

Waning of influenza vaccine protection: Evidence and implications for vaccine policy

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The Big Questions about Waning Vaccine Effectiveness

Within a given season, how much does effectiveness of
influenza vaccine decline with time since vaccination?

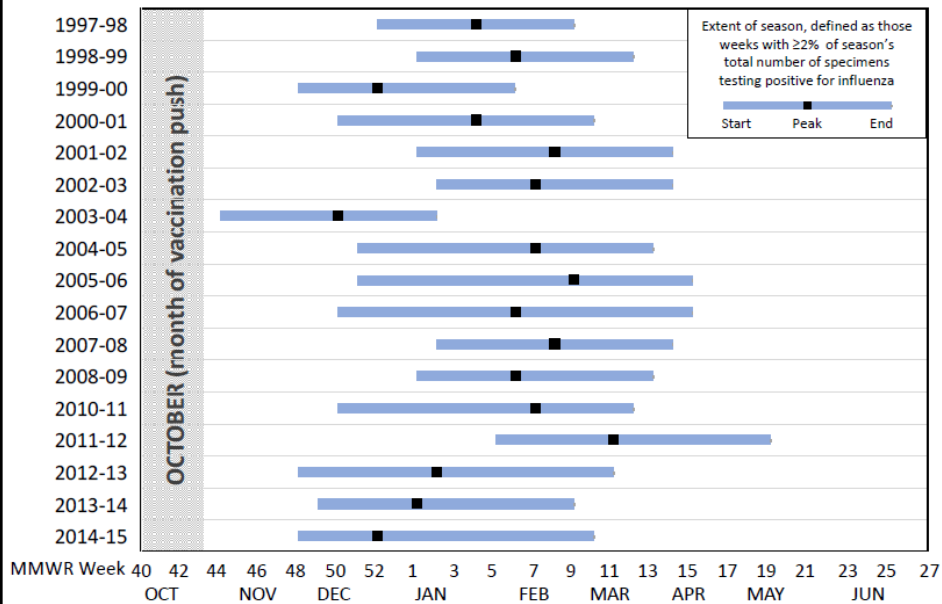
What should we do about this waning VE?

Are there implications for when vaccine should (or should not) be given?

SECTION I: SETTING THE STAGE

Timing of US flu seasons and influenza vaccination

Early flu seasons are as common as late ones



Timing of US influenza vaccination coverage

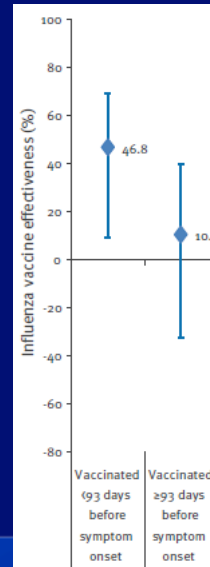
- **Vaccine often available in July**
- **Of the total number of people vaccinated in a given season:**
 - <1% are vaccinated by the end of August
 - About 7% are vaccinated by the end of September
 - About 90% are vaccinated by the end of December

SECTION II: THE EVIDENCE FOR WANING VE

A short tour of the epi evidence

Studies of waning VE: The earlier studies

- Observational studies of influenza VE in Europe suggested that vaccinated persons more often presented later in the 2011-12 season
- In Europe: 46.8% VE among those vaccinated <3 months ago vs 10.5% among those vaccinated ≥3 months ago (Kissling 2013)
- This suggested waning of VE but methods to assess waning were not well established and sample sizes were small

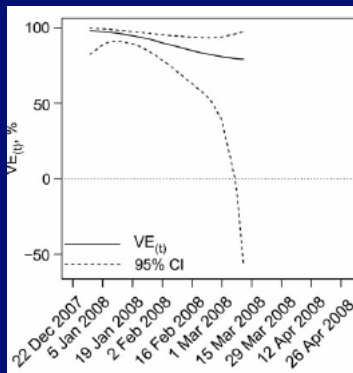


Studies of waning VE: The earlier studies

- Studies in Australia and the UK in the following season (2012-13) also saw waning VE
 - Sullivan (2014) saw VE of 37% among those vaccinated <3 months ago and VE of 18% among those vaccinated ≥3 months ago
- But the amount of waning was inconsistent across studies, age groups, and flu type/subtypes

Studies of waning VE: More recent studies (US, 2007-08)

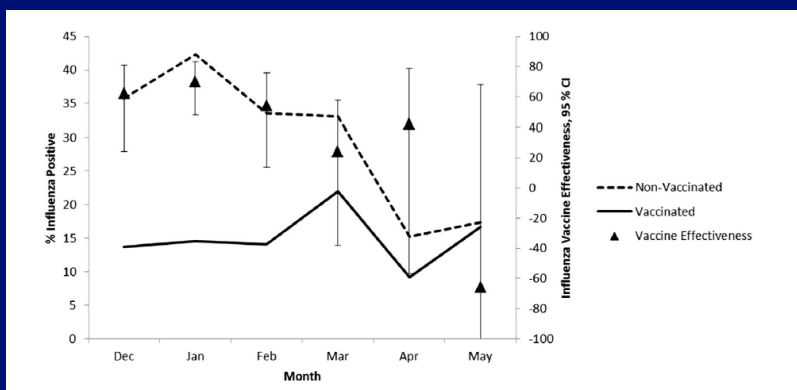
- Belongia (2014) saw modest waning of vaccine protection in Wisconsin (observational data, 2007-08)
 - Risk of flu increased 12% for every two weeks since vaccination
 - More pronounced waning at very young and very old ages
- Petrie (2016) saw modest waning of vaccine efficacy among adults in Michigan (RCT data, 2007-08)



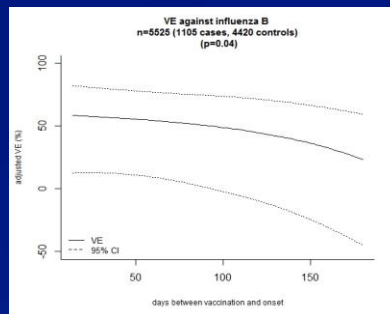
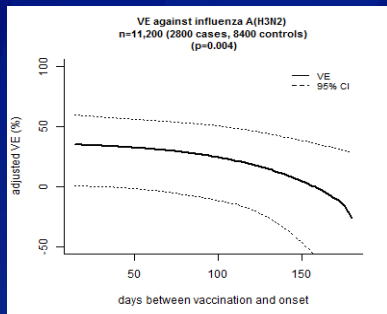
Petrie 2016

Studies of waning VE: More recent studies (US)

- Using 3 seasons of observational data, Radin (2016) saw steady VE for 6 months after vaccination, then a decline (most pronounced for flu B)



Studies of waning VE: More recent studies (US)



Ferdinands (2016) pooled data for 2011-12 through 2014-15:

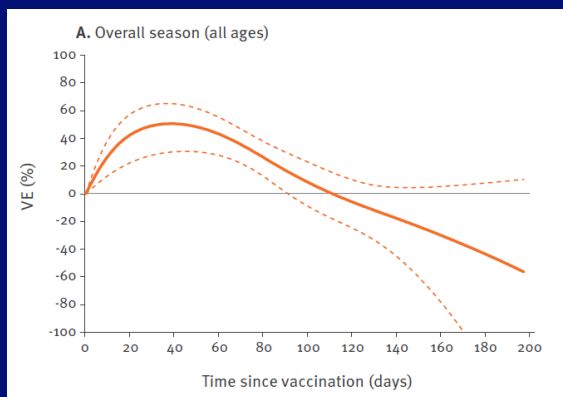
VE was highest shortly after vaccination

Decline in VE of about 7% per month

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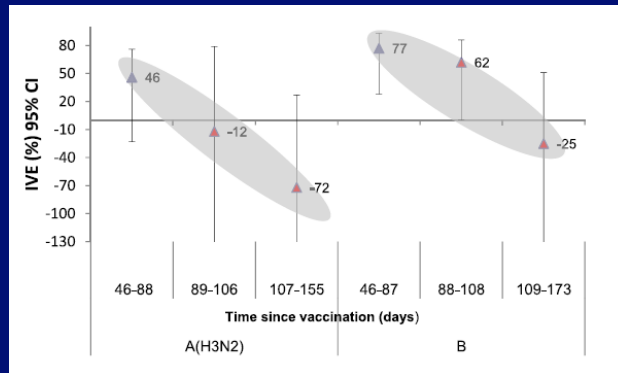
Studies of waning VE: More recent studies (Europe)

- Kissling (2016) pooled data from 5 seasons and saw pronounced waning against H3, mild waning against B, and no waning against H1 (H3 shown below)



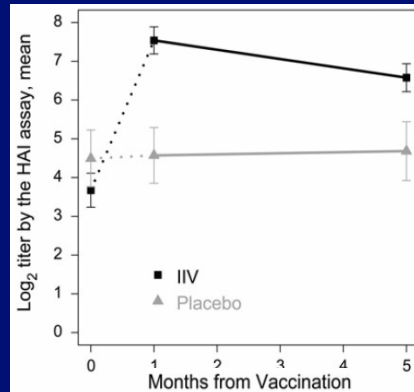
Studies of waning VE: More recent studies (Spain)

- Gherasim (2016) saw dramatic decline in VE in 2014-15 season in Spain



Post vaccination antibody titers

- We know from numerous studies that post vaccination antibody titers decline slowly over time
- For example, Petrie 2016 used an RCT of flu vaccination to evaluate post vaccination H3 antibody titers in adults
- It took >58 weeks for antibody levels to decline to half their original post vaccination levels



PART III: POLICY IMPLICATIONS OF WANING VE

2016-17 US ACIP Influenza Statement

“Optimally, vaccination should occur before onset of influenza activity in the community. Health care providers should offer vaccination by the end of October, if possible.....

Grohskopf et al., Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2016–17 Influenza Season, *MMWR*, August 26, 2016;65(5):1-54
www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm

2016-17 US ACIP Influenza Statement

“Optimally, vaccination should occur before onset of influenza activity in the community. Health care providers should offer vaccination by the end of October, if possible.....Community vaccination programs should balance maximizing the likelihood of persistence of vaccine-induced protection through the season with avoiding missed opportunities to vaccinate or vaccinating after onset of influenza circulation occurs.”

Grohskopf et al., Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2016–17 Influenza Season, *MMWR*, August 26, 2016;65(5);1-54
www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm

There's always a trade-off

Our results suggest that administering influenza vaccines closer to the start of the influenza season may increase VE slightly in some groups. However, we also found that the flu vaccine offered moderate and significant protection against influenza infection for the duration of the influenza season or up to 6 months postvaccination. Since the start of the flu season varies each year, it is somewhat difficult to predict the most opportune time to vaccinate each year. Radin 2016

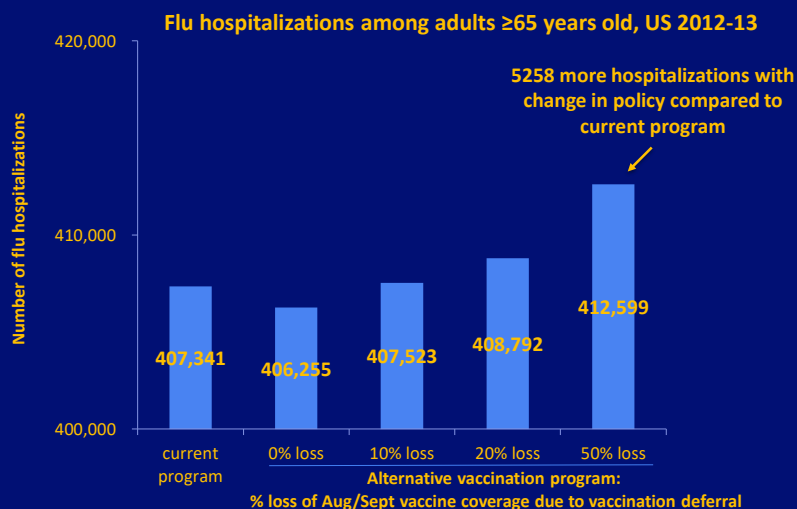
The incremental benefits in overall efficacy that could be achieved by delaying vaccination would come at the cost of missed vaccination opportunities and increased risk of early season infection prior to vaccination. Petrie 2016

Ferdinands 2016.... careful consideration of the risks and benefits of delaying vaccination is needed before contemplating changes to current vaccine recommendations.

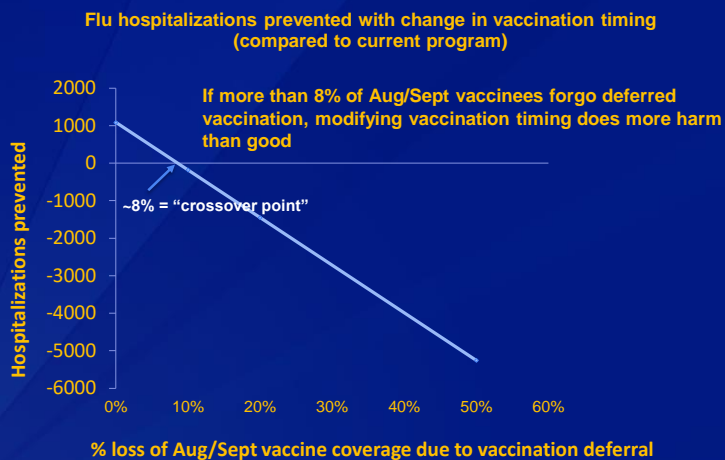
Exploring the trade-offs of delayed vaccination

- Model to estimate burden of influenza under observed waning VE and varying vaccination timing
- Recommendation against vaccination in August and September--vaccination begins in October
- A proportion of people who would have been vaccinated in August and September get vaccinated in October (“deferred vaccinees”) and the remaining don’t get vaccinated at all
 - CDC internet panel survey of pregnant women found 50% lower vaccine coverage among those who deferred vaccination
 - We varied the proportion of deferred Aug/Sept vaccinees who get vaccinated in October from 50% to 100%

Results: Flu hospitalizations (total)



Results: Prevented flu hospitalizations



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Conclusion

- For the 65+ age group, delaying vaccination until October is likely to have a net negative impact (more flu hospitalizations) if more than 8% of deferred vaccinees (from August and September) do not get vaccinated
- This result is based on 2012-13 as a prototypical season and will likely vary with other seasons (and age groups)
- It is too early to recommend for or against a vaccine policy change until we understand how these results vary with important factors (like amount of waning)

Discussion

- We need to know more about...
 - ...what happens if people defer vaccination until October
 - How much does coverage go down?
 - When do “deferred vaccinees” end up getting vaccinated?
 - ...how “deferred vaccinees” differ from others (older? sicker?)
 - ...how well vaccine providers could absorb deferred vaccinees
- We need to evaluate...
 - ...what happens if flu season were to start earlier or later
 - ...flu outcomes over a range of plausible waning rates
 - ...other age groups

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For more information, contact Jill Ferdinands at jferdinands@cdc.gov

Exploring the trade-offs of delayed vaccination

- We built a model to estimate burden of influenza under different waning VE and vaccination timing scenarios
- We simulate a cohort of people as they move through time during an influenza season. Each person can:
 - get vaccinated or not
 - get flu or not
 - get hospitalized or not
- In this model, VE varies with time since vaccination, allowing us to
 - predict the number of flu hospitalizations for a given season
 - explore what happens if we delay vaccination (e.g., until October)
 - explore what happens if flu season arrives earlier or later than usual

The trade-off model: Framework

- To explore trade-offs, we modeled the U.S. population of people aged ≥ 65 year in the 2012-13 season
 - 43,145,356 people (assumed unvaccinated as of July 1)
 - 66% end-of-season vaccination coverage
 - 26% average (across-season) vaccine effectiveness observed in the US Flu VE Network for this age group
 - Circulating flu was predominantly A(H3N2), which some think may have more pronounced waning (especially in the elderly)
 - 2012-13 had “typical” timing of flu season with peak in early January

**The trade-off model:
Some very important assumptions**

- VE wanes at the rate seen by Ferdinands (2016) for A(H3N2), ~7% per month
- An alternative vaccine program would recommend against vaccination in August and September, so that all vaccination begins in October
- A proportion of people who would have been vaccinated in August and September get vaccinated in October (“deferred vaccinees”) and the remaining don’t get vaccinated at all
 - CDC internet panel survey of pregnant women found that women who deferred vaccination had half the coverage of women who did
 - We varied the proportion of deferred Aug/Sept vaccinees who get vaccinated in October from 50% to 100%