A RESEARCH REVIEW™
PRODUCT REVIEW

MF59®-Adjuvanted Inactivated Quadrivalent Influenza Vaccine (Fluad® Quad) for Older Adults

Making Education Easy 2021

About the Reviewer

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This review summarises data relevant to the use of the MF59-Adjuvanted inactivated quadrivalent influenza vaccine (Fluad®Quad) for the prevention of seasonal influenza in adults aged ≥65 years, against the background of a high burden of disease in older adults and factors that can reduce vaccine effectiveness. The effects of COVID-19 on influenza and influenza vaccination are also discussed. This review is sponsored by Seqirus (NZ) Ltd.

Influenza in the elderly

The elderly are disproportionally affected by seasonal influenza.[1-3] They experience more complications, exacerbation of comorbidities, and excess mortality than younger people. Indeed, influenza is the leading cause of infectious death among elderly people who are also the age group most at risk of respiratory complications.[2]

Ninety percent of influenza-related deaths occur in people aged ≥65 years as do 70% of influenza-associated hospitalisations.[4,5] Moreover, the presence of comorbid medical conditions magnifies the risk of complications and death from influenza in the elderly.[2] The greater burden of illness in the elderly makes them a priority for influenza immunisation campaigns.

Expert comment: COVID-19 has shown us how our appreciation of respiratory viruses is very biased by how we test. It is misleading to think that influenza is always more severe than a common cold, and the chances of being accurately diagnosed with influenza depend on whether a person has "classical" influenza symptoms, test availability and timing of presentation. In other words, there is a huge under-recognition of influenza infection, particularly when it is so commonly part of a mixed respiratory infection. The likelihood of being tested and diagnosed with influenza appears to be greatly affected by how quickly results are expected to come back from the laboratory, and how likely clinicians are to think of influenza. This is compounded by the fact that influenza in the elderly is less often classical in its presentation and highly variable in frequency from year to year.

We have found that the introduction of point-of-care testing for influenza in the emergency department has greatly changed our understanding of influenza and given the opportunity to treat with oseltamivir in a clinically-useful timeline. Generally, 25–30% of people with acute febrile respiratory illness requiring admission have influenza, at least in "normal" years.

With so many caveats on the data, it is difficult to comment on the true impact of influenza in NZ, and in the elderly. Modelling data from NZ suggests that the impacts on mortality and admission to hospital are similar to those observed overseas,[1] with 5- to 10-times greater mortality in those over 65 years of age, a huge under-recognition of influenza-related mortality, and excess mortality and morbidity in Māori and Pasifika.

The year 2020 provides us with a unique opportunity to assess the effect of influenza on morbidity and mortality, because the COVID-19-related border closures have essentially eliminated the introduction of influenza into NZ this winter. Perhaps we will truly understand the wider impacts of influenza this year.

Reference: 1. Kessaram T, et al. Estimating influenza-associated mortality in New Zealand from 1990 to 2008. Influenza Other Respir Viruses. 2015;9(1):14-9.

Influenza vaccination in the elderly

The WHO recommends seasonal influenza vaccination for people aged >65 years as does the NZ Ministry of Health.[6,7] Influenza vaccination is the most cost-effective approach to influenza prevention.[2] However, conventional influenza vaccines, most of which have been designed for younger populations, are less immunogenic and less effective in elderly compared with younger adults.

The ability of influenza vaccine to induce protection is related to age, with an efficacy of 70–90% in children and adults compared with 30–50% in those aged >65 years.[8,9] The impaired ability of elderly adults to mount adequate immune responses to influenza vaccination is attributed to immunosenescence.[10,11]

Immunosenescence

The reduced effectiveness of vaccination in the elderly compared with younger adults is mainly due to age-related alteration of their immune system, known as immunosenescence, whereby some immunological components are attenuated while others, such as inflammation, are amplified.[3]

Changes of the innate and adaptive immune system associated with ageing lead to increased susceptibility to infection and reduced immune responses to vaccination.[3,12] The effects of ageing on the immune system are multifactorial. They include progressive shrinkage of the bone marrow and thymus, diminished production of B and T cell progenitors, increased numbers of dysfunctional memory cells due to chronic antigenic stimulation, reduction of phagocytic functions, and increased production of pro-inflammatory cytokines (**Figure 1**).[12-14]

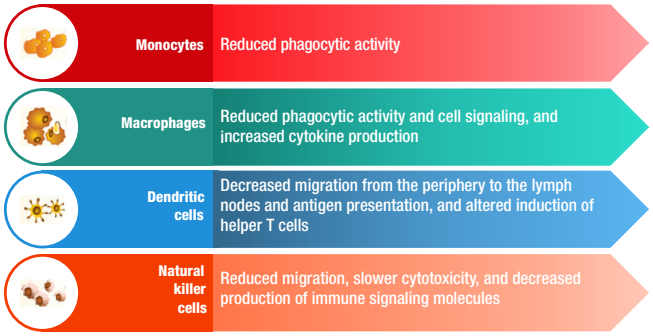

Figure 1. Immunosenescence: immune responses decline with ageing, leading to reduced vaccine responsiveness.[12-14]

MF59-Adjuvanted® influenza vaccines

Adjuvanted influenza vaccines are one strategy to increase immunogenicity in elderly patients.[2] Vaccine adjuvants, which range from small synthetic molecules to heterogeneous extracts of natural products, enhance the immune response to vaccine antigens.[15] They work by delivering a localised activation signal to the innate immune system, which in turn promotes antigen-specific adaptive immunity.

MF59-Adjuvant is an oil-in-water emulsion of mainly squalene (a naturally-occurring organic substance) stabilised with non-ionic surfactants.[15,16] It was first approved to be included in a licensed influenza vaccine for the elderly in Italy in 1997 and since then has been licensed for use in pandemic and seasonal influenza vaccines in many countries. Clinical trials have shown that MF59-Adjuvanted vaccines are more immunogenic than conventional non-adjuvanted vaccines in the elderly and are well tolerated with mild local reactions.[17,18]

Mechanism of action

Following injection of the squalene-based adjuvant MF59 in combination with antigen into the muscle there is recruitment and activation of resident monocytes, macrophages, and dendritic cells.[16] These immune cells respond by inducing secretion of a range of chemokines (CCL2, CXCL8, CCL4, CCL5), which stimulate an influx of phagocytic cells that engulf the antigen and differentiate into antigen-presenting cells (dendritic cells). These cells are responsible for the transport of antigen to the draining lymph node, which leads to activation of T and B cells and antibody production.

The adjuvant action of MF59 is attributed to the generation of a local immunostimulatory environment, characterised by chemokine-induced immune cell recruitment and activation, antigen uptake, and translocation and activation of adaptive immunity.[16] Research into the mechanism of action of MF59 has also demonstrated an increased breadth of antibody response, indicating that the adjuvant influences both the quantity and the quality of anti-influenza antibodies (see **Strain mismatch**).[19]

Immunogenicity

According to a systematic review that specifically quantified the effectiveness of MF59-Adjuvanted trivalent influenza vaccine (aTIV) in the elderly, available evidence from 11 studies suggests that MF59-Adjuvanted TIV is effective in real-world conditions, especially in preventing hospitalisations for influenza-related complications, and is superior to conventional non-adjuvanted vaccines:[20]

- Pooled analysis of four case-control studies showed vaccine effectiveness of 51% (95%CI: 39–61%) for MF59-Adjuvanted TIV against hospitalisations for pneumonia and influenza among community-dwelling elderly.
- Vaccine effectiveness against laboratory-confirmed influenza was also high at 60.1% in both community and mixed populations, although the confidence intervals were broad (95%CI: –1.3 to 84.3%) suggesting a low precision of estimates.
- Other single community-based studies showed high effectiveness of MF59-Adjuvanted TIV in preventing hospitalisations for acute coronary [87% (95%CI: 35–97%)] and cerebrovascular [93% (95%CI: 52–99%)] events.

In terms of relative vaccine effectiveness, the MF59-Adjuvanted TIV was generally significantly more effective than non-adjuvanted vaccines in preventing hospitalisations due to pneumonia and influenza [OR 0.75 (95%CI: 0.57–0.98)] and laboratory-confirmed influenza [OR 0.37 (95%CI: 0.14–0.96)] in two studies included in the systematic review.[20] These data are consistent with a recent case-control study involving 43,000 elderly subjects that found MF59-Adjuvanted TIV to be associated with a 39% (95%CI: 4–61%) reduced risk of hospitalisations for pneumonia and cerebrovascular/cardiovascular events as compared with non-adjuvanted TIV across 15 consecutive influenza seasons.[21]

Other factors affecting influenza vaccine effectiveness

In addition to immunosenescence leading to reduced vaccine responses in older adults, two other factors can also compromise the effectiveness of influenza vaccines: virus strain mismatch and egg adaptation.

Strain mismatch

Influenza viruses are constantly changing due to antigenic drift, which is the result of spontaneous changes in the structure of the surface glycoproteins, hemagglutinin and neuraminidase.[3] Antigenic drift necessitates adapting vaccine composition annually to integrate viral strains as similar as possible to the seasonal strains. However, drifted strains that appear after the annual influenza vaccine recommendation result in a vaccine strain mismatch and compromise the vaccine-induced immunity.[16]

Egg-adaptation mutations

The majority of influenza vaccines are produced by amplifying influenza viruses present in human respiratory samples in embryonated hens' eggs.[22] However, as human influenza A(H3N2) viruses adapt to grow in eggs, mutations can

occur in key proteins of the virus, especially the haemagglutinin, some of which can adversely alter virus antigenicity and potentially reduce vaccine effectiveness.[23]

Compensating for strain mismatch and egg-adaptation mutations

Clinical studies have shown that MF59-Adjuvanted vaccines provide better immunogenicity against circulating drifted seasonal strains that are different from the virus strains included in the vaccine.[17] An adjuvanted influenza vaccine broadens the immune response by creating more diverse, cross-reactive antibodies.[24] This may be important when there is a mismatch between the virus strains included in the vaccine and the strains circulating in the community. Del Giudice *et al.* showed that, when there was a major mismatch between the H3N2 vaccine strain and circulating strain during the Northern Hemisphere 2003–2004 influenza season, statistically significantly more elderly adults receiving the MF59-Adjuvanted vaccine containing A/Panama/2007/99 (H3N2) were seroprotected against the drifted variant A/Wyoming/3/2003 (H3N2) than those receiving a conventional non-adjuvanted vaccine.[25]

Until an approved alternative to traditional egg-based production for influenza vaccines is in widespread use, the addition of an adjuvant will help to augment the immune response to the antigens in egg-derived influenza vaccines.[26] Clinical studies have shown that MF59-Adjuvanted influenza vaccines are more immunogenic than non-adjuvanted vaccines (see **Immunogenicity section**).

Quadrivalent influenza vaccines

Influenza illness is caused by influenza A and influenza B strains. Although influenza A viruses account for the majority of influenza cases, influenza B is responsible for a significant proportion of the overall burden of influenza, especially in at-risk populations.[27,28] Since 1985, two antigenically distinct strains of influenza B viruses have circulated globally. Because conventional TIVs contain only one B strain the protection they provide against influenza is reduced should the other B strain predominate in any given season.[28]

The inclusion of a second B strain in influenza vaccines to form a quadrivalent influenza vaccine (QIV), containing both A and both B influenza strains recommended by health authorities, offers the potential for broader protection than TIVs and also helps to reduce the difficulties of predicting the circulating B lineage and choosing the influenza B vaccine component.

Although a standard-dose QIV is available in NZ and is indicated for use in adults (as well as children aged ≥3 years),[7] the MF59-Adjuvanted influenza vaccine is the first adjuvanted QIV developed specifically for elderly adults.

MF59-Adjuvanted inactivated QIV (Fluad Quad)

The MF59-Adjuvanted, inactivated QIV (aQIV) provides active immunisation against four influenza virus strains (two A subtypes and two B types) contained in the vaccine.[24] aQIV is indicated for active immunisation against influenza in people aged ≥65 years.[11]

Composition

aQIV contains influenza virus surface antigens (haemagglutinin and neuraminidase) of each of four antigens representative of the influenza virus strains expected to circulate in the Southern Hemisphere winter as recommended by the WHO.[24]

aQIV is prepared from virus grown in embryonated hens' eggs and inactivated with formaldehyde before purification and combination with MF59.[24] MF59 is composed of squalene (9.75 mg) as the oil phase, stabilised with the non-ionic surfactants polysorbate 80 (Tween 80; 1.175 mg) and sorbitan trioleate (Span 85; 1.175 mg), in citrate buffer, sodium citrate dihydrate (0.66 mg), citric acid monohydrate (0.04 mg), and water for injection.[16,24]

Dosage and administration

aQIV is administered as a single 0.5 mL dose by intramuscular injection, preferably into the deltoid muscle of the upper arm.[24] Annual revaccination is recommended because immunity declines in the year after vaccination and due to circulating strains of influenza virus changing from year to year (see **Strain mismatch section**).

Mechanism of action

aQIV stimulates antibody responses to the viral surface glycoproteins of the four influenza virus strains (two A subtypes and two B types) contained in the vaccine.[24] The inclusion of the second B strain in aQIV provides additional benefit compared with aTIV.

The MF59 Adjuvant broadens the immune response to the vaccine, which provides greater protection against heterologous strains of the virus.[24] This may be important when there is a mismatch between the virus strains included in the vaccine and the strains circulating in the community (see **Strain mismatch section**).

KEY CLINICAL TRIAL

Immunogenicity and safety of MF59-Adjuvanted quadrivalent influenza vaccine versus standard and alternate B strain MF59-Adjuvanted trivalent influenza vaccines in older adults[29]

Authors: Essink B et al.

Methods: This was a multicentre, double-blind, randomised, controlled non-inferiority trial that compared the immunogenicity, reactogenicity, and safety of aQIV with aTIV (Fluad; aTIV-1) and an alternative B strain MF59-Adjuvanted TIV (aTIV-2) in elderly adults during the 2017–2018 Northern Hemisphere influenza season. Immunogenicity was assessed using the hemagglutination inhibition (HI) assay conducted on serum samples collected before and 21 days after vaccination.

Study population: A total of 1,778 subjects were randomised (2:1:1) to receive aQIV (n=889), aTIV-1 (n=445), or aTIV-2 (n=444); with 1776 subjects receiving a vaccine and 1760 subjects completing the study. The median age of the study population was 71 years (range: 65–97 years).

Immunogenicity: Based on HI assay geometric mean titre ratios and seroconversion rate differences, both the primary and secondary end-points were met: aQIV was non-inferior to aTIV-1 and aTIV-2 for all four strains (primary endpoint; **Figure 2a**) and aQIV was superior for the alternative B strains (secondary endpoint; **Figure 2b**).

Tolerability: Solicited adverse events showed that the reactogenicity and safety profiles of the aQIV and aTIV comparators were generally comparable.[29,30] Injection-site pain, fatigue, and headache were the most common (≥10%) AEs. There were no marked differences in the frequencies of individual local or systemic adverse events across the aQIV and the aTIV groups. The majority of adverse events reported were of mild or moderate severity and resolved within 2–4 days.

Expert comments: This study is a classical influenza vaccine study, which relies on immunogenicity rather than efficacy. There is no doubt that the newer adjuvanted quadrivalent vaccines are superior to the adjuvanted trivalent vaccines but unfortunately this study did not include standard-dose quadrivalent vaccines in the control groups. The differences in response to influenza B are neither here nor there as far as I am concerned. It is difficult to drill down to individual patient effects in these studies, and timing can be everything with influenza vaccination. Vaccine efficacy is affected by the previous experience of the vaccinee, i.e. what influenza strains and vaccines they have been exposed to, and how closely related that season's circulating strain is. The pre-vaccination antibody levels in this study show a great deal of strain variation, with low levels to the A viruses. Presumably these antibodies are the result of both influenza infection and non-adjuvanted vaccination; it would be interesting to see how baseline and seroconversion rates look before and after repeat adjuvanted influenza vaccination in subsequent years. Real-world use of influenza vaccines includes repeated yearly vaccination, which can have quite variable effects on immunity in relation to persistent or slowly drifting strains, as opposed to new strains.

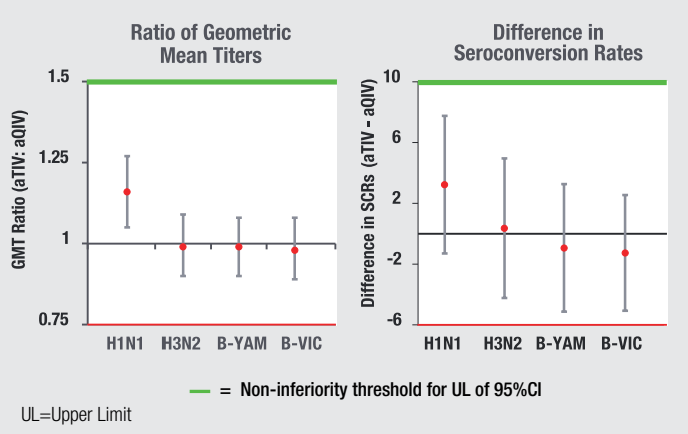

Figure 2a. Primary Immunological Endpoint met: aQIV non-inferior to aTIV1/2 for all strains

Primary immunological end-point: analysis of non-inferiority of aQIV versus both aTIV comparators based on HI assay geometric mean titre ratios and seroconversion rate difference.[29] For influenza A (H1N1 and H3N2), data from both aTIV-1 and aTIV-2 groups were pooled in the comparison with aQIV. B Victoria (B-VIC) comparisons were between aQIV and aTIV-1. B Yamagata (B-YAM) comparisons were between aQIV and aTIV-2.

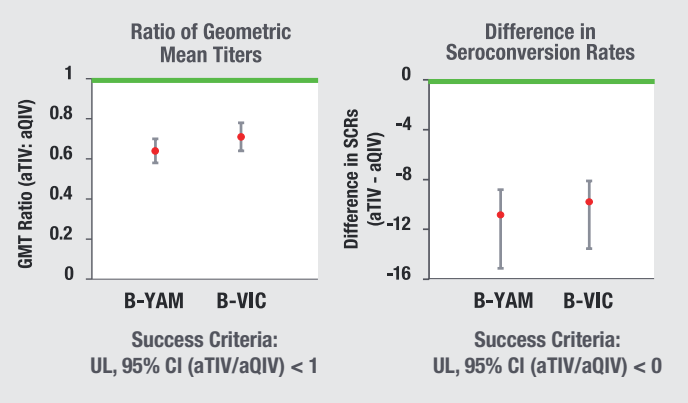

Figure 2b. Secondary Immunogenicity Endpoint: Superiority met for alternate B strain

Secondary immunological endpoint: analysis of superiority based on HI assay geometric mean titre (GMT) ratios and seroconversion rate (SCR) differences.[29] The GMT ratio was determined as aTIV-2:aQIV for B Victoria (B-VIC) and aTIV-1:aQIV for B Yamagata (B-YAM). The SCR difference was between aTIV-2 and aQIV for B-VIC and aTIV-1 and aQIV for B-YAM.

Influenza vaccine availability and uptake

Given that the elderly are one of the populations with the highest burden of disease,[7] influenza immunisation is recommended and offered free to people aged ≥65 years in NZ.[31]

Globally, more than 114 million doses of aTIV have been administered across 29 countries over the past 20 years.[30] In NZ, more than 1.35 million doses of influenza vaccine were distributed during 2019. This equated to just over one quarter of the whole population (270 doses per 1000 population).[7] Uptake of publicly-funded influenza vaccine for individuals aged ≥65 years was estimated at around 63% in 2019. Being based on funding claims this figure is likely to be an underestimate of the coverage.

Effect of COVID-19 on influenza

In 2020, the implementation of public health measures (physical distancing restrictions and improved hand hygiene) and the national lockdown, which began on 25 March and ended on 27 April, to prevent the spread of COVID-19 also created unfavourable conditions for influenza transmission.

Rates of self-reported influenza-like illness (via the FluTracking surveillance system) have been substantially lower in 2020 compared with 2019 and 2018 (**Figure 3**).[32] Confirming that the public health measures implemented to prevent transmission of COVID-19 have reduced the rate of influenza infection, none (0%) of 111 specimens collected between 2 June and 24 July 2020 from patients presenting to general practices with influenza-like illness symptoms were influenza positive compared with 763 of 1,244 specimens (61.3%) testing positive for influenza for the same period in 2019.[33]

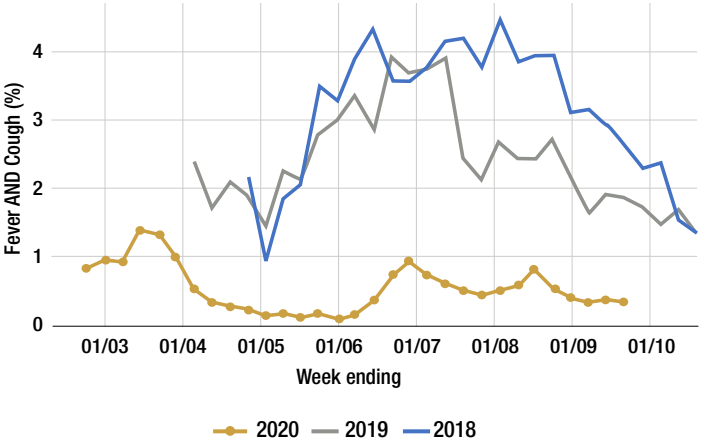

Figure 3. Weekly proportions of influenza-like illness symptoms (fever and cough) reported to FluTracking by participants in 2020 compared with 2019 and 2018.[32]

Effect of COVID-19 on influenza vaccine uptake

The lower incidence of influenza during 2020 (as a result of public health measures to contain the spread of COVID-19) should not lessen the importance of the seasonal influenza immunisation campaign. As with COVID-19, reducing the incidence of influenza, particularly the number of elderly people contracting the disease, will help to reduce pressure on the healthcare system.

Increasing the uptake of seasonal influenza vaccination is expected to help ameliorate the healthcare system stress caused by the additional circulation of COVID-19.[34] Emerging preliminary evidence suggests that influenza vaccination may reduce morbidity and mortality associated with COVID-19, including in the elderly.[35]

With public health messaging, especially that targeting people aged ≥65 years, there has been increased uptake of the influenza vaccine in NZ compared with previous years (**Figure 4**).[36] As of 22 May 2020, 1.7 million influenza vaccine doses had been distributed. Influenza vaccine uptake has been highest in individuals aged ≥65 years.[37]

Demand for influenza vaccines is also expected to increase globally. The UK and other Northern Hemisphere countries are considering mass influenza vaccination campaigns to reduce pressure on healthcare systems as part of their planning for an expected second wave of coronavirus in the autumn and potentially dual epidemics of COVID-19 and seasonal influenza (winter 2020-2021).[38]

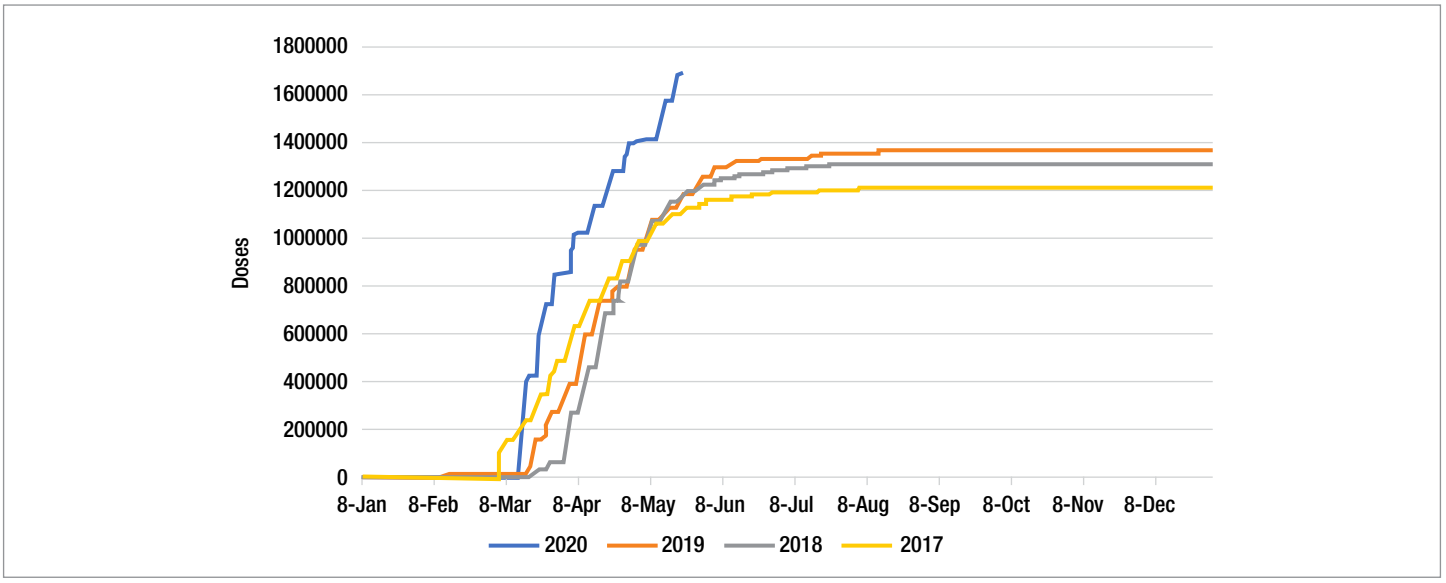

Figure 4. Cumulative number of influenza vaccine doses distributed in NZ in 2020 (as of 22 May) compared with prior years.[36]

EXPERT'S CONCLUDING COMMENTS

Influenza vaccination is always a tricky subject because of how unreliable personal or clinical impressions are of whether a respiratory illness is influenza, and then how likely someone is to get a PCR test. This makes it hard for individuals to gauge how successful influenza vaccine is for them, and this is further compounded by the seasonal variability in types, frequency, and vaccine match.

Another problem with vaccines in general is that they are often most needed in those who have less-well functioning immune systems, who do not necessarily respond well to vaccines. Better adjuvants are a very attractive advancement in vaccinology. This particularly applies to influenza, which is by far the biggest vaccine programme in adults. We may not always get the perfect match of vaccine and circulating strain but better adjuvants undoubtedly produce a broader and more intense immune response, which is particularly needed in the elderly and immune suppressed.

It is interesting that the border restrictions for COVID-19 have essentially wiped out circulating influenza this season. This is elegant evidence for how influenza is introduced by travellers from overseas and then circulates, often in children. COVID-19 also drove a record year for influenza vaccination, which hopefully will increase the pool of people who have had influenza vaccination without serious "side effects". At least this year no one will be able to say that the vaccine gave them the flu!

Shutting borders is obviously effective, but not well tolerated. Our influenza control options now include:

- Staying away from others when sick
- Early diagnosis using PCR
- Early treatment with oseltamivir
- Childhood vaccination
- Using the most effective vaccines available.

TAKE-HOME MESSAGES

- Influenza and its complications are the leading cause of preventable infectious death in older adults.
- Due to immunosenescence, influenza susceptibility is increased and vaccine effectiveness is reduced in the elderly compared with younger adults.
- Adjuvants are substances added to vaccines to boost the immune response.
- Addition of the squalene-based adjuvant MF59 to influenza vaccine compensates for loss of vaccine effectiveness due to immunosenescence, strain mismatch, and egg-adaptive mutations.
- There is a need for vaccines for the elderly population that offer higher and broader protection against both homologous and mismatch (heterologous) virus strains.
- aQIV is the first MF59-Adjuvanted quadrivalent influenza vaccine to be approved for use in adults aged ≥65 years.
- aQIV stimulates a comparable immune response to aTIV against homologous influenza strains and has a similar reactogenicity and safety profile.
- aQIV has demonstrated higher immunogenicity against an additional B strain indicating that it could provide a broader protection against influenza than aTIV in older adults.
- Influenza incidence has declined due to preventive measures against COVID-19 at the same time as demand for influenza vaccination has increased due to concerns about COVID-19.
- Increased uptake of seasonal influenza vaccination should help to ameliorate healthcare system stress caused by dual influenza and COVID-19 epidemics.

REFERENCES

1. Uyeki TM. Influenza. Ann Intern Med. 2017;167(5):Itc33-itc48.
2. Pop-Vicas A, et al. Influenza in the elderly: a mini-review. Gerontology. 2011;57(5):397-404.
3. Ciabattini A, et al. Vaccination in the elderly: The challenge of immune changes with aging. Semin Immunol. 2018;40:83-94.
4. Thompson WW, et al. Influenza-associated hospitalizations in the United States. JAMA. 2004;292(11):1333-40.
5. Thompson WW, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003;289(2):179-86.
6. Krammer F, et al. Influenza. Nat Rev Dis Primers. 2018;4(1):3.
7. Anonymous. Influenza. In: Immunisation Handbook 2020 [Internet]. Wellington: Ministry of Health. Available from: https://www.health.govt.nz/publication/immunisation-handbook-2020. [Date accessed: 06/09/20].
8. Osterholm MT, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12(1):36-44.
9. Jefferson T, et al. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet. 2005;366(9492):1165-74.
10. Monto AS, et al. Influenza control in the 21st century: optimizing protection of older adults. Vaccine. 2009;27(37):5043-53.
11. McElhaney JE. The unmet need in the elderly: designing new influenza vaccines for older adults. Vaccine. 2005;23 Suppl 1:S10-25.
12. Weinberger B, et al. Biology of immune responses to vaccines in elderly persons. Clin Infect Dis. 2008;46(7):1078-84.
13. Plowden J, et al. Innate immunity in aging: impact on macrophage function. Aging Cell. 2004;3(4):161-7.
14. Hazeldine J, et al. The impact of ageing on natural killer cell function and potential consequences for health in older adults. Ageing Res Rev. 2013;12(4):1069-78.
15. O'Hagan DT, et al. Towards an evidence based approach for the development of adjuvanted vaccines. Curr Opin Immunol. 2017;47:93-102.
16. Kommareddy S, et al. Chapter 13. In: Schijns V, et al., editors. Immunopotentiators in modern vaccines. MF59: A safe and potent adjuvant for human use. Cambridge, MA: Academic Press (Elsevier). 2017: 249-62.
17. Durando P, et al. MF59-Adjuvanted vaccine: a safe and useful tool to enhance and broaden protection against seasonal influenza viruses in subjects at risk. Expert Opin Biol Ther. 2010;10(4):639-51.
18. Podda A. The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-Adjuvanted vaccine. Vaccine. 2001;19(17-19):2673-80.
19. Del Giudice G, et al. Inactivated and adjuvanted influenza vaccines. Curr Top Microbiol Immunol. 2015;386:151-80.
20. Domnich A, et al. Effectiveness of MF59-Adjuvanted seasonal influenza vaccine in the elderly: a systematic review and meta-analysis. Vaccine. 2017;35(4):513-20.
21. Lapi F, et al. Adjuvanted versus nonadjuvanted influenza vaccines and risk of hospitalizations for pneumonia and cerebro/cardiovascular events in the elderly. Expert Rev Vaccines. 2019;18(6):663-70.
22. Subbarao K, et al. A tale of two mutations: beginning to understand the problems with egg-based influenza vaccines? Cell Host Microbe. 2019;25(6):773-5.
23. Wu NC, et al. Preventing an antigenically disruptive mutation in egg-based H3N2 seasonal influenza vaccines by mutational incompatibility. Cell Host Microbe. 2019;25(6):836-44.e5.
24. Medsafe. Fluad Quad New Zealand data sheet. Greenlane, Auckland: Seqirus (NZ) Ltd. December 2020. Available from: Available at: https://www.medsafe.govt.nz/Profs/Datasheet/f/FluadQuadinj.pdf
25. Del Giudice G, et al. An MF59-Adjuvanted inactivated influenza vaccine containing A/Panama/1999 (H3N2) induced broader serological protection against heterovariant influenza virus strain A/Fujian/2002 than a subunit and a split influenza vaccine. Vaccine. 2006;24(16):3063-5.
26. Harding AT, et al. Efforts to improve the seasonal influenza vaccine. Vaccines (Basel). 2018;6(2):19.
27. Ambrose CS, et al. The rationale for quadrivalent influenza vaccines. Hum Vaccin Immunother. 2012;8(1):81-8.
28. Tisa V, et al. Quadrivalent influenza vaccine: a new opportunity to reduce the influenza burden. J Prev Med Hyg. 2016;57(1):E28-33.
29. Essink B, et al. Immunogenicity and safety of MF59-Adjuvanted quadrivalent influenza vaccine versus standard and alternate B strain MF59-Adjuvanted trivalent influenza vaccines in older adults. Vaccine. 2020;38(2):242-50.
30. Data on file. Seqirus Inc. 2019.
31. Anonymous. Influenza vaccines. Auckland: Immunisation Advisory Centre. Last update date: September 2020. Available from: https://www.immune.org.nz/vaccines/available-vaccines/influenza-vaccine. [Date accessed: 14/08/20].
32. Anonymous. Flu surveillance and research: FluTracking. Auckland: Institute of Environmental Science and Research (ESR), New Zealand Government. Last update date: 19/07/20. Available from: https://www.esr.cri.nz/our-services/consultancy/flu-surveillance-and-research/. [Date accessed: 30/07/20].
33. Anonymous. Flu surveillance and research: community activity. Auckland: Institute of Environmental Science and Research (ESR), New Zealand Government. Last update date: 24/07/20. Available from: https://www.esr.cri.nz/our-services/consultancy/flu-surveillance-and-research/. [Date accessed: 30/07/20].
34. Grohskopf LA, et al. Addressing influenza vaccination disparities during the COVID-19 pandemic. JAMA. 2020;324(11):1029-1030.
35. Rubin R. What happens when COVID-19 collides with flu season? JAMA. 2020;324(10):923-5.
36. Anonymous. Influenza vaccinations for 2020. Wellington: PHARMAC. Last update date: 25 May 2020. Available from: https://www.pharmac.govt.nz/medicines/medicines-information/flu-vaccines-pharmacs-role/influenza-vaccinations-for-2020/. [Date accessed: 16/09/20].
37. Anonymous. Flu surveillance and research: vaccination. Auckland: Institute of Environmental Science and Research (ESR), New Zealand Government. Last update date: 24/07/20. Available from: https://www.esr.cri.nz/our-services/consultancy/flu-surveillance-and-research/. [Date accessed: 30/07/20].
38. Sample I. Demand for flu vaccine soars as countries plan for second COVID-19 wave. The Guardian. Issue date: 14 June 2020. Manchester: Guardian News & Media Limited.

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