7-13-19

JAMA 2019 Jul 2; 322:49

State Legislation to Boost Vaccination Coverage

Legislative action in California resulted in fewer children entering kindergarten without up-to-date vaccination status.

Vaccine hesitancy, identified by the World Health Organization as one of ten current threats to global health (https://www.who.int/emergencies/ten-threats-to-global-health-in-2019), has resulted in decreasing vaccination coverage in some regions of the U.S. Legislative efforts to encourage vaccination by tightening requirements on and finally eliminating personal exemption from immunization for children entering kindergarten were enacted in California over the past 5 years, and a recent study demonstrated improved vaccination rates after the personal exemption elimination (NEJM JW Pediatr Adolesc Med July 2019 and *Pediatrics* 2019; 143:e20183301). Now the same investigators report the effect of these new actions on vaccination rates, focusing on geographic clusters with high exemption rates in California.

The rate of children entering kindergarten without up-to-date immunizations increased from 7.8% in 2000 to 9.8% in 2013, prior to the legislative actions, and then decreased to 4.9% in 2017 after personal exemption elimination. The decrease was initially due to a reduction in conditional admissions (allowing children to enroll in school without complete immunizations) but was followed by further reduction after personal exemptions were eliminated. The proportion of kindergartners enrolled in a school with rates of immunization ≥95% (the rate considered necessary for herd immunity for measles and pertussis) rose from 46% in 2012 to 76% in 2016, and the number of schools with high rates of kindergartners without up-to-date vaccinations decreased from over 3000 schools in the 2012–2013 school year to 1613 during 2016–2017.

COMMENT: Parents who fail to completely immunize their child due to a personal belief are placing the child, as well as the community, at risk. We have many laws in place to protect children (car seats, smoking bans, swimming pool fencing), and vaccination should be no different. California has enacted legislation making it more difficult for parents to deny their children the freedom from vaccine-preventable diseases, and these laws seem to have reduced pockets of risk in many areas. Other states should follow suit.

CITATION(S): Pingali SC et al. Associations of statewide legislative and administrative interventions with vaccination status among kindergartners in California. *JAMA* 2019 Jul 2; 322:49. (https://doi.org/10.1001/jama.2019.7924)

Davis MM and Shah SK. Outbreaks of vaccine-preventable diseases: Responding to system failure with national vaccination requirements. *JAMA* 2019 Jul 2; 322:33. (https://doi.org/10.1001/jama.2019.8251)

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Pediatrics 2019 Jun 10

Waning Effectiveness of the Acellular Pertussis Vaccine

Children fully vaccinated against pertussis are still at risk, which increases with time since immunization.

The original pertussis vaccine, derived from the cellular components of *Bordetella pertussis* in the 1940s, was highly effective but caused adverse side effects (fever, febrile seizures). In the 1990s, it was replaced with a less reactogenic acellular pertussis vaccine. Five doses of the vaccine by age 4 to 6 years and a booster between 11 and 12 years are currently recommended. Despite high rates of vaccination, we continue to see large pertussis outbreaks.

To determine risk for pertussis by vaccination status and time since vaccination, researchers followed 470,000 children born between 1999 and 2016 from age 3 months to 11 years. During the monitoring period, they identified 738 cases of pertussis, 603 in fully vaccinated children. Compared with fully vaccinated children, pertussis risk was 13 times higher in unvaccinated children and doubled in undervaccinated children. Pertussis immunity waned over time; in fully vaccinated children aged 19 to <84 months, pertussis risk was 5 times greater at ≥3 years since vaccination versus <1 year, and in those aged 84 to 132 months, risk was doubled at ≥6 years since vaccination versus <3 years.

COMMENT: This study adds significantly to our understanding of how immunity provided by the acellular pertussis vaccine wanes over time. More than four out of five pertussis cases in this cohort were among fully vaccinated children, indicating that immunity provided by the current acellular pertussis vaccine is suboptimal. This fact makes it all the more important to adhere to the vaccination schedule. The whole-cell pertussis vaccine, though more reactogenic, seems to have been more effective.

CITATION(S): Zerbo O et al. Acellular pertussis vaccine effectiveness over time. *Pediatrics* 2019 Jun 10; [e-pub]. (https://doi.org/10.1542/peds.2018-3466)

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Pediatrics 2019 Jun 10

Childhood Shingles Incidence in the Chicken Pox Vaccination Era

Varicella zoster vaccine reduced risk for subsequent herpes zoster by 72% between 2003 and 2014.

Herpes zoster (HZ) is a result of reactivation of varicella zoster virus (VZV) sometime after chicken pox, the primary infection caused by the virus. Although the incidence of HZ is lower in children than in adults, it is well described, and children with primary VZV before age 1 year are at greatest risk. Children can also develop HZ after vaccination, but the risk for reactivation following vaccination has been challenging to study, requiring a large number of children infected with vaccine-type virus (vaccinated) and wild-type virus (unvaccinated).

In this study, researchers assessed physician-documented HZ incidence and VZV vaccination status during 2003 to 2014 among 6.4 million children enrolled in six healthcare organizations. Results include the following:

- Overall, 50% of children were vaccinated for VZV during the study period; this rate increased over time, reaching 91% in 2014.
- Incidence of HZ was 74 per 100,000 (61 per 100,000 for laboratory-confirmed HZ) and declined by 72% over time.
- HZ incidence was 78% lower in vaccinated children (38 per 100,000) than in unvaccinated children (170 per 100,000).
- Among 1-year-olds, vaccinated children had a higher HZ rate than unvaccinated children, but among children aged 5–17 years, vaccinated children had a significantly lower risk for HZ than unvaccinated children.
- Children vaccinated with two VZV vaccine doses, as is recommended, had 50% lower risk for HZ compared with those who had received just one dose.

COMMENT: This vaccine does double duty: in addition to protecting children from varicella zoster infection, and all the complications that can result, the vaccine significantly reduces the incidence of herpes zoster. Although further evidence supporting the benefits of vaccinating children should not be necessary, these findings provide just that.

CITATION(S): Weinmann S et al. Incidence of herpes zoster among children: 2003–2014. *Pediatrics* 2019 Jun 10; [e-pub]. (https://doi.org/10.1542/peds.2018-2917)

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J Pediatr Adolesc Gynecol 2019 Jun 7

Medical Therapy Choice for Menstrual Suppression in Adolescents with Disabilities

Depo-Provera intramuscular injections most effectively suppressed menstruation in a small series of young women with disabilities.

Menstrual suppression in adolescents with disabilities is an important part of care given the anxiety that can surround this issue. Combined oral contraceptive pills (COCPs) have traditionally represented first-line treatment but show varying efficacy.

To compare the effectiveness of COCPs, depot medroxyprogesterone acetate (Depo-Provera) intramuscular injections, and a progesterone-containing intrauterine system (IUS) in this setting, investigators conducted a retrospective chart review in 68 adolescents with disabilities who presented to an Australian gynecology clinic between 2005 and 2015. The primary outcome was the proportion of patients achieving menstrual suppression after three outpatient visits. The researchers also examined time from first treatment to first observed menstrual suppression and number of outpatient appointments required to achieve suppression.

COMMENT: Of the 46 adolescents who used Depo-Provera at some point during the study, 35 (76%) achieved menstrual suppression with that modality, compared with 20 of 29 (69%) who used an IUS and only 7 of 16 (44%) who used a COCP. On average, menstrual suppression was achieved in 12.9 months using any modality, and 57% of patients achieved it after one appointment.

While previous studies recommend COCPs as first-line treatment for menstrual suppression in adolescents with disabilities, this study suggests Depo-Provera to be more effective. However, this benefit needs to be weighed against the threat to bone health associated with Depo-Provera use. Bone density screening should be considered in these patients, especially in those who remain on this agent for prolonged time periods. While these results are noteworthy, the overall take-home message is still that this is a medically complex patient group for whom there is no "one size fits all" strategy for menstrual suppression. The appropriate management will vary by patient and must be highly individualized.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

CITATION(S): Leeks R et al. Menstrual suppression in paediatric and adolescent patients with disabilities ranging from developmental to acquired conditions: A population study in an Australian Quaternary Paediatric and Adolescent Gynaecology Service from January 2005 to December 2015. *J Pediatr Adolesc Gynecol* 2019 Jun 7; [e-pub]. (https://doi.org/10.1016/j.jpag.2019.05.005)

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JAMA Intern Med 2019 Jun 24

Commonly Used Anticholinergic Drugs Are Associated with Excess Risk for Dementia

The association was significant for antidepressants and many other drugs.

Anticholinergic drugs have been associated with excess dementia risk in prior observational studies. Now, researchers explored this relation in this case-control study that involved about 3.6 million older adults (age, ≥55) without dementia who had at least 11 years of visit data in an English general practice database. During a median follow-up of ≈6 years, 128,000 patients developed dementia, of whom ≈59,000 were age-matched to 226,000 controls without dementia. A total standardized daily dose (TSDD) was calculated for each patient with a validated assessment based on strength, daily dose, and length of use for each of 56 drugs with anticholinergic properties.

In multivariable analyses, the adjusted odds ratio for developing dementia was 1.49 for patients with TSDD >1095 (equal to 3 years of use of a standard dose of a drug with strong anticholinergic properties) compared with patients who had no use. AORs were similar for antidepressants (aOR, 1.29), antiparkinson drugs (aOR, 1.52), bladder antimuscarinic drugs (aOR, 1.65), and antipsychotic drugs (aOR, 1.70.) To account for "protopathic bias" (i.e., the possibility that these drugs were prescribed for early symptoms of not-yet-diagnosed dementia), the researchers undertook additional analyses that were limited to dementia cases that were diagnosed ≥3 years and ≥5 years after initial anticholinergic exposure, and results were similar to those in the initial analysis.

COMMENT: The authors estimate that the population-attributable risk of anticholinergic drug use might explain 10% of all dementia. Although the usual concerns about causality in observational studies apply here, the biological plausibility (excess risk for dementia because of cholinergic depletion) leads editorialists to suggest that a deprescribing study of specific drug classes most associated with dementia — and for which acceptable alternatives exist — would be a good place to start.

CITATION(S): Coupland CAC et al. Anticholinergic drug exposure and the risk of dementia: A nested case-control study. *JAMA Intern Med* 2019 Jun 24; [e-pub]. (https://doi.org/10.1001/jamainternmed.2019.0677)

Campbell NL et al. Preventing Alzheimer disease by deprescribing anticholinergic medications. *JAMA Intern Med* 2019 Jun 24; [e-pub]. (https://doi.org/10.1001/jamainternmed.2019.0676)

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Ann Intern Med 2019 Jun 18

Does Inpatient Opioid Use Lead to Outpatient Opioid Use?

In opioid-naive people, inpatient opioid administration led to continued outpatient opioid use at 3 months and 1 year.

Whether inpatient administration of opioids correlates with long-term outpatient opioid use is unclear. Investigators retrospectively evaluated postdischarge outpatient use of opioids among nearly 150,000 previously opioid-naive (i.e., no prescribed use in the 1 year prior to admission) medical and surgical inpatients at 12 community and academic hospitals in a single Pennsylvania healthcare system during 5 years.

Almost half of patients received opioids during their hospital stays, and nonopioid analgesics were used infrequently (<25% of the time) prior to opioid administration. In adjusted analysis (excluding opioid administrations within 24 hours following surgery), patients who received opioids during their hospital stay, compared with those who did not, were twice as likely to have outpatient opioid use at 3 months (6% vs. 3%) and 1 year (8% vs. 4%).

COMMENT: This study shows a high rate of inpatient opioid administration, limited use of nonopioid analgesics, and an association between inpatient opioid administration and long-term outpatient opioid use. Although the contribution of inpatient opioid initiation to the larger opioid crisis might be relatively small, it might be time to consider initiating inpatient opioid stewardship programs.

CITATION(S): Donohue JM et al. Patterns of opioid administration among opioid-naive inpatients and associations with postdischarge opioid use: A cohort study. *Ann Intern Med* 2019 Jun 18; [e-pub]. (https://doi.org/10.7326/M18-2864)

Larochelle MR and Bohnert ASB. Opportunities to address first opioid prescriptions to reduce incident long-term opioid use. *Ann Intern Med* 2019 Jun 18; [e-pub]. (https://doi.org/10.7326/M19-1394)

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New Draft Lyme Disease Guidelines Issued

An update to the 2006 guideline includes clarification on pharmacologic treatment in children.

The Infectious Diseases Society of America, American Academy of Neurology, and American College of Rheumatology have issued new draft guidelines on Lyme disease. Among the many recommendations:

- Prophylactic antibiotics (a single dose of oral doxycycline) should be administered to patients within 72 hours of removing a tick after a high-risk bite, but not after lower-risk bites. High-risk bites must meet all of the following criteria: from an *Ixodes* tick, in a highly endemic area, and from a tick engorged and attached for 36 hours or more.
- For erythema migrans, preferred treatments include 10 days of doxycycline or 14 days of amoxicillin, cefuroxime axetil, or phenoxymethylpenicillin.
- For patients presenting with meningitis, painful radiculoneuritis, mononeuropathy multiplex, or acute cranial neuropathies, along with plausible exposure to high-risk ticks, Lyme testing is recommended. Routine testing is not recommended for patients with other neurological syndromes or psychiatric illnesses.
- The groups suggest against routine testing in children presenting with developmental, behavioral, or psychiatric disorders.
- Additional antibiotics are not recommended in patients with persistent or recurring nonspecific symptoms (e.g., pain, fatigue) after treatment for Lyme disease but who don't have evidence of reinfection or treatment failure.

The guideline also includes information on evaluating patients presenting with “chronic” Lyme disease, who often have other underlying disorders.

Infectious diseases specialist Dr. Paul Sax comments: "Comprehensive and evidenced-based, these guidelines are a welcome update to the previous version, which is now more than a decade old. Nonetheless, their release will undoubtedly engender controversy given the widely disparate and strongly held views on the topic."

COMMENT — PEDIATRICS AND ADOLESCENT MEDICINE

Deborah Lehman, MD

These new guidelines update the 2006 guidelines and highlight the recommendation that doxycycline is a safe alternative in children of all ages for the treatment of Lyme disease and is the drug of choice in children who are β-lactam allergic, but amoxicillin is preferred for children under age 8 years. In addition, because Lyme arthritis can mimic septic arthritis, it should be considered in children presenting with large joint arthritis when there is a compatible exposure history.

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Gastroenterology 2019 May 29

Randomized Trial Supports Long-Term Safety of Proton-Pump Inhibitors

Previously reported increased risks for serious adverse events are not shown, except for enteric infection.

In recent years, observational studies have suggested associations between the use of proton-pump inhibitors (PPIs) and multiple adverse outcomes, including pneumonia, hip fracture, dementia, enteric infections (including *Clostridium difficile*), cerebrovascular events, chronic renal failure, diabetes, chronic obstructive pulmonary disease (COPD), and mortality. However, these studies are limited by inherent methodological weaknesses resulting in possible residual confounding and other biases.

In a large prospective, randomized, controlled study, the safety of PPI use (pantoprazole 40 mg once daily) was compared with placebo in 17,600 patients aged ≥65 years with stable coronary or peripheral artery disease (78% men; 23% smokers). During a median follow-up of 3 years, results were as follows:

- There were no significant differences in rates of pneumonia, fracture, new diagnoses of diabetes mellitus, chronic kidney disease, dementia, COPD, gastric atrophy, cancer overall, and cancers of specific primary sites.
- There was an increased rate of enteric infections other than *C. difficile* in patients on pantoprazole (1.4% vs. 1.0%; *P*=0.04).
- *C. difficile* infection was twice as common with pantoprazole use; however, the difference was not statistically significant (the total number of events was 13).

COMMENT: This is the largest study of PPIs to date and the first prospective, randomized trial evaluating their long-term safety. These data substantiate the excellent safety profile of PPIs except for a small increase in enteric infections and cast doubt on findings of serious adverse events in recent observational studies.

Although physicians must always carefully consider the risks and benefits of all prescribed medicines and only use the recommended doses and durations of treatment, these high-quality, long-term safety data should reassure both physicians and their patients needing PPIs.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

CITATION(S): Moayyedi P et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology* 2019 May 29; [e-pub]. (https://doi.org/10.1053/j.gastro.2019.05.056)

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J Am Geriatr Soc 2019 Jun; 67:1182

Polypharmacy Impairs Gait in Elders

And most older patients are amenable to stopping unnecessary medications.

In older patients, polypharmacy (5 or more regular prescriptions) has been associated with risks for falls, disability, and death, over and above risks associated with the illnesses the drugs are intended to treat. To examine the association between polypharmacy and falls in more detail, Canadian researchers prospectively evaluated gait patterns among 249 older adults (age, ≥65) without gait-impairing neurological diagnoses. At baseline, the 176 patients who were taking more than five medications (mean, 9 prescriptions) were older, had more diagnosed illnesses, reported more falls in the previous year, and (on formal gait testing) walked considerably more slowly and haltingly than the other 73 patients. During 5 years of follow-up, gait parameters worsened more rapidly in the high-med group, even after controlling for age and comorbidity. The researchers calculated that every additional medication increased independent risk for gait deterioration by about 15% and increased fall risk by 5%.

In another study from Australia, researchers administered a questionnaire addressing patients' willingness to have their prescription lists thinned. About 600 older patients (or their caregivers) provided reactions to statements such as "Sometimes I think I take too many medicines," "I think one or more of my medicines may not be working," and "If my doctor recommended stopping a medicine I would feel that he/she was giving up on me." Most patients and caregivers agreed they would be willing to stop a medication on a physician's recommendation, confirming previous similar research.

COMMENT: Both clinicians and their older patients are to blame for those long lists of pills — physicians might prefer not to tamper with stable regimens, whereas patients often become oddly attached to familiar regimens. These studies reemphasize that the goal of cutting back medications to the minimum is vital, especially in frail elders.

CITATION(S): Montero-Odasso M et al. Polypharmacy, gait performance, and falls in community-dwelling older adults. Results from the Gait and Brain Study. *J Am Geriatr Soc* 2019 Jun; 67:1182. (https://doi.org/10.1111/jgs.15774)

Reeve E et al. Attitudes of older adults and caregivers in Australia toward deprescribing. *J Am Geriatr Soc*2019 Jun; 67:1204. (https://doi.org/10.1111/jgs.15804)

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JAMA 2019 Jun 18; 321:2362

Increasing Suicide Rates among U.S. Adolescents and Young Adults

A striking rise was observed in the last 4 data years available, especially among adolescent boys.

Suicide rates in the U.S. have increased over the past two decades. There has been particular concern about adolescents, given reported increases in anxiety, depression, and self-harm behaviors.

In recent data from the CDC, suicide rates increased among the 15-to-24-year age group between 2000 and 2017. In 2017, there were 6241 suicides in this group (5016 in males and 1225 in females). More-detailed trends by age group, gender, and time are as follows:

For the 15-to-19-year age group:

- The 2017 suicide rate was 11.8/100,000, with an over threefold higher rate in males versus females.

- The rate increased from 2000 to 2017 overall, with no change from 2000 to 2007, an increase from 2007 to 2014, and a much steeper increase from 2014 to 2017.
- In males, an increase occurred from 2007 to 2015 and much more strikingly from 2015 to 2017.
- In females, there was an increased trend from 2010 to 2017.

For the 20-to-24-year age group:

- The 2017 suicide rate was 17/100,000, with an over fourfold higher rate in males versus females.
- The rate increased from 2000 to 2017, with increased trends from 2000 to 2013 and 2013 to 2017.
- In males, the trend increased from 2000 to 2013 and more strikingly from 2013 to 2017.
- In females, the trend increased from 2000 to 2017.

COMMENT: In 2017, the suicide rate among adolescents and young adults reached its highest point since 2000, with a much higher rate in males than in females. Moreover, there was a striking rise in the suicide rate over the most recent four years, especially in males. Pediatricians should consider these statistics as they talk to adolescents. Inquiring about thoughts of self-harm is paramount, as is identifying the risk factors and stressors that underlie these feelings. Having a protocol in place for referral to a mental health team is important in order to address concerns that are identified during an office visit.

CITATION(S): Miron O et al. Suicide rates among adolescents and young adults in the United States, 2000-2017. *JAMA* 2019 Jun 18; 321:2362. (https://doi.org/10.1001/jama.2019.5054)

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BMJ 2019 Jun 12; 365:l2147

Gabapentinoid Medications Might Not Be as Benign as You Think

Multiple adverse behavioral and psychomotor associations are found with these drugs although the effects might be confined to pregabalin.

Clinicians often prescribe gabapentin and pregabalin for pain, sleep, and anxiety symptoms, and some view these drugs as safe alternatives to benzodiazepines and opioids in, for example, patients with alcohol use, chronic insomnia, or chronic pain disorders. Thus, use of these medications has been increasing. Researchers in Sweden conducted a within-subjects epidemiological study of almost 200,000 people aged ≥15 with ≥2 prescriptions for gabapentin or pregabalin in 2006–2013.

Periods of using gabapentinoids were associated with greater risks than nontreatment periods for suicidal behavior (hazard ratio, 1.26), unintentional overdose (HR, 1.24), head and bodily injuries (HR, 1.22), and traffic accidents (HR, 1.13). In subanalyses, the effects were mostly confined to pregabalin, appeared to be greatest in adolescents and young adults, and were absent in people aged ≥55.

COMMENT: The specific association of these adverse effects with pregabalin validates the U.S. placement of this drug in the same schedule as benzodiazepines, which also makes it harder to prescribe than gabapentin. However, the two medications are mechanistically similar. Recent data showing that gabapentin's analgesic effects for fibromyalgia pain are less robust than previously thought (Cochrane Database Syst Rev 2017; 1:CD012188) suggest caution in prescribing it for nonneuropathic pain. In my practice (which is not focused on chronic pain), I do not prescribe pregabalin due to concerns about abuse and dependence, and I confine my prescription of gabapentin to patients with problematic insomnia (but only at low doses and only if the drug is clearly effective) and specific patients whose alcohol abuse is driven by anxiety not responsive to standard antidepressant treatments used for anxiety.

CITATION(S): Molero Y et al. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: Population based cohort study in Sweden. *BMJ* 2019 Jun 12; 365:l2147. (https://doi.org/10.1136/bmj.l2147)

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