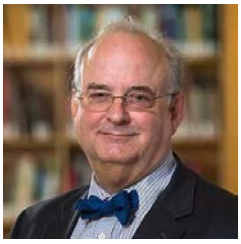
OVERVIEW

Each year, respiratory syncytial virus (RSV) infects up to 10% of older adults who live in congregate settings and predisposes to an increased of hospitalization and death, particularly in those with comorbid cardiopulmonary disease. Angela Branche, MD, and Stefan Gravenstein, MD, MPH, compare the burden of RSV with other viral infections in older adults and emphasize the importance of and how to make the diagnosis. They discuss the symptomatic management, but emphasize the importance of instituting preventive measures since there are no approved medications for acute or preventive treatment of RSV in older adults. They highlight the several vaccines that are in late phase development to prevent RSV infection in older adults.

CONTENT AREAS

- Burden of disease
- RSV vs other viral infections
- Diagnosis
- Preventive measures
- Vaccines

FACULTY



Stefan Gravenstein, MD, MPH
Director, Division of Geriatrics and Palliative Medicine
The Warren Alpert Medical School of Brown University
Providence, Rhode Island

TARGET AUDIENCE

This activity is intended for family medicine physicians, primary care physicians, nurse practitioners, nurses, and other healthcare professionals who care for older adults.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Discuss the burden of disease related to respiratory syncytial virus (RSV) infection in adults
- Explain the risk factors for RSV infection in adults
- Identify opportunities to reduce the risk for serious RSV-associated complications in older adults
- Integrate prophylactic vaccinations related to RSV into the routine management of older adults

FACULTY

Angela Branche, MD
Assistant Professor, Department of Medicine
University of Rochester Medical Center
Rochester, New York

Stefan Gravenstein, MD, MPH
Professor of Medicine
Director, Division of Geriatrics and Palliative Care
Brown University
Providence, Rhode Island

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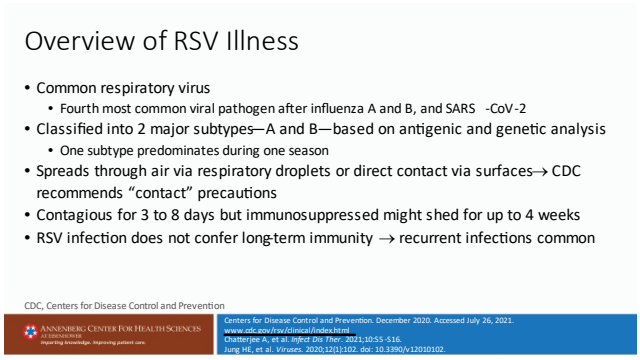
CONTACT INFORMATION
For help or questions about this activity please contact Continuing Education:
ce@annenberg.net
Annenberg Center for Health Sciences
39000 Bob Hope Drive
Dinah Shore Building
Rancho Mirage, CA 92270
Phone 760-773-4500
Fax 760-773-4513
8 AM – 5 PM, Pacific Time, Monday – Friday

Editor's Note: This is a transcript of a webcast presented in November 2021. It has been edited and condensed for clarity.

Stefan Gravenstein, MD, MPH: Respiratory syncytial virus (RSV) was really first discovered as a cause of bronchiolitis in children back in '57. And the thought from then, and through the '60s and '70s, was that it was mostly a mild infection in young adults, as part of families, and mostly a problem with kids. I'm going to give you 3 fun facts as we go. And one of those fun facts has to do with why kids are different than older adults when it comes to RSV. Infants who have some of the most severe outcomes with RSV among the younger group, all have airways and alveoli that are roughly the same in number as adults. But because this is in a small package, these airways are quite small. And that means it takes less inflammation and bronchospasm to cause obstructions and therefore to easily get croup. The symptoms of wheezing and croup are pretty common in kids, especially infants. Not so common in older adults, although you can get it in there, too.

It's one of 3 reasons children present differently from older adults with RSV infection. In the '90s, it was recognized that older adults could also get more severe disease. And, since then it's been suggested as a cause of serious illness in community dwelling, older adults. And we're going to go over some of that data shortly.



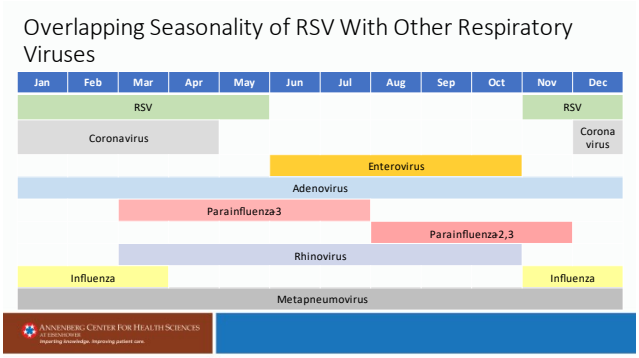
It's a common respiratory—a negative sense RNA virus—and it's the fourth most common viral pathogen after influenza A and B. And before SARS-CoV-2, it was the third most common—until SARS-CoV-2 came around. It's been classified into 2 major subtypes, A and B, and that's based on an antigen and genetic analysis of this. And typically, in a given season, it's one or the other subtypes that is dominant in circulation, not both. And, back to the first bulletin of SARS-CoV-2, this last year it has been the number 1 viral pathogen in circulation.

When we went to lockdown, pretty much influenza and RSV went away until just a few months ago when people started circulating again. RSV had a faster bounce back. And now we're also seeing a little bit of flu again. RSV spreads through droplets, and you've heard the same story about what happens with SARS-CoV-2. This is also something that spreads by droplets. RSV lands on the eyes, noses, or mouth. It transmits through the air and it lands on surfaces where you can get it on your hands and then self-inoculate through fomites. It binds to and infects airway epithelial cells. It's a little different from flu and SARS-CoV-2. Influenza has a specific sialic acid receptor that it binds to, and those are in the ciliated respiratory cells.

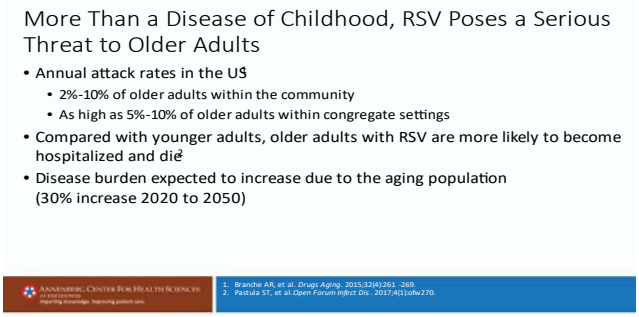
SARS-CoV-2 has an ACE2 receptor that it looks for that it binds to, pretty low concentration in the airways, in the apical acinar glands of the salivary ducts and in the conjunctiva. It's a little different in where it can settle than RSV, whereas RSV can get into that epithelium in a variety of places. You've also heard about how contagious RSV is. It's contagious in most healthy people for a few days to a week or so, but in immunosuppressed and in very young children, they could shed up to 4 weeks. RSV doesn't confer long-term immunity. Once you get infected, within a few months to a year you're completely susceptible again for a recurrent infection. When we think about how RSV spreads you may have heard of the R naught for Coronavirus, absent any controls, the R naught is

around 8 or 9. For RSV, it's closer to 3 or so. And influenza is probably closer to 2.

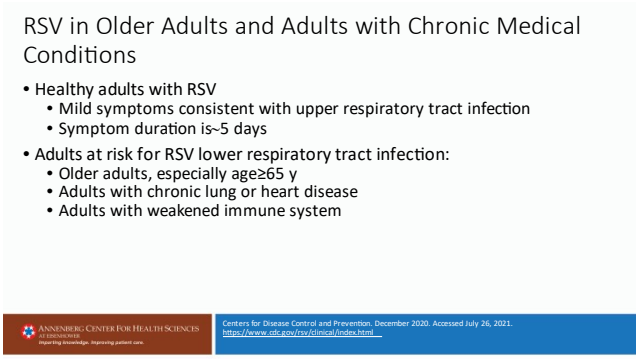
And if you wanted to predict when the next RSV epidemic is going to occur, you can predict that now, with about a 70% accuracy, 4 weeks ahead of time based on activity and understanding what the doubling time is. The CDC recommends contact precautions to keep it from spreading.



Here's the seasonality for RSV, and you can see the green bar at the top shows you that it's fall and winter. And that's pretty much the same as influenza, which is down here in yellow, and coronavirus. The typical beta-coronavirus, not the SARS-CoV-2, which is currently around, but the beta-coronavirus that causes the common cold has that same seasonality. And that's different from rhinovirus, which we usually think of as common cold or parainfluenza. Adenovirus and metaviruses are year round. RSV is more of a seasonal trend. And in tropical areas, both flu and RSV, and the beta-coronavirus, tend to be more year-round than seasonal like this.



It's more than a disease of childhood. It poses a really a serious threat to older adults. And the annual attack rate has been estimated around 2% to 10% of older adults. And when you pack them together in close settings, it's closer to 10% than it is to 2% because of the efficiency of spread. Compared with younger adults, older adults with RSV are more likely to become hospitalized and die. And in older adults, in terms of the morbidity and mortality, it looks increasingly as bad as influenza does. The disease burden, we can expect that will increase, because from 2020 to 2050—over the next 30 years— there's going to be a huge increase in the population over age 65 years. Overall, we'll expect about a 30% increase in RSV and RSV prevalence.



The group that's at greatest risk for complications from RSV are those that have underlying chronic medical conditions. If they're healthy, they typically get mild symptom consistent with a cold and a respiratory tract infection, and they're done in about 5 days. But adults who are older—and 65 years is sort of an arbitrary cutoff, you could make it 70 years—adults with chronic lung disease or heart disease, adults with weakened immune systems, have symptom duration that's often longer, and shed the virus for a lot longer.

The most common conditions we think of that create worse outcomes are asthma, chronic obstructive pulmonary disease (COPD), and heart failure.

Comorbidities Increase Risk of Hospitalization Among Older Adults Who Develop RSV

Patients with medical claim for RSV diagnosis identified using the Medicare 5% national sample administrative database between July 1, 2011, and June 30, 2015

Associated Risk Condition	Odds Ratio (95% CI)*	*P* Value
Osteoarthritis	0.72 (0.51-1.02)	0.062
High cholesterol	0.75 (0.55-1.03)	0.074
Asthma	0.79 (0.50-1.24)	0.303
Coronary artery disease	1.16 (0.82-1.65)	0.411
Stroke	2.00 (1.02-3.96)	0.045
Congestive heart failure	2.06 (1.40-3.02)	<0.001
Chronic obstructive pulmonary disea	2.12 (1.49-3.02)	<0.001
Solid organ transplant	2.52 (0.88-7.22)	0.085
Stem cell transplant	2.53 (0.21-29.70)	0.461
Chronic kidney disease	4.37 (2.74-6.98)	<0.001
Hematologic malignancy	5.17 (2.02-13.20)	0.001

*Odds ratio >1 indicates that the variable is a positive predictor of hospitalization among patients who were initially hospitalized as compared with patients who were never hospitalized

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Wyffels V, et al. *Adv Ther*. 2020;37:1203 -1217.

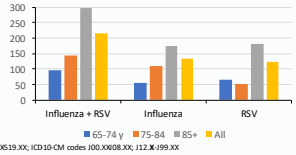
Stroke, heart failure, COPD, CKD, and then malignancy solid organ transplants, things that affect the immune system—are highly significant in a risk for hospitalization.

This is a study that Bosco published last year, where they were looking at medical claims for RSV diagnosis in a 5% sample of all Medicare patients in the US.

RSV Is an Important Cause of Cardiorespiratory Hospitalization

- Retrospective analysis for 6 respiratory seasons (2011-2017)
  - Medicare Provider Analysis and Review inpatient claims and Minimum Data Set
- Long-stay (≥100 d) residents of long-term care facilities age ≥65 y

Attributable Cardiorespiratory* Hospitalization Rate (per 100,000 person-years)



*ICD-9-CM codes 390.XX459.XX; ICD10-CM codes 100.XX199.XX; ICD9-CM codes 460.XX519.XX; ICD10-CM codes J00.XX008.XX; J12.X-J99.XX

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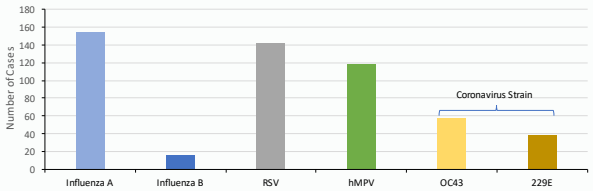
Bosco E, et al. *JAMA Netw Open*. 2021;4(6):e2111806.

If you look at this comparing influenza to RSV, and this is divided by age groups, the blue is 65 to 74 years, the orange is 75 to 84 years, and the gray is 85 years plus. And you can see the older they get, they get greater cardiorespiratory hospitalization with each of those decades. And the yellow is the average of those 3. This is a retrospective analysis for 6 seasons, and it was looking at specifically long-stay residents. Long-stay residents are those people who live in nursing homes and have been there for at least 100 days. And typically, those are the people who are going to be permanent residents of nursing homes. You can see this age-dependence for cardiorespiratory hospitalization with RSV.

Viral Pathogens in Hospitalized Patients



229E, Coronavirus strain 229E; hMPV, human metapneumovirus; OC43, Coronavirus strain OC43; RSV, respiratory syncytial virus

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Falsey AR, et al. *N Engl J Med*. 2005;352(17):1749 -1759.
Walsh EE, et al. *J Infect Dis*. 2013;208(10):1634-1642.

If you take all comers, as they arrive in the hospital and you test them for viruses, you can see that RSV ranks right up there with Influenza A. Human metapneumovirus is not quite different. One of the things that's relevant about this is that you have slightly different isolation precautions depending on which virus you're diagnosed with. Then the beta-coronaviruses don't cause nearly as much hospitalization in terms of their overall contribution.

RSV Infection in Older Adults

- Rates of office visits for RSV vs influenza were lower in healthy adults but similar for high-risk adults
- For hospitalized patients, RSV and influenza resulted in similar
  - lengths of stay (14 vs 8 days)
  - ICU admission (15% vs 12%)
  - mortality (8% vs 7%)
- RSV accounted for:
  - 11.4% of COPD exacerbations
  - 10.6% of pneumonia admissions
  - 7.2% of asthma admissions
  - 5.4% of CHF admissions

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit

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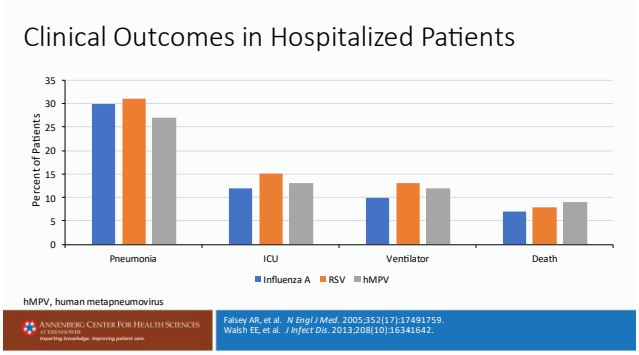
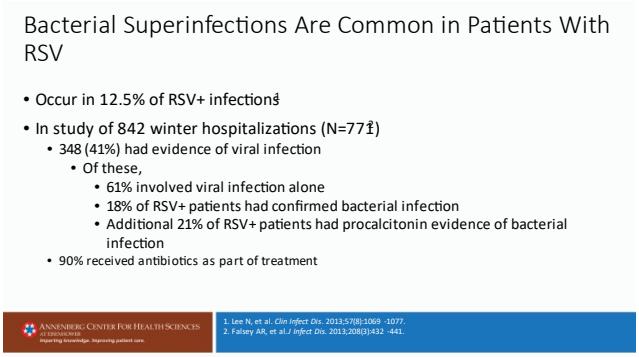
Falsey A, et al. *N Engl J Med*. 2005;352(17):1749 -1759.

In the office setting, RSV compared to flu are much lower in healthy adults, but similar in high-risk adults. The likelihood of showing up and getting your clinical attention in the office setting seems to be a fraction of it with RSV, but once they arrive in the hospital, these 2 are pretty close. For hospitalized patients, RSV and flu are similar.

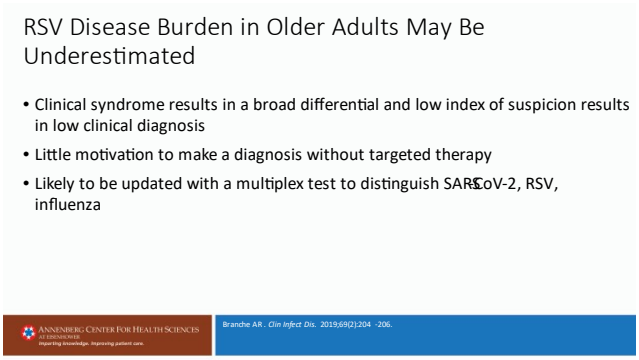
The lengths of stay are 14 vs 8 days. ICU admissions, 15% vs 12%. Mortality, 8% vs 7%. RSV accounts for about 11% of COPD exacerbations, pneumonia admissions, about 7% of the asthma admissions and about 5% to 6% of heart failure admissions.



Pneumonia about the same. ICU percent of patients about the same. Ventilator use similar, where blue is flu and orange is RSV and gray is human metapneumovirus. And mortality is similar between these 3 groups. The bad respiratory viral infections stack up similarly.



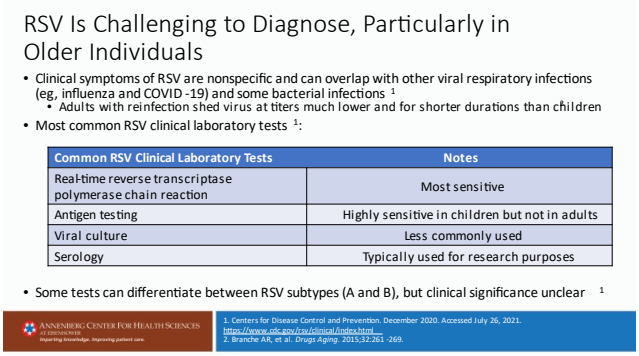
A complication of any viral infection can be a bacterial superinfection. And it's been estimated that somewhere between 10% and 15% of RSV infections will have a bacterial superinfection. Of people that were hospitalized—so this is 842 winter hospitalizations in 771 people—about half of those people had evidence of a viral infection, 41% is the actual number. And of these, two thirds only had a viral infection. And about 1 in 5 had RSV plus a bacterial superinfection. And of the 21% of the RSV patients had a procalcitonin evidence of bacterial infection on top of that other 18%. So, 30%, 40% or so of RSV patients will have some evidence of bacterial infection. Ninety percent of them received antibiotics. And so if only 40% have a bacterial super infection, it suggests that there's a substantial proportion that maybe didn't need an antibiotic in their management.



RSV gives a disease burden, but we probably undercount it quite a bit. When I think about, in the outpatient clinic, how often do we actually test for an RSV? And if we don't have an index, a suspicion for it, we may miss it. We may empirically end up treating somebody for something that they don't have, whether it's with an antibiotic for a bacterial infection that they don't have, or whether it's with an antiviral, say the flu when they have RSV and the flu antivirals don't have a place for treating RSV. In general, the idea of testing for RSV hasn't been something people have really thought about because there hasn't been a targeted therapy. Now because SARS-CoV-2 has been around, when people come in with respiratory infections, we have a lot more reasons to want to know what they're infected with.

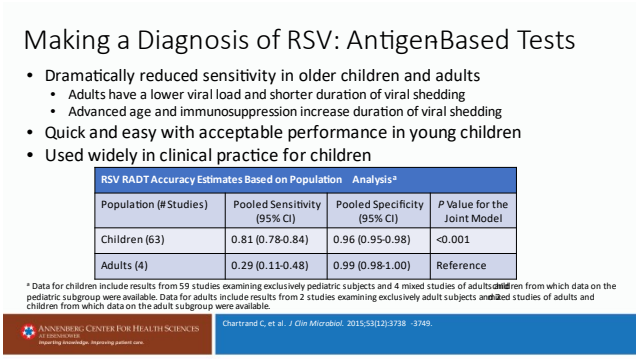
If given the day that they present, you could get a negative SARS-CoV-2 test, and they might still have SARS-CoV-2, but it's, generally speaking, not that likely that they'll have 2 viral infections at once. If you do a multiplex test to see what they have, and the SARS-CoV-2 is negative, and the RSV is positive, or flu

is positive, it actually helps you say, "Oh, we're not going to have to quarantine the family. We're going to be okay. And we can manage this supportively or with an influenza antiviral if they have flu. Because we haven't been looking for it and looking to distinguish SARS-CoV-2 from other things, that hasn't been available. But I think there's going to be a shift in how we do this in outpatient settings.

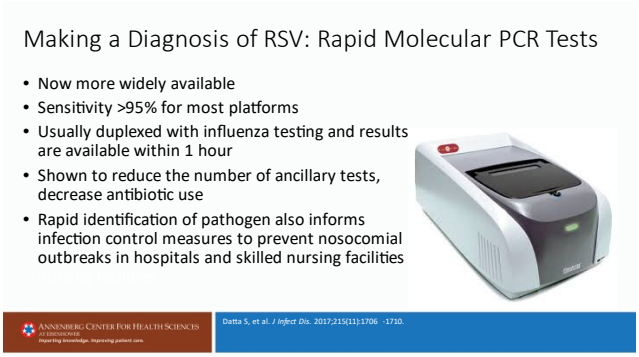


We can't really distinguish the clinical symptoms between these various viral infections because they overlap too much. Without a test, you can't be confident, unless it's the only virus that's actually circulating in the community. Adults also don't shed as much virus, especially the relatively healthy adults, and they shed it for shorter durations than children. You may end up getting a negative test, even if they have an infection.

The kinds of tests that we have are the PCR tests and there are now some PCR tests out there for multiplex testing. Antigen test works really well in kids, not so well in adults. In kids, it has about an 80% sensitivity, in adults closer to 30%. Viral culture isn't used that much. And it takes too long to get the result back to act on it. And serology, typically, you won't have for a couple of weeks. We use that mostly in a research setting, not elsewhere. Some tests can differentiate between the RSV subtypes A and B, but we don't yet know whether it matters, whether you have 1 subtype or the other in terms of outcomes or, for that matter, for whether vaccines or other drugs work.

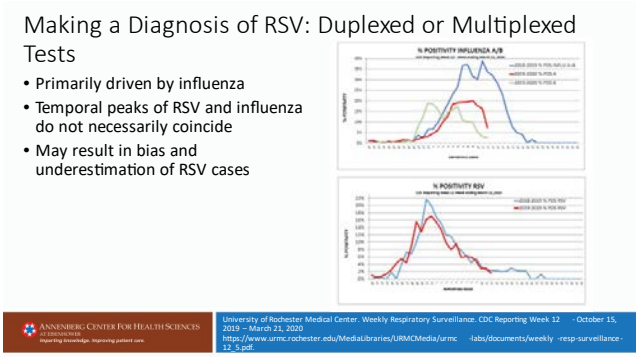


If you make a diagnosis using an antigen-based test that's appropriate for kids, and you can see here, 81% sensitivity and 96% specificity in older adults, you only get a 30% sensitivity, which means you miss 70% of them. But if it is positive, it's 99% specific. A highly reliable to tell you that, that's the pathogen if it turns up positive, but it just isn't great because it misses so many of them. It's quick and easy, and it's what is used in a lot of the pediatric offices.

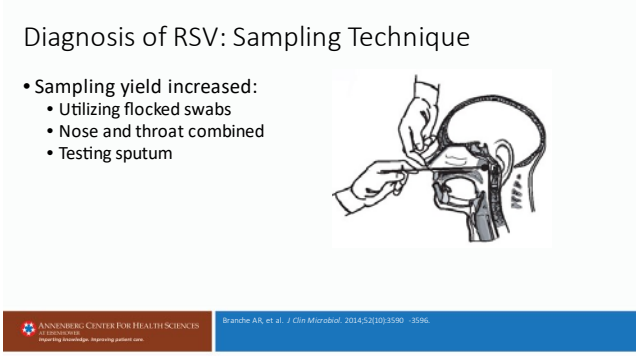


Here's an image of a RT-PCR machine. These rapid molecular PCR tests, they're more widely available now and sensitivity is greater than 95% from this platform. It overcomes the drawback of that antigen test. They're usually duplexed. Typically, these tests have been now used a lot for the SARS-CoV-2 infections and now paired SARS-CoV-2 and influenza. And, more recently, SARS-CoV-2, influenza, and RSV can be gotten together as a multiplex assay. And that reduces the use of ancillary test by 15%, 20%. It reduces the risk for giving an antibiotic that's not appropriate by 15% to 20%. And it gives you rapid

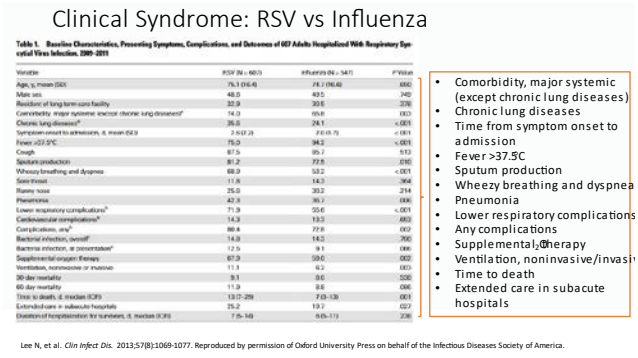
identification with an hour, you can find out what the pathogen is and then decide whether that should inform infection, control measures. For example, if this person lives in congregate housing, a nursing home, or visits an adult daycare setting.



This is from the University of Rochester, published last year, and this is looking at duplexed or multiplexed tests. Primarily, getting the test has been driven by flu in the community. The temporal peaks of RSV and flu don't necessarily coincide and that can produce a bias. And so here they're showing you some of that when you look at this positivity. The blue line is 2018/2019 positive flu A and B. The red is flu A and the green is flu B. And if you look at RSV in the 2018/2019 season, the red here is the 2019/1920 and the green is the 2019/1920 for A and B, and blue is both, but you can see the blue curve here below for RSV is shifted off to the left. Since they're getting it when they're thinking about flu. But you may be underestimating RSV if you won't have it during other parts of the season. You can see RSV is more common out here to the left. They overlap, but they don't overlap exactly. And they might be shifted one way or the other, depending on a whole bunch of features, including the behaviors of people out there. We don't have a lot of RSV or flu right now because people are still, relatively speaking, isolating themselves. But as they start letting go of their guard, and you can see that when you see people attending games in the stadiums and so forth and reappearing in restaurants unmasked and back at gatherings, that will not just increase the SARS-CoV-2 case rate, which is currently flattening out in the country, it'll also allow for the reintroduction spread of RSV and flu. And as you've heard, that has begun.

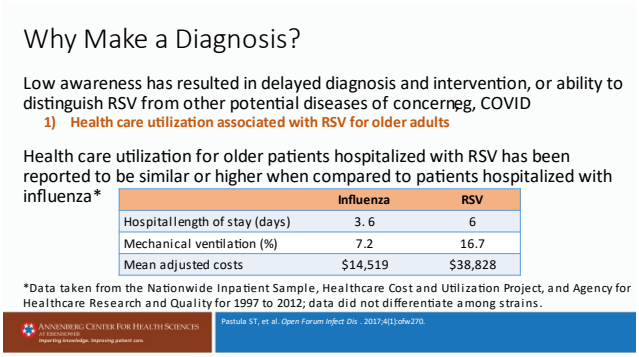


If you're going to get a test for RSV, you want to use a flocked swab. You can see this direction is pointing it toward the ear canal. I've seen a lot of folks, when you're supposed to lift up the front of the nose a little bit, and when I see people doing these tests, a lot of times they're aiming up toward the eye, the angle of the nose, but it's actually supposed to go straight back to the ear canal. When you put it in, I'm typically twirling this to let it go past things. I don't have to push it past the turbinates. I twirl it and it finds its way around it, as it goes back. By the time you hit the posterior pharynx, if you're doing it properly, what'll happen is you'll see a little tear come out. It shouldn't be uncomfortable unless you're too rough. You really just have to take your time to do that. You can also do a throat swab at the same time and you can test sputum. If you do all 3 of those together, you get a higher yield. You get a greater likelihood of getting somebody test positive that has positive. Back in the '90s, we did a study in nursing home residents where we separated out a nasal pharyngeal specimen from a throat swab and for RSV specifically, about half of them that were positive by the nose were negative by the throat and vice versa. Doing a combination of tests really makes a difference in the outcome.



The comorbidities, if you exclude chronic lung disease, are a major difference between flu and RSV. Chronic lung diseases, by themselves, are also different between these 2 in terms of distinguishing the syndromes. The time to symptom onset is longer for RSV. Fever, and in this case fever is 37.5°C, is also different between these 2 groups. RSV isn't quite as febrile as flu. And with SARS-CoV-2, we published a paper last year where we talked about using a lower threshold for SARS-CoV-2 screening in older adults. If you use 38°C, you miss about 75% of older adults because they never hit that mark when they have a SARS-CoV-2 infection. If you drop it down to 37.2°C, that's 99°F, you pick up about 75% of them. You still miss 25%. RSV has the same problem. If you have your threshold too high, you're going to miss most of them. Seventy-five percent are caught at a 37.5°C threshold vs 94% for flu. And you need a lower threshold of temperature if you're going to find more of them. So not having a fever, because some older adults can get infected and not have a fever, shouldn't be a reason to not sample and test them if you're thinking about, for example, prescribing an antibiotic. Doing the test correctly and getting that test to get a result will help drive that decision. If they're producing sputum, that's also different. RSV produces more sputum. The way that RSV when it infects, it has a fusion protein. When it gets into a cell, it fuses it with the next cell to produce these syncytia, which is why it's called respiratory syncytial virus. And that creates greater sputum production as these cells then begin to slough off. Different risks for pneumonia, a little bit higher for RSV than for flu. Lower respiratory complications also for these reasons. And because of the mechanism with syncytia, I think, is different.

Getting any complications, needing oxygen is a bit higher with RSV ventilation, and noninvasive and invasive also is a little higher, and time to death is different. In RSV, the disease progresses a little more slowly, both in the natural evolution, but also if they're going to die, it takes a little longer before they die. And it's a bigger deal in extended care and in subacute hospitals, there's a greater use of these with RSV.



Why bother making a diagnosis? There's a low awareness of RSV in general, and that includes people like me who know something about RSV. I still don't systematically test for it, and I'm starting to change what I do. A reason to know this is that RSV really maps to healthcare utilization. Perhaps also incorporate utilization, including and knowing can help with antibiotic stewardship and diagnostic stewardships. You don't have to be testing say for SARS-CoV-2 or other things. When we look at it that's in other versions of hospital utilization, RSV has not quite doubled the length of stay in the hospital, not quite, a little bit more than double mechanical utilization. And a little more than double in adjusted costs in older patients who get RSV. And that difference grows, the older they get.

Why Make a Diagnosis? (cont)

Low awareness has resulted in delayed diagnosis and gaps in knowledge

1) Health care utilization associated with RSV for older adults
2) **Long-term morbidity and mortality associated with RSV infection in this population**

	Better	Worse	Same	Total
MRC	72 (37.7)	45 (23.5)	74 (38.7)	191
L-B IADL	50 (25.3)	60 (30.3)	88 (44.4)	198
Barthel ADL	74 (37.9)	63 (32.3)	58 (29.7)	195
GFI	80 (52.6)	50(32.9)	22 (14.5)	152

- 13% mortality at 6 months after discharge
- Change in subjects living independently from 40%→ 32%

Barthel ADL = Barthel Index for Activities of Daily Living (0 -100); GFI = Groningen Frailty Index (0 -15) and Mini-Cog instrument ; L-B IADL = Lawton -Brody Instrumental Activity of Daily Living Scale (0 -8); MRC = Medical Research Council Breathlessness score (1-5).

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Branche A, et al. Unpublished data. 2021.

Long-term, morbidity, mortality, RSV infection is also a little different. You can look at measures of functional status, better and worse vs the same. These are a bit worse with functional measures for activities of daily living. 13% mortality at 6 months after discharge change in subjects, living from independently to dependently, 40% to 32%.

Why Make a Diagnosis? (cont)

Low awareness has resulted in delayed diagnosis and gaps in knowledge

1) Health care utilization associated with RSV for older adults
2) Long-term morbidity and mortality associated with RSV infection in this population
3) **Risk stratification to inform future vaccine efforts**

	October 2017 – April 2018		October 2018 – April 2019		October 2019 – April 2020	
Age groups	Rochester, NY	New York City	Rochester, NY	New York City	Rochester, NY	New York City
	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
18-49 y	9.95 (6.61-14.98)	8.43 (4.78-14.83)	9.09 (5.92-13.94)	11.94 (7.42-19.20)	7.79 (4.91-12.36)	7.72 (4.28-13.95)
50-64 y	57.50 (43.82-75.45)	47.24 (31.67-70.47)	63.03 (48.62-81.70)	57.08 (39.67-82.13)	40.91 (29.64-56.46)	33.46 (20.80-53.82)
≥65 y	138.20 (114.46-166.86)	212.00 (168.58-266.60)	136.92 (113.30-165.46)	255.56 (207.43-314.86)	139.48 (115.62-168.26)	214.90 (171.16-269.83)

Branche A, et al. Unpublished data. 2021.

Why make a diagnosis? The third is the risk stratification to inform future vaccine efforts. Case rates increasing October through April 2017-18, 18-19 and 19-20. This was of course in March when we started lockdown for SARS-CoV-2. You can see these are really quite high in this over 65 group compared to the other 2 groups.

Why Make a Diagnosis? (cont)

Low awareness has resulted in delayed diagnosis and gaps in knowledge

1) Health care utilization associated with RSV for older adults
2) Long-term morbidity and mortality associated with RSV infection in this population
3) **Risk stratification to inform future vaccine efforts**

	Incidence Rate	Incidence Rate	Rate Ratio (95% CI)
Age-groups	**COPD**	**No COPD**	
18-49 years	24.87	7.83	3.18 (0.99-10.17)
50-64 years	204.76	32.25	6.35 (2.00-20.11)
≥65 years	1077.36	80.32	13.41 (4.29-41.98)
Age-groups	**Diabetes**	**No Diabetes**	
18-49 years	65.39	5.86	11.16 (3.45-36.13)
50-64 years	116.77	34.79	3.36 (1.06-10.63)
≥65 years	501.82	77.93	6.44 (2.06-20.17)
Age-groups	**CHF**	**No CHF**	
20-39 years	295.23	8.88	33.23 (10.14-108.90)
40-59 years	485.84	25.87	18.78 (5.92-59.55)
60-79 years	688.58	90.24	7.63 (2.43-23.93)

CHF, congestive heart failure

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Branche A, et al. Unpublished data. 2021.

Risk stratification to inform future vaccine efforts. If you know that there's these specific populations where you have added risk, it should give you added reason to potentially test them and know that they might be in store for complications so you might monitor them differently.

What do you do right now? Well, right now, symptomatic management is the mainstay for current therapy for most adults. The use of steroids, especially for patients with underlying lung disease. How you deal with COPD exacerbations and bronchodilators—neither of those are approved by the FDA for RSV infection in older adults—but both of these are things that we do. Humidified oxygen has been approved and so, thinking about these things, in immunocompromised, you might also consider giving ribavirin, something we mostly use in kids. And in kids, we use monoclonal antibodies. We haven't been using that in older adults, experimental therapies are available, too.

An ounce of prevention is worth a pound of cure. Preventing RSV is a much better approach than acute treatment because there isn't any approved medication for acute treatment of older adults. And antivirals generally work better if somebody's already had a vaccine or something else ahead of time. And if they don't have to be hospitalized you can attenuate the severity of disease.

Take-Home Lessons from the COVID19 Pandemic

- Older adults who contract a viral respiratory infection are particularly susceptible to poor health outcomes, including death
- General preventive measures, including proper masking and social distancing, are effective in reducing viral spread
- People find lifestyle changes to prevent infection difficult to follow long term
- Vaccination helps
  - prevent the spread of infection
  - reduce infection severity

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Take home lessons from the COVID 19 pandemic is that older adults who contract a viral respiratory infection are particularly susceptible to poor health outcomes, including death. If you do the general preventive measures like masking, distancing, and so forth, you can be effective in reducing viral spreads. People can find lifestyle changes to prevent infection difficult to follow long term. So, you're seeing pushback on our constraints, asking people to wear masks when they go shopping and so forth.

That's the hard thing to follow through. A solution to this would be to have a vaccine that can keep them from getting sick in the first place and hopefully prevent the spread of infection. And if they still get infected, reduce the severity of infection like we get with SARS-CoV-2 vaccines.

General RSV Prevention Measures

- Perform frequent hand hygiene
- Masking
  - Double mask
  - Hook and loop
  - Properly fitted
- Cover coughs and sneezes
- Stay home when sick
- Avoid those who are sick
- Keep high-touch surfaces clean and disinfected
- Isolate infected patients in health care settings

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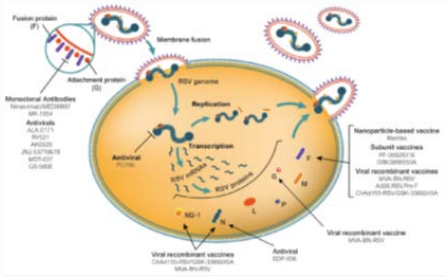
Centers for Disease Control and Prevention. Accessed July 27, 2021. December 2020. https://www.cdc.gov/rsv/high_risk/older-adults.htm
Centers for Disease Control and Prevention. Accessed July 27, 2021. December 2020. https://www.cdc.gov/rsv/about/prevention.html

Frequent hand hygiene, masking, and when you mask, we talked about double masking being more effective than single masked, especially if they're homemade. Hook and loop, but where you can twist the loops if you're using ear loops and making sure they fit properly. A clue about proper fit is they don't fog your glasses with your glasses on. Keeping them home when they're sick, avoid those who are sick, keeping high touch surfaces clean and disinfected. So, these are all practices that we do in nursing homes already. And then, isolating infected patients in healthcare settings.

Treatment Targets



F, fusion protein; G. attachment glycoprotein; L, large viral polymerase; M, matrix protein; M2 -1 protein, transcription factor; N, nucleoprotein; P, phosphoprotein

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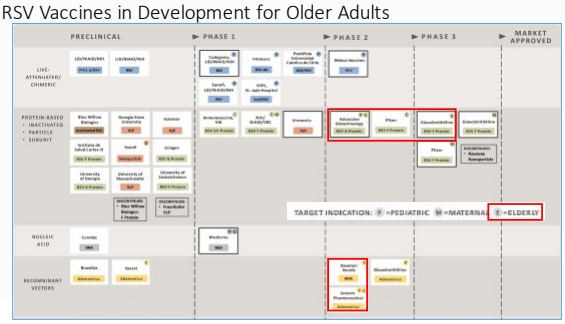
Here is an image of the virus as it was shown by Domachowske. What you're supposed to see on the top left is this blowout of the surface of the RSV virus. What you see are these fusion proteins and vaccine targets. Most of them are targeting this fusion protein. Some of them have targeted the G protein, which is an attachment protein. The fusion proteins' function is when the virus infects a cell, it allows that cell diffuse with the next cell over and propagate the infection across cells without having to necessarily leave the cells. But it also buds off to then go infect other cells. This is a negative sense RNA virus, much like SARS-CoV-2. It gets into the cell and you can target antivirals for this step where the RNA needs to start making copies of itself. The RNA itself uses the ribosomes already in cells to then make out the proteins. These various proteins that are produced by this, including the fusion protein and the G protein, become antiviral targets, and also vaccine targets. Most of the vaccines have actually targeted the fusion protein and there's 2 versions of this fusion protein, a prefusion protein and a postfusion protein. And, from the data that I've seen, it looks like those targeting

prefusion proteins might, in fact, have better function.

RSV Vaccines in Development for Older Adults



Adapted from PATH.org. Updated April 7, 2021. https://www.path.org/resources/rsv -vaccine -and-mab-snapshot/. Accessed July 29, 2021. NCT03572062. https://www.clinicaltrials.gov/ct2/show/record/NCT03572062?term=NCT03572062&draw=2&rank=1 .

Different vaccines that are in different stages of development. You can see a few here in phase 3. Some of these are specifically targeting older adults. The F protein, here's one for G protein, F protein, F protein, and so forth. For the recombinant vaccines for SARS-CoV-2, and the adenovirus vectors are being used for this, too. They're for older adults. There's one from Moderna for mRNA, adenovirus vector from Janssen and Bavarian Nordic. Then from Pfizer and GSK, you can see some in phase 3 trials here targeting F protein.

RSV Vaccines in Development Targeting Older Adults

Platform	Phase	Formulation/Antigen	Results
mRNA-1777	1	mRNA Prefusion RSV F	Neutralizing antibodies; RSV F -specific serum antibodies; RSV -specific CD4 and CD8 T cells
VXA-RSVf	1	Vector-based RSV F	N/A
PanA d3-RSV	1	Vector-based RSV F, N, M2	RSV-specific IgG and IgA; T cell -mediated IFN-γ
Ad26.RSV.PreF	2	Vector-based Prefusion RSV F	Ongoing
MVA-BN-RSV	2	Vector-based RSV F, G, N, M2	Well tolerated; neutralizing antibodies; T cell -mediated IFN-γ
MEDI-7510	2	Subunit Postfusion RSV F + GLA -SE	RSV F-specific IFN-γ; did not meet primary endpoint
GSK3844766A	3	Subunit Prefusion RSV F + AS01	Ongoing
ResVax	3	Particle-based RSV F trimers	Acceptable safety and tolerability; RSV -specific serum IgG; neutralizing antibodies; did not meet primary endpoint

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Rearranged in a slightly different way, you can see here what the target is of these different vaccines. Some of them use a single target like this one, RSV, just the fusion protein, and some others have other things mixed in like an adjuvant or other proteins than are part of the virus. In general, the data from these vaccines where there's data available look like they're pretty well tolerated. It looks like they develop a neutralizing antibody, which should be able to prevent disease. We'll have to wait for the phase 3 data to know whether they're, in fact, effective.

Shared Decision-Making

Consider that a strong recommendation from a clinician is the single most effective strategy to vaccine acceptance.

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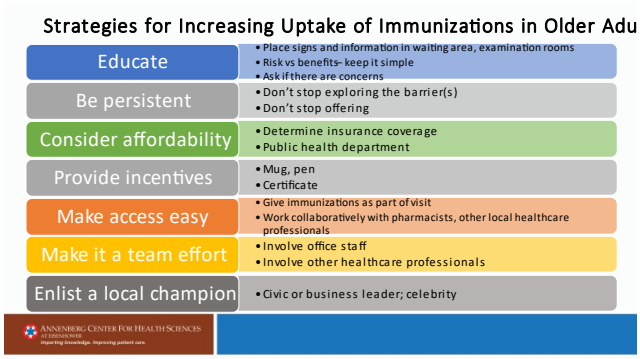
When you try to recommend a vaccine, whether it's a flu vaccine or a SARS-CoV-2 vaccine or a pneumococcal vaccine, regardless of the patient's disposition on taking a vaccine, their likelihood of accepting a vaccine begins with the clinician making a strong recommendation.

This should not be, "I think this would be a good day for you to get your vaccine." Instead, you frame it, "Today, we're going to get you your influenza vaccine or your SARS-CoV-2 vaccine." When I do this, I try to present it that this isn't just an opinion or a good idea, this is part of their care. This is part of what good care looks like. Yes, they can refuse it. They can refuse anything that you suggest. But I think if you don't go in with the expectation that they're going to be accepting the vaccine, you're going to find people declining vaccine that you could have gotten to yes. And gotten that added protection. It's true for all of the licensed vaccines that you should have a strong recommendation.



When you go through the discussion with them and talk about this, you do want to educate. As you make it, "I'm going to have you get this vaccine." and you have signs in the lobby to say flu vaccine available and so forth. You put it in the examination rooms, risks, and benefits. So, if I were doing this for a SARS vaccine, the risk of having an uncontrolled SARS infection relative to the risk of getting SARS-CoV-2 vaccine is a fraction of the risk with the vaccine where you have a controlled immune response, than a natural infection where you have no control. It's just whatever the body happens to do.

[And what about patients] asking, or if there are concerns. If there's barriers, I don't stop exploring the barriers and I need to ask them. I'm going to say, "You're going to get the vaccine. Do you have any questions? I can tell you more about it." But often they're itching to get out of there if they have a ride with them and so forth. If they have some hesitancy or some issues with acceptance, I'll work my way through this list of things. If these vaccines are free, like the SARS vaccine is, the influenza vaccine's covered by health insurance and so forth.

There might be incentives that you can use, you make it as a standard part of visit. It's an expectation. You can work collaboratively with the pharmacist in the community. If your pharmacist doesn't communicate with you that they're giving vaccines to your patients, then there's still some work to do so that you can get quality credits for that. Involve your office staff. The way it works in our office is that expectation, you're going to get your vaccine today, starts with the check-in nurse. And, if there's any pushback, they say, "Well, if you're reluctant, you're going to have to talk with the doctor about this or whoever your clinician provider is." It's like going to the principal's office. And I think that helps reduce the number of discussions that actually make it to me and allows me to stay on time for my visits.

You can enlist a local champion. When we've done our campaigns for the SARS-CoV-2 this past year, we've identified local champions for the nursing homes and nursing home staff that could add to our voices as part of what we do. And I think the SARS-CoV-2 discussions are more complicated because there's a question about whether this is part of civic duty, as opposed to just taking care of yourself. And that gets a more complicated discussion about mandates and so forth, which we won't entertain today.

There's a lot of resources out there available through the American Academy of Family Physicians, the CDC, the Immunization Action Coalition, the Institute for Vaccine Safety, the National Center for Immunization and Respiratory Diseases, and NIAID.

I told you before that I had 3 fun facts. The first of those that I gave you was the fun fact of the smaller airways that kids have. The second fun fact that I would tell you is that a way that kids and older adults differ is that older adults have immunosenescence. They have this reduced response to new antigens.

When kids get an infection, they have this very quick pick-up in cytokines, those chemical messengers that tell the white cells to come in and recruit them and bring them into action [more rapidly] than older adults, and those very same cytokines that help recruit other cells also circulate in the blood. Even if there's no virus in the blood, the cytokines do circulate and they get in the brain and they turn on the temperature receptors in the hypothalamus.

The kids have a higher cytokine kick. They get higher fevers than older adults who have a lower cytokine kick. That kick kicks up faster, recedes faster. In older adults, it comes up slower. Doesn't get quite as high. Lasts a lot longer, sometimes even weeks, and then comes down again. They're quite different. That changes the clinical presentation that they have. Children don't have prior immunity. They have also greater peak viral shedding. They have more easily transmissible disease, much like in people who have SARS-CoV-2 vaccines. If you have had no vaccine, you have peak shedding that skyrockets up and stays up for a few days where you're at peak transmissibility. If you get a vaccine, the time it peaks is shortened quite a bit. The days where you can shed efficiently is actually quite a bit less.

The third difference between older adults and kids is that older adults are more likely to have underlying diseases that generate a different set of outcomes. In kids, bronchiolitis is probably the most important thing, but in older adults, you've heard of COPD and heart failure and so forth, and they can have much worse outcomes. Those are the 3 fun facts.

I'm going to summarize now what we've talked about, and the first thing was that RSV in general is under-recognized in older adults. They have an altered presentation, but that presentation—that nuance of how they're different that helps a little slower progression and so forth—doesn't actually help you clinically distinguish one person from the next, RSV vs something else. I think with SARS-CoV-2, if they happen to have loss of sense of smell or a dry cough, like the captopril cough, that might help you in your mind triage them into one or the other, but you can get a loss of sense of smell with both RSV and flu. It's just not very common with them. You can get a cough that could be a nonproductive cough with those 2. The dry cough for SARS-CoV-2 actually has an acoustic signature that's pretty similar to the ACE inhibitor cough.

It might be that at some point we'll have a way to get that recorded and compare it, maybe make a diagnosis without a blood test. Being aware that it's out there might also make you lean toward getting a multiplexed test, which increases your yield for knowing what they're coming in for with respiratory infection, and making you direct what your intervention's going to be with SARS-CoV-2, where we're going to have antivirals available someday vs monoclonal antibody vs influenza, where there's now 3 classes of antivirals available vs RSV, where we don't have any antivirals yet, but they're in development. For all 3 of these, of course, we have vaccines. So, we do need a primary approach for RSV, and that's vaccination. That is something that we're now in the process of developing.