevitably result in unimaginable devastation in any part in the World.

Table Comparision of 2020-2021 Seasonal Influenza Vaccination for in Hong Kong and Korea (Up to end of Oct, 2020)

	Hong Kong (22)(23)	Korea(1)
Total population	7.5 million	19 million
Seasonal Influenza Vaccination Distribution	1) Government Vaccination Program (Free) <ul style="list-style-type: none"> - ≥ 65 years - Residents of residential care homes - Chronic medical problems - Pig farmers and pig slaughtering industry - Poultry workers - Healthcare workers - Age 6 months to 12, 50 to <65 years and pregnant women receiving CSSA 2) Vaccination Subsidy Scheme <ul style="list-style-type: none"> - Age 6 months to 12 or studying in primary school - ≥ 50 years - Person with intellectual disability - Pregnant women - Reciving diasbility allowance - '100% disabled' or "requiring constant attendance' under CSSA 3) Seasonal Influenza Vaccination School Outreach Programme (Free)	1) Government vaccination program (Free) <ul style="list-style-type: none"> - 6 months to 18 years - ≥ 62 years - Pregnant women 2) Self fund
Vaccinatated population	Free or subsidised = 359000 Self funded = unknown Total = 359000 (at least 4.8% of the population)	Free = 10880069 Self funded = 676925 Total vaccination = 11556994 (60.8% of the population)

Abbreviations: CSSA = Comprehensive Social Security Assistance

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