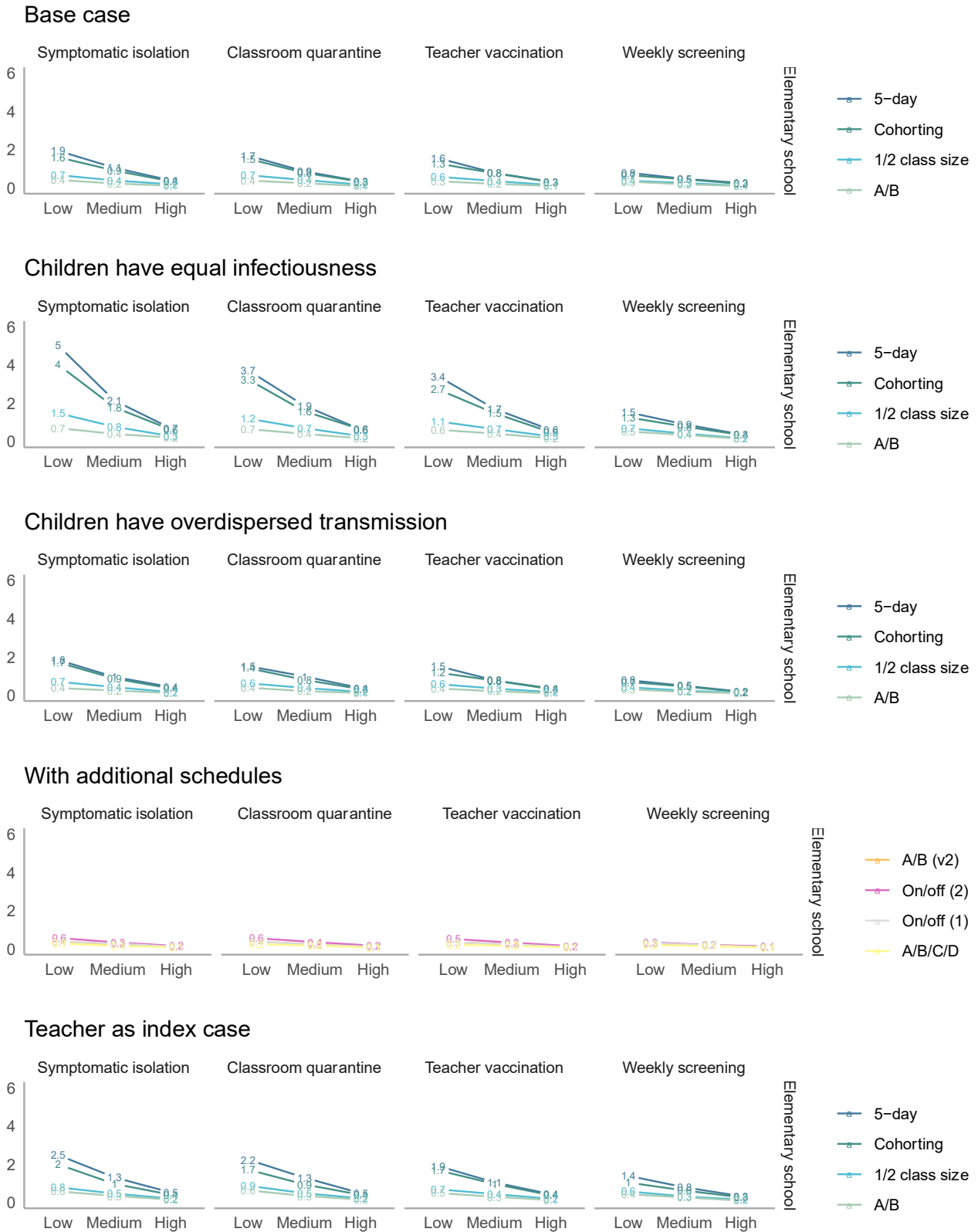


Supplementary Material*

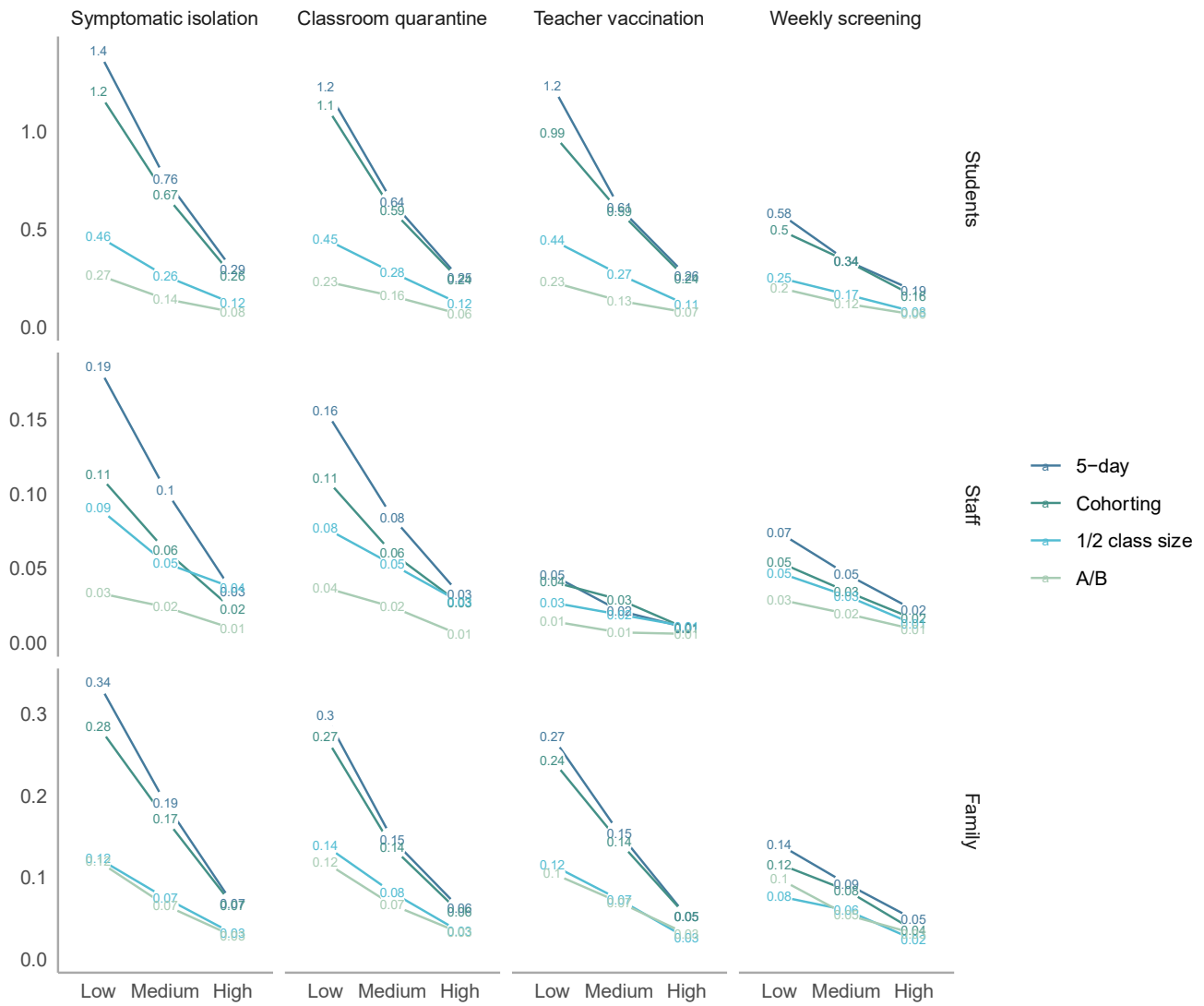
Bilinski A, Salomon JA, Giardina J, et al. Passing the test: a model-based analysis of safe school-reopening strategies. *Ann Intern Med.* 8 June 2021. [Epub ahead of print]. doi:10.7326/M21-0600

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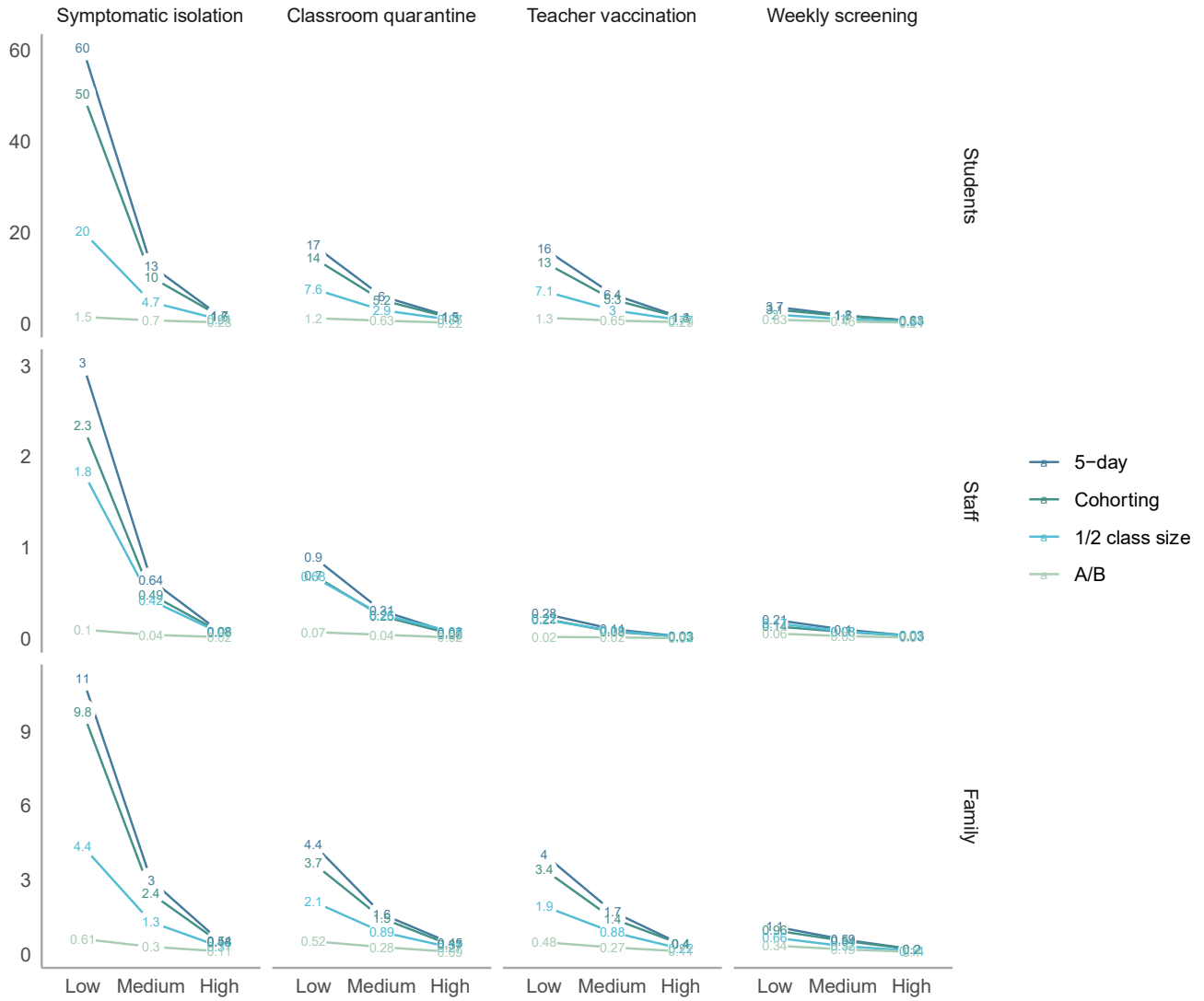
* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.



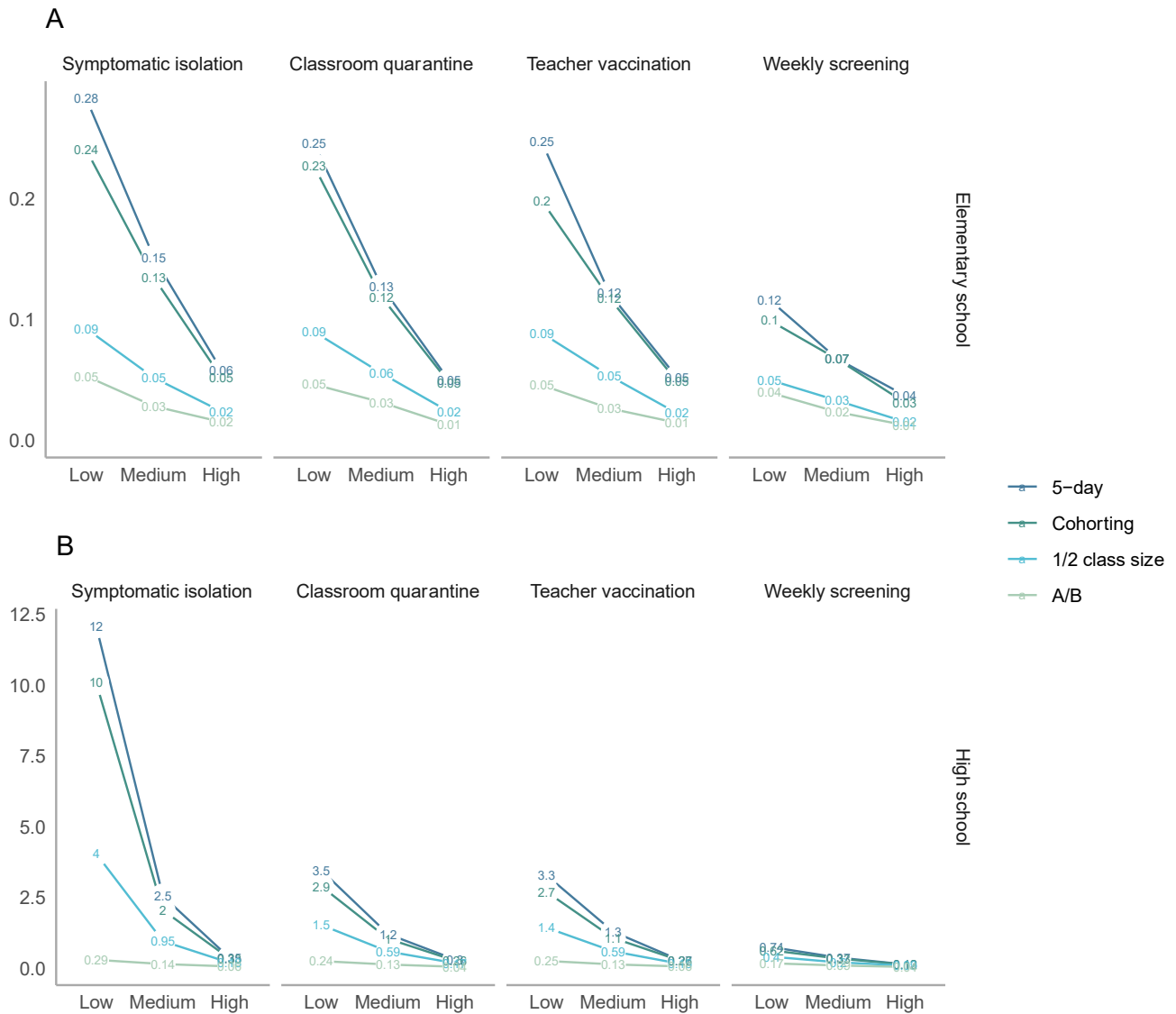
Supplement Figure 1: Sensitivity analyses (elementary schools) – average number of total secondary transmissions over 30 days (outside of the index case’s household) following a single introduction into a school community. The x-axes vary the level of mitigation, with low assuming minimal interventions and high assuming intensive interventions. Line colors correspond to scheduling strategies: A/B (v2) – hybrid model with half of students attending M/T and the other W/Th; On/off (2) – all students attend M/T; On/off (1) – All students attend M, A/B/C/D – hybrid model with one quarter of students each attending M, T, W, Th.



Supplement Figure 2: Sensitivity analysis - elementary school base case broken down by case type. Average number of total secondary transmissions over 30 days (outside of the index case's household) following a single introduction into an elementary school community. These include both transmissions directly from the index case, as well as from secondary and tertiary cases. The x-axes vary the level of mitigation, with low assuming minimal interventions and high assuming intensive interventions. Line colors correspond to scheduling strategies.

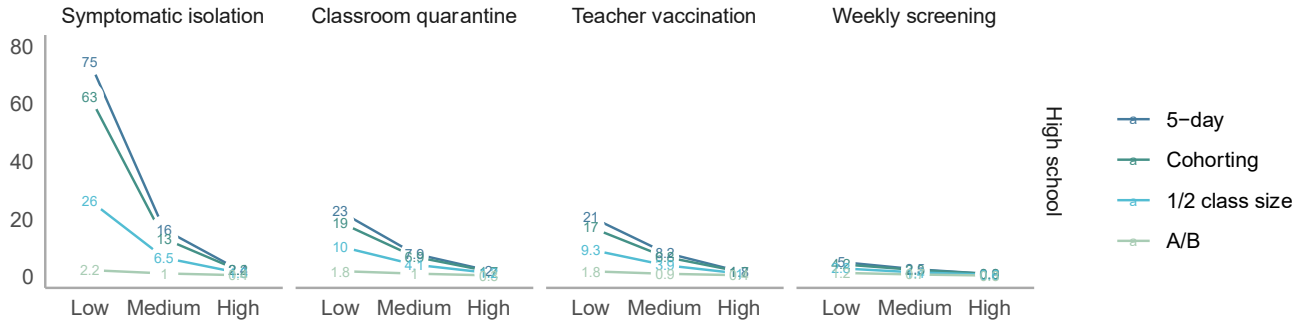


Supplement Figure 3: Sensitivity analysis - high school base case broken down by case type. Average number of total secondary transmissions over 30 days (outside of the index case's household) following a single introduction into a high school community. These include both transmissions directly from the index case, as well as from secondary and tertiary cases. The x-axes vary the level of mitigation, with low assuming minimal interventions and high assuming intensive interventions. Line colors correspond to scheduling strategies.

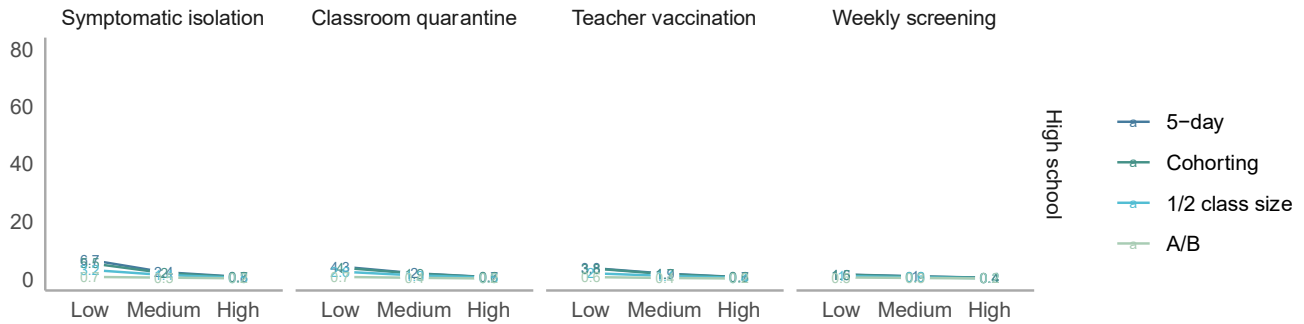


Supplement Figure 4: Average number of clinically symptomatic cases in staff and students over 30 days following a single introduction into a school community. These include both transmissions directly from the index case, as well as from secondary and tertiary cases. The top panel shows elementary schools, where children are assumed to be less susceptible and less infectious, while the bottom panel shows high schools. Note that y-axes differ across rows. The x-axes vary the level of mitigation, with low assuming minimal interventions and high assuming intensive interventions.

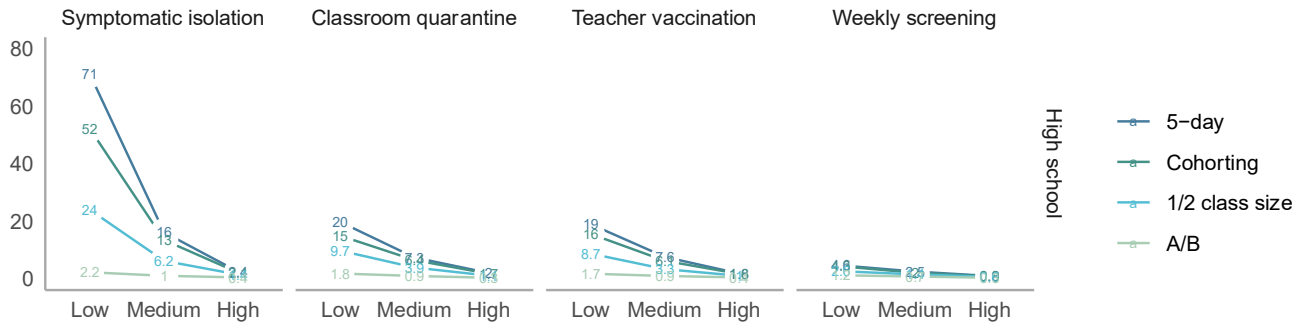
Base case



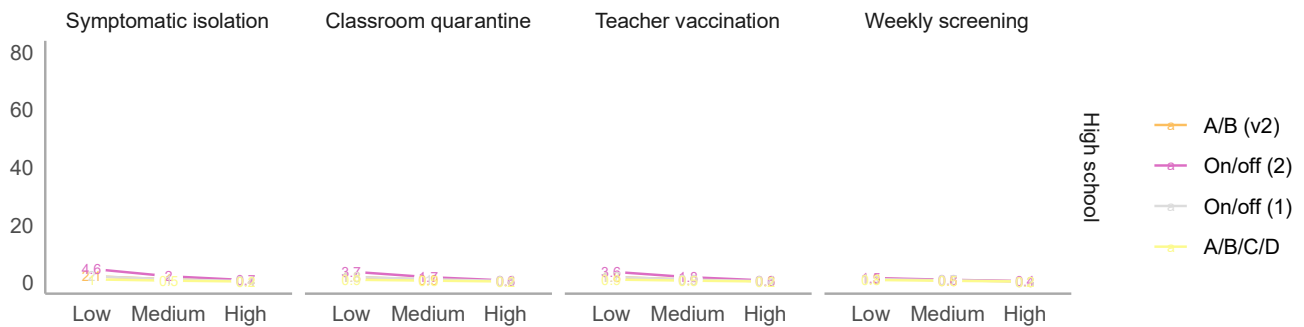
Adolescents less susceptible



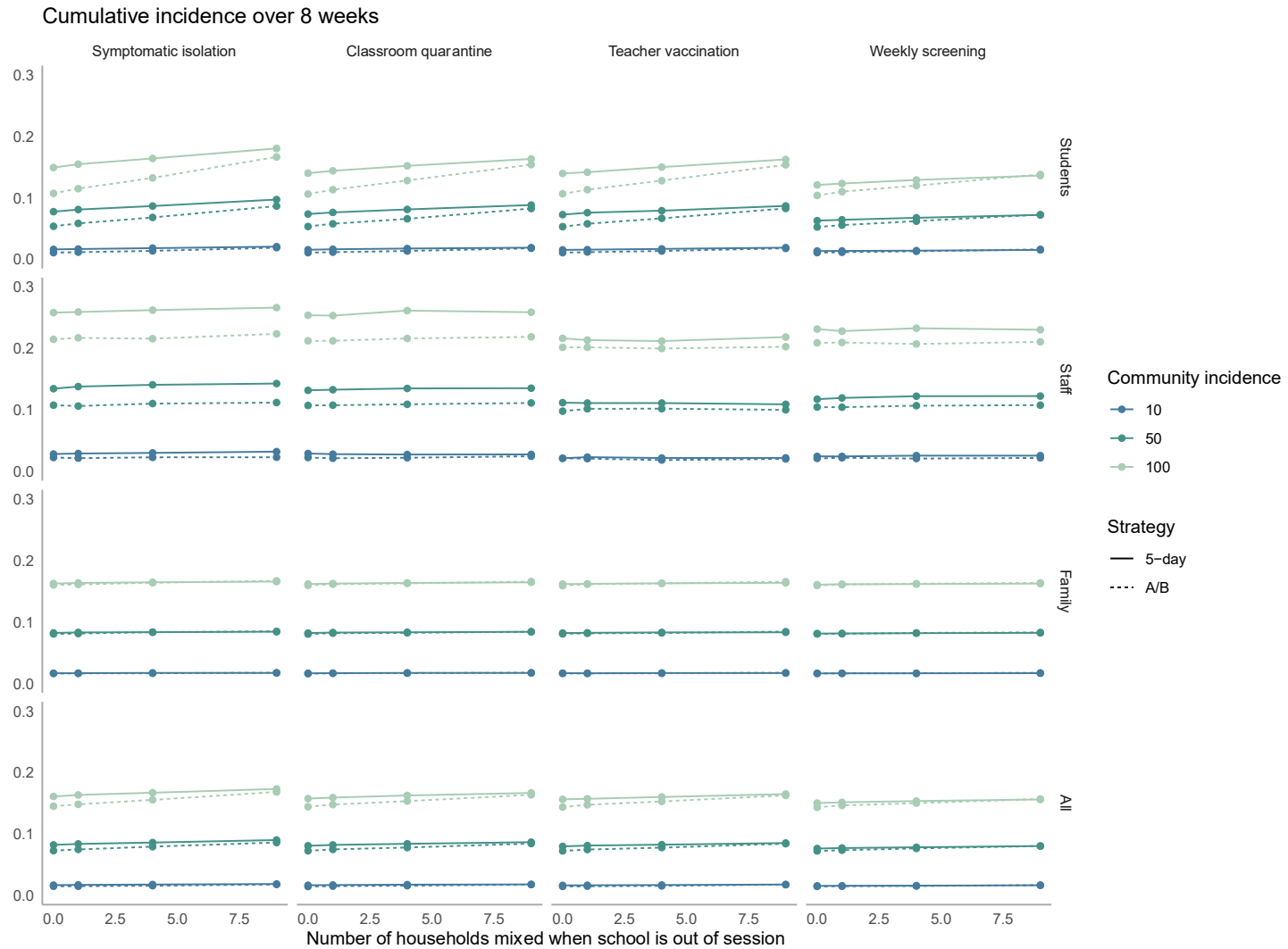
Adolescents have overdispersed transmission



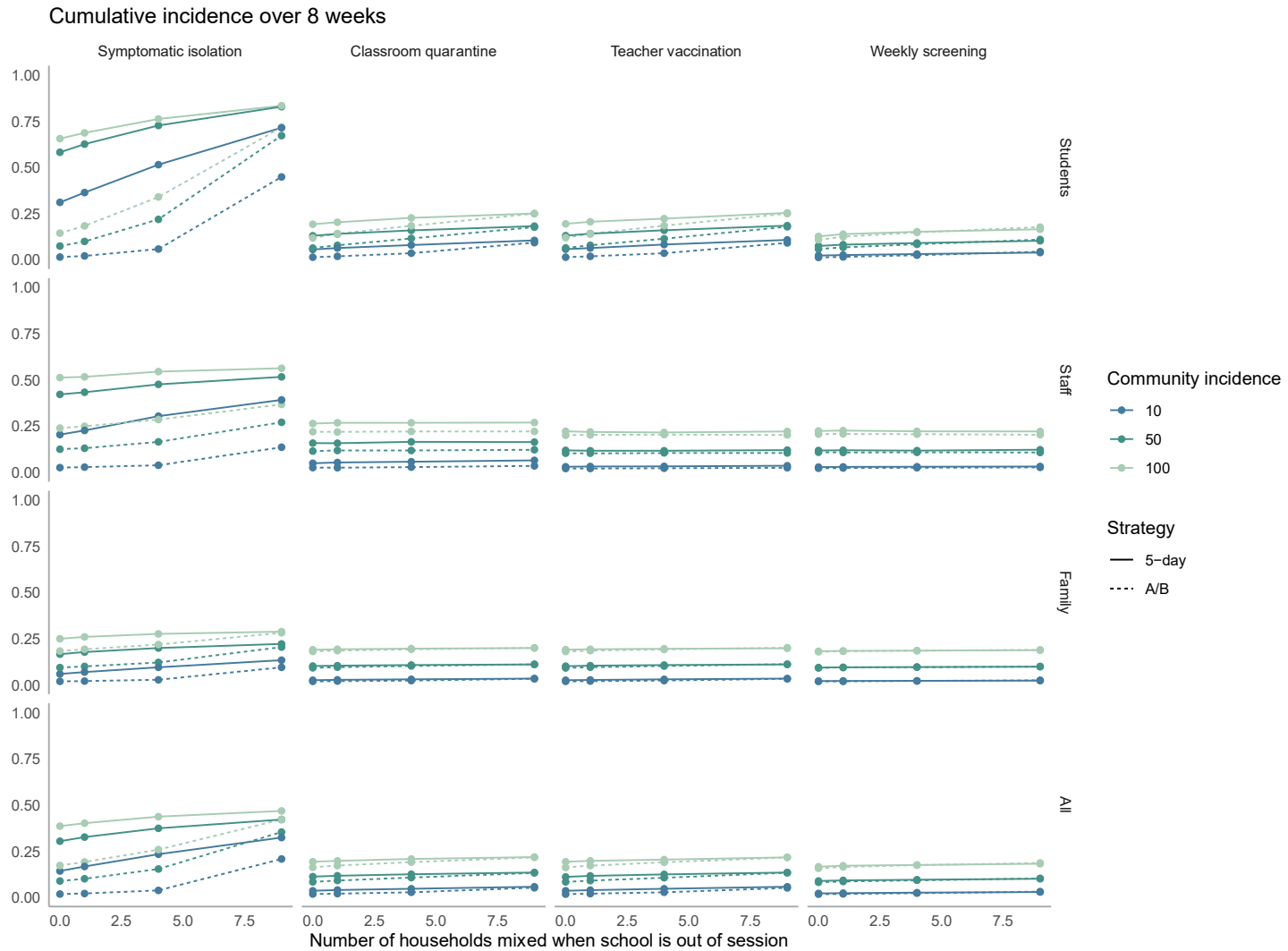
With different schedules



Supplement Figure 5: Sensitivity analyses (high schools) – average number of total secondary transmissions over 30 days (outside of the index case’s household) following a single introduction into a school community. The x-axes vary the level of mitigation, with low assuming minimal interventions and high assuming intensive interventions. Line colors correspond to scheduling strategies: A/B (v2) – hybrid model with half of students attending M/T and the other W/Th; On/off (2) – all students attend M/T; On/off (1) – All students attend M, A/B/C/D – hybrid model with one quarter of students each attending M, T, W, Th.



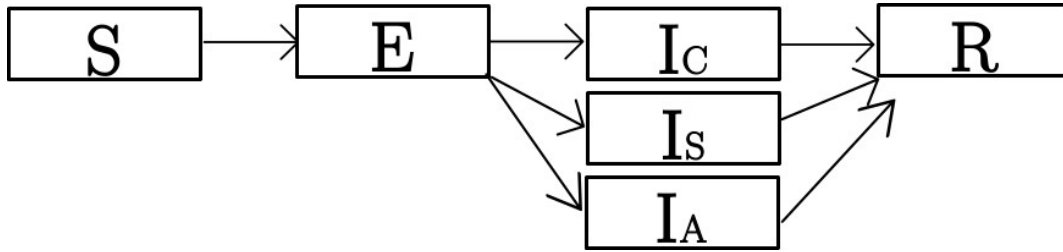
Supplement Figure 6: Cumulative incidence over 8 weeks in elementary schools across different levels of out-of-school mixing. The line colors correspond to the average daily community incidence per 100,000 population and the line styles correspond to the scheduling strategy. The x-axis shows the number of households with which each household mixes when school is out of session. The y-axis shows cumulative incidence over 8 weeks. Columns denote different isolation, quarantine, vaccination, and detection strategies, while rows show different population subgroups.



Supplement Figure 7: Cumulative incidence over 8 weeks in high schools across different levels of out-of-school mixing. The line colors correspond to the average daily community incidence per 100,000 population and the line styles correspond to the scheduling strategy. The x-axis shows the number of households with which each household mixes when school is out of session. The y-axis shows cumulative incidence over 8 weeks. Columns denote different isolation, quarantine, vaccination, and detection strategies, while rows show different population subgroups.

MODEL

We created an agent-based stochastic SEIR model of COVID-19 transmission, as depicted in Supplement Figure 9, including susceptible (S), exposed (E), infectious with clinical symptoms (I_c), subclinical symptoms (I_s), or asymptomatic disease (I_a), and recovered individuals (R). Only individuals in the susceptible compartment could contract a new infection, and only those in an infectious compartment could transmit disease. Individuals with clinical symptoms (I_s) were assumed to self-isolate after the appearance of symptoms, an average of 2 days after the onset of infectiousness.



Supplement Figure 8: Model compartments.

At each daily time-step, we modeled dyadic interactions between individuals according to household, classroom, school, and childcare relationships, drawing parameter values from the distributions specified in Supplement Table 1. A SARS-CoV-2-infected individual i transmitted to susceptible individual j at time-step t with Bernoulli probability equal to:

$$p_{ijt} = c_{ijk}q_k s_j r_i a_i d_i$$

where c_{ijk} was an indicator variable equal to 1 if individuals i and j had contact type k at time t , q_k was the probability of transmission given one day of contact type k , r_i was the relative infectiousness of individual i (compared to full adult infectiousness), s_j was the relative susceptibility of individual j (compared to full adult susceptibility), and a_i was a multiplier of 0.5 if i had asymptomatic disease and d_i was a dispersion factor representing individual-level heterogeneity in transmissibility. For the duration of infection, we matched the serial interval of 5 days to capture the concentration of transmission at the start of infectiousness (and its impact on mitigation measures) (76). Additional considerations for these parameters are discussed in the text.

HOUSEHOLD STRUCTURE

We use a Framework for Reconstructing Epidemiological Dynamics (FRED) to generate household structures (58). For elementary schools, we sampled from households containing at least one child aged 5 to 10 to identify siblings attending the same school. For high schools, we sampled from households with students aged 14 to 17. For each student, we included two adults in the household, based on the average number of household members over 25. For each staff member, we also included a household adult contact, representing a partner or roommate with whom they had close contact. For computational simplicity, we used Maryland as a representative state, as sibling structure (the main parameter of interest) did not appear sensitive to location.

Maryland Elementary

Fraction of households with a child of age 1 containing a child of age 2

Age 2	10	0.08	0.12	0.12	0.14	0.06	1	
	9	0.09	0.12	0.14	0.05	1	0.05	
	8	0.11	0.13	0.05	1	0.05	0.13	
	7	0.13	0.06	1	0.05	0.14	0.12	
	6	0.05	1	0.06	0.13	0.11	0.11	
	5	1	0.05	0.12	0.11	0.08	0.07	
		5	6	7	8	9	10	
		Age 1						

Connecticut Elementary

Fraction of households with a child of age 1 containing a child of age 2

Age 2	10	0.07	0.11	0.14	0.17	0.04	1	
	9	0.1	0.12	0.15	0.05	1	0.04	
	8	0.14	0.15	0.06	1	0.04	0.16	
	7	0.15	0.07	1	0.07	0.15	0.13	
	6	0.07	1	0.06	0.15	0.12	0.09	
	5	1	0.07	0.14	0.13	0.09	0.06	
		5	6	7	8	9	10	
		Age 1						

Mississippi Elementary

Fraction of households with a child of age 1 containing a child of age 2

Age 2	10	0.1	0.1	0.12	0.12	0.07	1	
	9	0.12	0.15	0.12	0.08	1	0.07	
	8	0.12	0.11	0.07	1	0.07	0.12	
	7	0.14	0.08	1	0.07	0.11	0.12	
	6	0.08	1	0.09	0.11	0.14	0.1	
	5	1	0.08	0.14	0.12	0.11	0.1	
		5	6	7	8	9	10	
		Age 1						

Texas Elementary

Fraction of households with a child of age 1 containing a child of age 2

Age 2	10	0.09	0.11	0.13	0.15	0.08	1	
	9	0.12	0.14	0.14	0.06	1	0.08	
	8	0.14	0.15	0.07	1	0.06	0.15	
	7	0.15	0.09	1	0.07	0.14	0.13	
	6	0.07	1	0.09	0.15	0.14	0.11	
	5	1	0.07	0.15	0.14	0.12	0.09	
		5	6	7	8	9	10	
		Age 1						

Maryland HS

Fraction of households with a child of age 1 containing a child of age 2

Age 2	17	0.13	0.14	0.08	1
	16	0.14	0.06	1	0.08
	15	0.06	1	0.06	0.14
	14	1	0.05	0.12	0.12
		14	15	16	17
		Age 1			

Connecticut HS

Fraction of households with a child of age 1 containing a child of age 2

Age 2	17	0.13	0.14	0.07	1
	16	0.14	0.06	1	0.07
	15	0.06	1	0.06	0.14
	14	1	0.06	0.13	0.13
		14	15	16	17
		Age 1			

Mississippi HS

Fraction of households with a child of age 1 containing a child of age 2

Age 2	17	0.1	0.14	0.09	1
	16	0.14	0.1	1	0.09
	15	0.08	1	0.1	0.13
	14	1	0.08	0.13	0.1
		14	15	16	17
		Age 1			

Texas HS

Fraction of households with a child of age 1 containing a child of age 2

Age 2	17	0.13	0.14	0.08	1
	16	0.16	0.08	1	0.08
	15	0.08	1	0.08	0.14
	14	1	0.08	0.17	0.13
		14	15	16	17
		Age 1			

COMPARISON TO OBSERVED OUTBREAKS

A number of factors make formal calibration challenging for this paper. First, most data collection has been ad hoc, with some sources biased toward reporting large outbreaks and others toward high-mitigation schools who voluntarily collect and report data. Without data on school mitigation efforts, interpretation can be challenging. Other important factors also vary across schools, including testing practices, reporting procedures, and the definition of “contact”, with some including even brief contacts while others limiting the definition to more sustained interactions (e.g., >15 minutes without a mask). This section describes available data sources in comparison to our parameters and results. We emphasize that substantial uncertainty persists, and that screening or other surveillance is one of the best tools available for understanding a specific context and detecting outbreaks early.

DIFFERENCES IN INFECTIOUSNESS AND SUSCEPTIBILITY BY AGE

In our model, we assumed that young children (10 and under) were both less susceptible and less infectious than adults. To inform these assumptions, we used a meta-analysis on child susceptibility on those under 18-20 (62), which was consistent with best-fit model estimates (77) and another study on child infectiousness (78). We also used a number of contact tracing studies suggesting not just a difference between children and adults but also an age gradient in susceptibility and infectiousness with meaningful differences between elementary and high school students. These included a study from B’nei Brak, Israel on household infections (Figure 4, original study) (63) and two studies from France, which contrasted minimal elementary school outbreaks (despite introductions) with a larger high school cluster in an area with early COVID-19 exposure (8,64). Limited data from Iceland, with comprehensive contact tracing and sequencing, suggested a similar difference between young children and adolescents in infectiousness (79). Contact tracing data from South Korea on infectiousness, while more difficult to interpret due to concurrent exposures among household members and high PPE usage of guardians of infected children (80,81), was consistent with this finding (33). Last, while some studies suggest that susceptibility may continue increase with age after childhood, we assumed based on (63,82) that the difference between high school children and adults living in their home was negligible because most such adults are young or middle-aged, and potential differences appear to be driven by increased susceptibility among older adults.

We focused on data from contact tracing studies that used comprehensive testing of contacts because these were less likely to be biased. In particular, we did not want to interpret evidence that children were rarely identified as index cases (78) or had lower seroprevalence in some contexts as evidence that they were less susceptible or infectious (82). These differences could have been driven by the fact that children are less likely

to have symptoms and be tested and/or that their contacts were markedly reduced by school closures early in the pandemic. While household contact tracing studies with comprehensive testing avoided this issue, they could have had other biases. For example, children were unlikely to be caretakers of sick individuals compared to adults in the household and may have been shielded in houses with known cases, particularly in the midst of an unprecedented pandemic. Nevertheless, in general, higher household attack rates in children have been observed for seasonal influenza and H1N1, making lower estimates for COVID-19 particularly notable (83–88).

Still, these findings cannot differentiate between biological explanations for lower susceptibility in younger children (e.g., lower density of ACE2 receptor) and behavioral ones (e.g., easier to restrict socialization). In addition, some studies suggest higher susceptibility and/or infectiousness of young children than we include in our base case (89–93). While we model these possibilities in sensitivity analyses, the bulk of evidence on well-studied school outbreaks has pointed to important distinctions between elementary and high school-aged children. For example, when Israel experienced significant outbreaks upon return to school in the early summer, there was a significant outbreak of 178 cases in a middle/high school (concentrated in grades 7-9), but elementary school outbreaks were generally reported as smaller (e.g., 33 cases) (10,18). This difference was also apparent in informal databases, with high schools largely responsible for outbreaks of more than 50 people (e.g., in New Zealand and the US prior to social distancing and Australia, where a school outbreak was reported to be driven by high schoolers) (94–96). In the Netherlands, a health official was quoted saying that significant outbreaks occurred mainly in high schools and universities prior to an elementary school outbreak with B.1.1.7 (75). Exceptions often included significant outbreaks among teachers (e.g., in Chile (12) and Singapore (97)).

SECONDARY CASES

Our results are broadly consistent a few key features of observed data. First, well-studied cases have led to no or minimal outbreaks in a number of settings. In passive surveillance from the United Kingdom during the summer, in-school transmission was identified from 39% of index cases in secondary schools and 26% of cases in primary schools “in the context of small class or bubble sizes, half empty schools, and extensive hygiene measures.” This is similar to what we predicted with an A/B model in secondary schools with medium mitigation (36%) and a low mitigation scenario in elementary schools (23%). No onward transmission was found in Singapore or Ireland, each with 3 seed cases (9,98). In Rhode Island childcare settings, which had small class sizes, onward transmission was documented in 4/29 index cases (14%), consistent with 1/2 class size scenario and high mitigation (13%) (68). In North Carolina, minimal transmission was documented

with under a hybrid model with strong mitigation measures in place (32 secondary transmissions identified through 773 contact traced cases for 0.04 average secondary transmissions per index case) (99). Similarly, with masking and cohorting, rural Wisconsin schools reported few cases linked to in-school transmission (100). In this context, school COVID-19 incidence was lower than the local community rates, although this comparison was not age-adjusted for the fact that children generally have lower reported COVID-19 case rates than the general population.

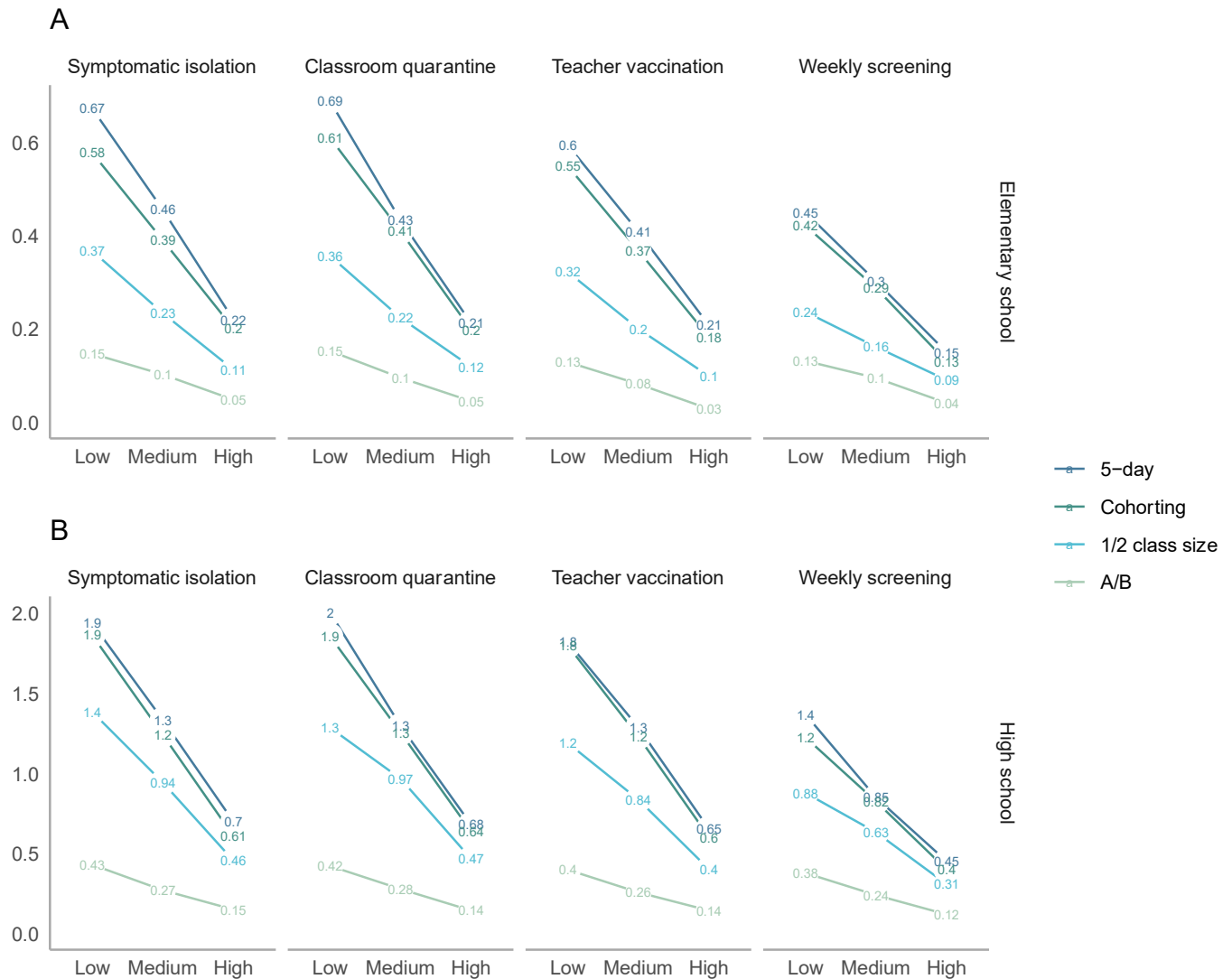
Limited testing in some of these studies may have missed subclinical cases. One paper estimated the number of direct secondary infections to students and staff from each introduced case in the context of weekly or biweekly testing in high-mitigation K-12 independent schools to be about 0.2 to 0.5, which is within the range of our estimates of average direct secondary transmission of with weekly testing and either high mitigation (0.09 to 0.45) or medium mitigation (0.16 to 0.85) (101) (Supplement Figure 10). Similarly, a study from Norway with rigorous quarantine and comprehensive testing estimated a 0.9% child-to-child school attack rate and 1.7% child-to-adult attack rate in primary schools. This is most congruent with our model of high mitigation under a 5-day schedule, under which we would expect approximately a 0.9% child-child attack rate and 1.8% child-adult attack rate for full-day contact over the course of infection (102).

Even accounting for stochastic variability, it is nevertheless possible that our results overestimate or underestimate transmission in environments with extremely well-controlled or poorly controlled transmission. For example, Hong Kong reported negligible transmission even in secondary schools with very strong mitigation (103). And, while difficult to interpret due to differences in “close contact” definitions across studies, some data may suggest higher attack rates than were modeled, such as 27% of contacts testing positive in data from Florida (104). (Even accounting for that fact that only 43% of contacts were tested, the implied lower bound of a 12% attack rate exceeds our modeled attack rates, particularly after accounting for reduced transmission from children and asymptomatic individuals and from non-full-day contacts.) Nevertheless, with a large range of modeled attack rates and sensitivity analyses, we aimed to capture much of the distribution of school-based attack rates.

Second, we included overdispersion, as several data sources showed signs of overdispersion with the possibility of large outbreaks alongside cases without apparent transmission. In the Rhode Island example, one outbreak involved 10 cases among contacts (10 children, four staff members, and one parent); in another study from Australia, 9 cases in early childhood education centers led to no onward transmission while one led to 13 infections (7). Calibrating overdispersion is challenging without extensive data; if large outbreaks were generally caused by a single index case, the level of overdispersion in our model may not capture such

extreme outcomes.

Last, we incorporated specific staff-staff interactions, as teachers were often overrepresented in outbreaks even in well-studied outbreaks, with 16% of staff and 10% of students having antibodies in a Chilean outbreak across multiple school levels (12). In the Australian study, adults comprised 8/18 of secondary cases identified (7).



Supplement Figure 9: Effective reproduction number, defined as average secondary transmissions following a single introduction into the school (students and staff). The top panel shows elementary schools, where children are assumed to be less susceptible and less infectious, while the bottom panel shows high schools. Note that axes differ across rows. The x-axes vary the level of mitigation, with low assuming minimal interventions and high assuming intensive interventions. Line colors correspond to scheduling strategies.

FREQUENCY OF INFECTIONS AND SUBCLINICAL INFECTIONS IN CHILDREN COMPARED TO ADULTS

Our model predicted both lower incidence of infections in children and a higher rate of underdiagnosis.

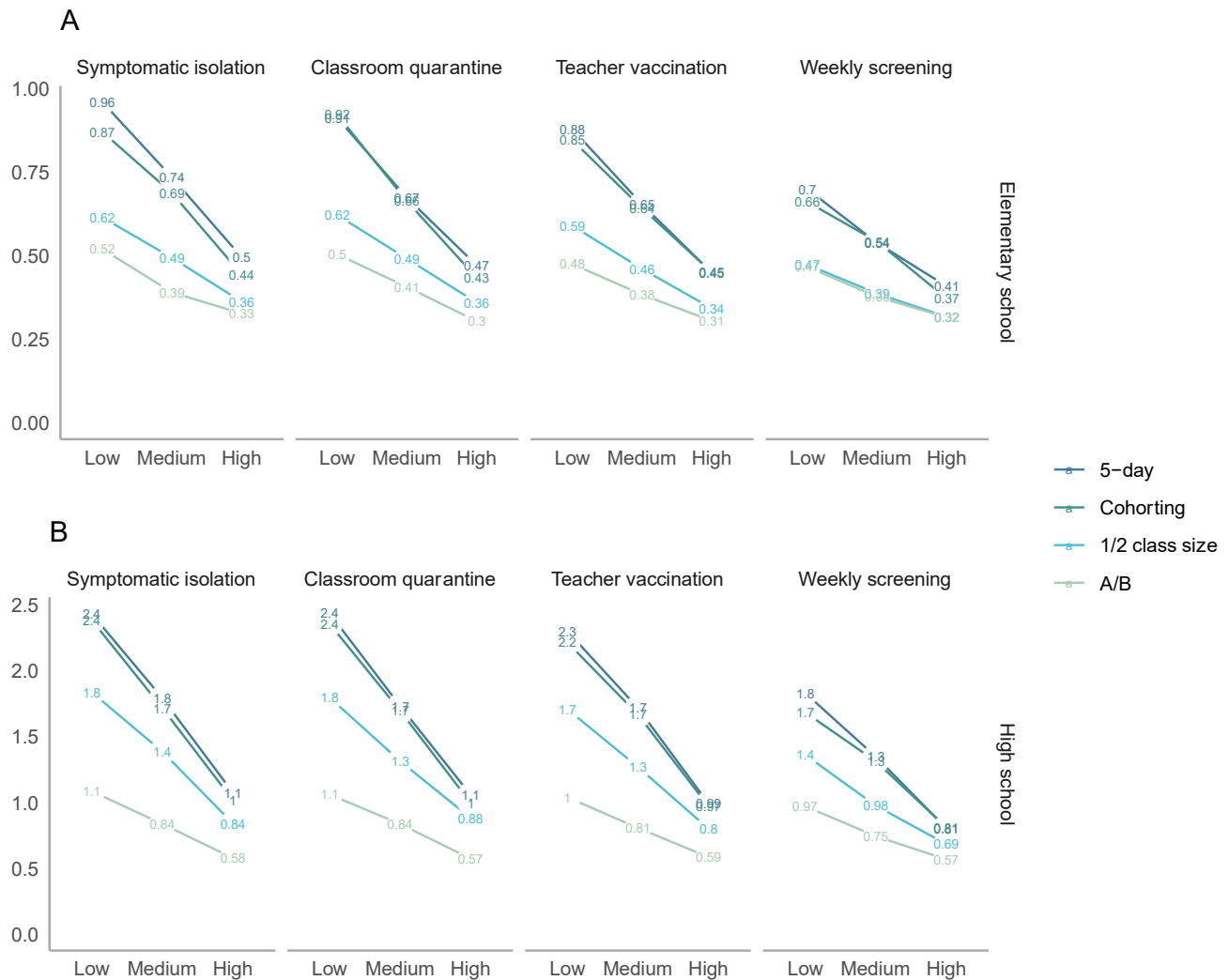
With these combined, we would expect to see fewer cases in children, but a smaller relative difference when comprehensive surveillance and/or random testing is conducted, which is consistent with observed data. For example, in passive surveillance from the United Kingdom, staff had more than 4 times the COVID incidence of students per 100,000 across all age groups; however, in random testing, observed prevalence was roughly equal among students and staff (105,106). In elementary schools in New York in fall 2020, schools reported substantially fewer cases in elementary school students than in staff per population, but in random surveillance testing from the same period in New York City (manually extracted and analyzed by others), prevalence was roughly equal in students and staff (107,108). While these are difficult to compare directly as people who self-isolate for symptoms are not present for random testing, the contrast remains striking. Less systematically, a major outbreak in an Israeli high school was detected from wide-scale testing after observing 2 unlinked cases (10), and the first Ontario school to participate in voluntary mass asymptomatic screening closed after uncovering a substantial number of previously undetected cases (109). In an analysis of two schools with biweekly or weekly testing, 3% of cases in elementary school-aged children, 25% in middle school-aged children, and 9% in high school-aged children were symptomatic at the time of testing, compared to 48% in adults (101).

EFFECTIVE REPRODUCTION NUMBER

In Supplement Figure 11, we display the effective reproduction number associated with different scenarios in the community. One modeling study estimated that from August through October 2020, there was an average effective reproduction number of 0.54 [0.44-0.62] for children 0-9 and 0.75 [0.59-0.89] for children 10-19 (110). School openings varied considerably across the country, making direct comparisons to these estimates challenging. For elementary schools, these estimates would be consistent with our model assuming full opening and high mitigation, hybrid opening or limited attendance and medium mitigation, or, as occurred, some combination of these with remote models. For high schools, it is most consistent with high mitigation, limited attendance, a hybrid model or again, more realistically, some combination of these with remote models.

POPULATION-LEVEL STUDIES

While we do not directly model full community incidence, two recent studies using quasi-experimental data to study the impact of school reopening on transmission were consistent with our observation that there is a higher risk of increased community transmission following school reopenings when initial transmission was high, contrasted to tight null effects when initial transmission was lower (111,112).



Supplement Figure 10: Effective reproduction number, defined as average secondary transmissions following a single introduction into the school community (students, staff, and families). The top panel shows elementary schools, where children are assumed to be less susceptible and less infectious, while the bottom panel shows high schools. Note that axes differ across rows. The x-axes vary the level of mitigation, with low assuming minimal interventions and high assuming intensive interventions. Line colors correspond to scheduling strategies.

INTERVENTIONS

It is challenging to discern the importance of specific interventions from available data, and we modeled a package of interventions, intended to reflect a combination of masking, distancing, and ventilation. In practice, school districts must discern how to select interventions to reduce transmission while maximizing educational time. For example, space constraints may be a barrier to returning full-time in person if 6' distancing is required. A recent paper examined the difference between 3' and 6' distancing in schools in Massachusetts, finding an IRR of 0.79 in students (95% CI: 0.53 to 1.18) and 0.92 in staff (95% CI: 0.67 to 1.25) after adjusting for demographics and community incidence (113). Applying a non-inferiority interpretation to these confidence intervals, they suggest that we can rule out with high confidence that 6' distancing

has an IRR of less than 0.53 in students and 0.67 in staff compared to 3' distancing. Similarly, a systematic review found that mask-wearing by non-health care workers can reduce individual-level infection risk by 47%, although specific evaluation of the benefit in school settings is not available (114). Given the harms of lost educational time and the potential for other interventions like high adherence to masking, ventilation, and/or testing to be able to substitute for greater distancing, schools with high adherence to other prevention measures may feel comfortable moving from 6' to 3'.

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