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Influenza vaccination in the COVID-19 era

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ABSTRACT

Influenza spreads globally annually with significant paediatric and adult attack rates and considerable morbidity, mortality and the exacerbation of extant chronic disease. In the northern and southern hemispheres, outbreaks occur mainly in the respective winter seasons. Influenza vaccination is available but only partially effective. In the absence of a vaccine, in winter, novel coronavirus COVID-19 will also circulate in parallel with seasonal influenza. Thus far it appears that with the current strains of these two viruses, the clinical outcome of co-infection is not significantly worse than infection with COVID-19 alone. However, several strains of influenza circulate, including strains still to come. Similarly, COVID-19 has several strains, with probably more to come. This paper discusses these issues and estimates ideal minimum influenza vaccination coverage based on an estimated influenza Basic Reproduction Number (R0) of 0.9–2.1 so as to obtain herd immunity or approach it. There is a strong argument for attempting near universal population coverage with the annual influenza vaccine leading up to next winter.

1. Influenza

Influenza is an infectious disease caused by one of the influenza viruses (RNA, Orthomyxoviridae) [1]. The word Influenza comes from the Italian "influence" and refers to the aetiology of the disease, and this was initially ascribed to unfavourable astrological influences [2].

Viruses only replicate in living cells, a multi-step process that involves cell invasion and the takeover of cellular mechanisms so as to produce viral copies which are then released [1]. The way that the influenza viral genome is assembled permits facile antigenic changes that bypass innate and developed immunity, with pandemic potential [1]. Pandemics occur circa thrice per century and may kill tens of millions such as the 1918 influenza that had a mortality of 50 and 80 million [3].

Surface influenza virus hemagglutinin glycoprotein is integral to infectivity, functioning both as an attachment factor and a membrane fusion protein. Strains that are easily transmitted have hemagglutinin proteins that bind to receptors in the upper respiratory tract, while more severe strains bind to receptors deep in the lungs [4]. Influenza may also affect animals, including pigs, horses, and birds [5].

2. Transmission

Influenza spreads in three main ways [4], and it is worth noting that children are much more infectious than adults [6].

1. Droplet spread: an infected person sneezes or coughs disseminating the virus through droplets of mucus which enter directly into the eyes, nose or mouth of another person present within 1–2 m. A sneeze or cough releases more than half a million viral particles.
2. Airborne: Medical procedures that cause air to travel at high speed over respiratory mucosae and epithelium, inducing the production of aerosols of various sizes, including droplet nuclei which remain suspended in air and can be inhaled.
3. Contact: Hand-to-eye/to-nose/to-mouth transmission, from contaminated surfaces or from direct personal contact.

3. Morbidity and mortality

Influenza spreads globally annually and symptoms may be mild to severe. This disease annually causes three to five million cases of severe illness and 290,000–650,000 deaths [4]. Complications include viral pneumonia, secondary bacterial pneumonia, sinusitis, and the exacerbation of extant health problems such as asthma or heart failure [4]. Death is commonest in the high risk groups: the young, the old, pregnant women and those with health problems including the immunocompromised, transplant recipients, and individuals with severe chronic diseases [4]. Influenza may also exacerbate chronic health problems such as emphysema, chronic bronchitis, asthma, ischaemic heart disease and congestive heart failure [4]. Smoking is another risk factor [7] as is air pollution [8].

Common symptoms such as fever, headaches and fatigue are the result of the release of proinflammatory cytokines and chemokines (e.g. interferon and tumor necrosis factor) that are produced by influenza-infected cells [9], potentially resulting in life-threatening cytokine storms as is believed to have been the cause of high mortality in the 1918 influenza pandemic [10].

In the United States it has been estimated that annually, influenza

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causes approximately 36,000 deaths and more than 200,000 hospitalizations [11]. The country's average annual economic cost is over $11 billion [12].

4. Infection rates

Circa 20% of unvaccinated children and 10% of unvaccinated adults are infected annually [13]. In the northern and southern hemispheres, outbreaks occur mainly in the respective winter seasons, while around the equator, outbreaks may occur at any time of the year [4]. Larger outbreaks known as pandemics are less frequent and these are defined as disease outbreaks prevalent over a wide area, from a group of countries to the entire world.

5. Mutation and vaccination

Due to influenza's high mutation rate, any particular vaccine usually confers protection for no more than a few years. Indeed, vaccine effectiveness is annually estimated at 25–60% [14].

For this reason, each year, the World Health Organization predicts which influenza strains are likeliest to circulate in the next year allowing pharmaceutical companies to produce targeted vaccines [4]. The vaccine does not include all active strains in any particular season and it is thus occasionally possible for a new or overlooked and therefore non-included strain to become prevalent and widespread [4]. The vaccine induces immunity after circa two weeks [4]. It is worth noting that this vaccine can precipitate reactions similar to true infection, albeit not as severe or long-lasting as actual disease [4].

Accurate data on vaccine efficacy is lacking but a review of children in good health showed that vaccination seemed to lower the risk of getting influenza from 30% to 11%. Not enough data was available to draw definite conclusions with regard to serious complications such as pneumonia or other reasons for hospitalization [15]. An equivalent review for adults indicated a 60% reduction in risk of catching influenza after vaccination [16]. Seasonal influenza vaccination is cost-effective especially in children [17] and the elderly [18].

6. Influenza in Malta

The World Health Organisation noted that there were 184 influenza and pneumonia deaths in Malta in 2017 (a typical year) and this was 6.3% of total deaths [19]. Vaccination coverage for influenza in Malta in the over 65 year age group is high compared to the rest of the European Union, reflecting extensive use of health promotion and educational campaigns, as well as wide and free availability of the vaccine [20]. However, immunisation rates at 55–60% remain below the WHO recommended target of 75% [20].

7. COVID-19 and Malta

The current COVID-19/coronavirus pandemic was initially identified in Wuhan, China, in December 2019 [21], and has globally resulted in almost 5 million infections and well over a third of a million deaths [22–25]. The first case identified in Malta was on the 7th March 2020 and thus far, the country has fared overall well with less than 600 total cases and 6 deaths.

8. Influenza and flu vaccination in the COVID-19 era

Infection with one pathogen does not preclude co-infection with a second or more pathogens. Next winter, in the likely absence of an effective COVID-19 vaccine, it is almost certain that influenza strains will circulate in conjunction with COVID-19. Thus far, it appears that with the current strains of these two viruses, the clinical outcome, is not significantly worse than infection with COVID-19 alone [26]. However, several strains of influenza circulate, including strains still to come. Similarly, COVID-19 has several strains, with probably more to come.

Mater Dei Hospital infectious disease consultants noted that “Early studies from China did not show evidence of COVID-19 and influenza co-infection. However it is now known that these two virus can co-infect the same patient. In our experience co-infected patients did not fare worse compared to patients just infected with COVID-19. The argument in favour of universal influenza vaccination would probably lean on the side of decreasing hospital stays due to complications and therefore alleviating the hospital and other health systems from the significant pressure of dealing with both covid and influenza in the same period” (Drs. Tonio Piscopo and Charles Mallia Azzopardi, Infectious Disease Consultants – joint personal communication).

Our hospital paediatric infectious disease colleague independently concurred: “This year we will be facing a bigger challenge: seasonal influenza that is still not fully preventable confounded by the COVID-19 pandemic. Children are susceptible to both, may be co-infected and can transmit both respiratory viruses to others. We still do not have full understanding of the immune response to these viruses. Immune dysregulation is one of the features observed in individuals presenting with severe COVID-19 disease and is likely the explanation for the inflammatory syndromes incorporating a spectrum of manifestations classically seen in Kawasaki disease and Toxic Shock syndrome reported in children. Similar to COVID-19 disease, lymphopaenia is also observed in individuals with severe influenza and is associated with a higher mortality. Presently, data on the clinical manifestations and severity of disease with influenza A and SARS-CoV-2 co-infection are very limited. What we know is that in the current COVID-19 pandemic, the US has its highest mortality from pneumonia and influenza since 2004, although not yet reaching the rates observed during the influenza A H1N1 pandemic in 2009. Bacterial superinfection is one of the deadliest complications of influenza. The upcoming flu season will be a challenge not only not to miss sequential or mixed infections with influenza and SARS-CoV-2, but also to decide on treatment including which patients will benefit from antibiotics. Vaccination against influenza and pneumococcal disease will be important to mitigate these infections. This is especially important for children who are known to play an important role in transmission of influenza and the pneumococcus to the elderly. Considering that rates of effectiveness of traditional inactivated influenza vaccines in the elderly are modest due to immunosenescence, in the current COVID-19 era direct protection of the elderly through pneumococcal vaccination would be equally important” (Dr. David Pace, Paediatric Infectious Disease Consultant).

Hospital virology is of the same opinion: “Every year is an influenza year and the season is fast approaching. We usually expect this season between November and May in our hemisphere. Come October the influenza vaccine is made available to the public so that one may produce antibodies to neutralize the virus. This year however is going to be quite unique because the flu like symptoms may not necessarily be due to influenza but also due to the COVID-19 virus. Also due to availability of receptors for haemagglutinin (Influenza) or ACR2 receptors (COVID-19) on human host cells one may end up with an infection with either or worse than that: a double infection. Hence I encourage everyone to take the vaccine this year and hence avoid this complex scenario and possibly a double pathology. Do not miss out on the Influenza vaccine this year!” (Dr. Christopher Barbara, Virologist and Clinical Chairman, Pathology Department).

Mater Dei Respiratory physicians concur: “Around 55% of patients with moderate to severe Asthma receive influenza vaccination in Malta, however it is hoped that more will take up the vaccination because of the possibility of concurrent covid infections (GINA guideline). Influenza vaccination can reduce serious illness, such as lower respiratory tract infections requiring hospitalization and death in COPD patients (GOLD guidelines). Patients are urged to protect themselves with influenza vaccine in particular due to increased risk of COVID-19 infection” (Dr. Martin Balzan, Consultant Respiratory Physician, Deputy Chairman of Department of Medicine and President of the

Medical Association of Malta – personal communication).

Public Health in Malta is fully cognisant of the importance of the influenza vaccine: “the Superintendent of Public Health at this point continues, as always, to strongly encourage the uptake of the annual seasonal influenza vaccine. This advice applies even more so as in the upcoming winter as we expect to have COVID-19 circulating with influenza, and it will be possible for individuals to become infected with the two viruses simultaneously” (Professor Charmaine Gauci, SPH Malta – personal communication), a stand completely backed by Deputy Prime Minister and Health Minister Mr. Chris Fearne who appealed to everyone to be vaccinated against influenza when the vaccine is available next October (Hon. Mr. Chris Fearne – personal communication).

9. Calculations

The following estimates are based on a worst case scenario, the assumption that there is an insignificant amount of innate immunity to next winter's circulating strain/s of influenza virus. Influenza has a variable Basic Reproduction Number (R0) but seasonal influenza is estimated as having an R0 of 0.9–2.1 [27]. Herd immunity is reached at 1-1/R0 [28]. For the upper R0 value of 2.1, this implies that herd immunity would be reached if 52.3% of the population were to be immune. If the influenza vaccine were to be effective in 50% of cases given, if all of the population were to take it, herd immunity would almost be reached.

Hypothetically, the midpoint R0 for 0.9–2.1 is 1.5. If 33.3% of the population were to be immune for strains with R0 of 1.5, herd immunity would be achieved. If the population were to be 80% vaccinated, even a vaccine that is only 50% effective would still provide herd immunity (calculator link).

Studies in Malta have shown that advice to patients, female sex and patients' age predicted vaccination, while past side effects to the influenza vaccine and presence of comorbidities predicted non-vaccination [29]. Patients who had been recently hospitalised also seemed likelier to take the vaccine while a significant proportion of non-hospitalised patients are unaware of the indication to vaccinate despite being in high-risk groups [30]. Findings are similar in other populations [31].

Health promotion campaigns favouring influenza vaccination should be cognisant of these and other potential factors that may sway the community toward taking the vaccine. Above all it is critical that new “out-of-the-box” systems are planned to ensure that all at-risk groups have easy access to influenza vaccination. Indeed access to vaccination is often the main obstacle to getting the influenza vaccine, particularly in elderly patients with reduced mobility.

Mandatory vaccination requirements may also need to be explored, especially in healthcare workers who can be the source of transmission in healthcare settings. This approach has been adopted in several countries, such as the USA [32]. This approach on its own, however, is not enough. It is critical that educational campaigns constantly highlight the dangers of presenteeism among healthcare workers and the risks of infection to patients and colleagues from such practices [33]. In anticipation of a higher vaccine uptake, Malta has ordered 200,000 flu vaccines for its half million population for next winter [34].

10. Conclusion

In balance, it is clear that the universal uptake of the influenza vaccine would be ideal this winter, especially in the at-risk groups. An almost universal uptake may engender herd immunity and thus protect those in who the vaccine is ineffective. Furthermore, a decrease in hospital visits and admissions will alleviate hospitals and allow services to better cope with COVID-19 complications as lockdowns are inevitably relaxed [35,36].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2020.105116.

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