Natural history and management of nonalcoholic fatty liver disease in adults

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INTRODUCTION — Nonalcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation (eg, heavy alcohol consumption) are present. NAFLD may progress to cirrhosis and is likely an important cause of cryptogenic cirrhosis [1-4].

This topic will review the natural history and treatment of NAFLD. The pathogenesis, clinical manifestations, and diagnosis of NAFLD are discussed separately. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults".)

DEFINITIONS

NAFL versus NASH — Nonalcoholic fatty liver disease (NAFLD) is subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). In NAFL, hepatic steatosis is present without evidence of inflammation, whereas in NASH, hepatic steatosis is associated with hepatic inflammation that histologically is indistinguishable from alcoholic steatohepatitis [5,6]. Other terms that have been used to describe NASH include pseudoalcoholic hepatitis, alcohol-like hepatitis, fatty liver hepatitis, steatonecrosis, and diabetic hepatitis.

NAFLD activity score — One way of differentiating NAFL from NASH is to obtain a liver biopsy and calculate the NAFLD activity score (NAS) [7]. The NAS is the sum of the biopsy's individual scores for steatosis (0 to 3), lobular inflammation (0 to 2), hepatocellular ballooning (0 to 2), and fibrosis (0 to 4) [7]. An NAS <3 corresponds to nonalcoholic fatty liver (NAFL), 3 to 4 corresponds to borderline nonalcoholic steatohepatitis (NASH), and a score ≥5 corresponds to NASH. (See "Histologic scoring systems for chronic liver disease", section on 'Nonalcoholic fatty liver disease'.)

NATURAL HISTORY — Patients with nonalcoholic fatty liver disease (NAFLD) may eventually develop cirrhosis. Cirrhosis develops when simple steatosis progresses to steatohepatitis and then fibrosis. Among patients with cryptogenic cirrhosis, up to 70 percent have risk factors for NAFLD [1,4]. While the risk of disease progression among patients with NAFLD has been evaluated in multiple studies, the results have been variable, and the risk of developing advanced fibrosis among patients with NAFLD is unclear [3,4,8-19]. However, it appears that patients with simple steatosis on biopsy are at very low risk for developing significant fibrosis, whereas those with nonalcoholic steatohepatitis are at higher risk [20]. In addition, some patients with fibrosis show regression of their disease [8-10].

Risk factors for progression — A number of risk factors for liver disease progression have been identified in patients with NAFLD. One of the most important risk factors is histologic evidence of hepatic inflammation.

This was examined in a systematic review that included 187 patients with paired biopsies that were assessed for both inflammation and fibrosis [10]. It found that 4 of 23 patients (17 percent) with no inflammation on initial biopsy went on to develop advanced fibrosis, compared with 84 of 170 (49 percent) with inflammation. The median time to develop advanced fibrosis among those with inflammation on the initial biopsy was 4.2 years, compared with 13.4 years for those without inflammation. After adjusting for potential confounders, the presence of any inflammation on the initial biopsy increased the chance of progressing to advanced fibrosis 2.5-fold compared with patients who did not have inflammation.

Other factors that have been associated with disease progression or advanced fibrosis include:

- Older age [10,17,21,22]
- Diabetes mellitus [23]
- Elevated serum aminotransferases (≥2 times the upper limit of normal in one study) [21-24]

- Presence of ballooning degeneration plus Mallory hyaline or fibrosis on biopsy [25]
- Body mass index ≥28 kg/m^2 [21]
- Higher visceral adiposity index, which takes into account waist circumference, body mass index, triglycerides, and high-density lipoprotein level [26]
- Coffee consumption has been associated with a lower risk of progression [27]

Several statistical models have been described to predict fibrosis, but none has been extensively validated [17,21,24,28,29]

Heavy alcohol use among patients with or at risk for NAFLD is associated with hepatic steatosis, hepatic injury, and fibrosis progression [30-34]. As an example, in a study of 71 patients with NAFLD followed for a mean of 14 years, 17 patients (24 percent) had fibrosis progression [33]. Heavy (more than 60 g of alcohol on one occasion for men or 48 g for women) episodic drinking was more common in those with fibrosis progression than in those without progression (47 versus 11 percent).

Some studies suggest that the consumption of as little as two drinks per day in those who are overweight (and one drink per day in those who are obese) is associated in hepatic injury [31]. However, other data suggest that light or moderate alcohol consumption may have beneficial effects on the liver. This was seen in a cross-sectional study that compared 251 life-time nondrinkers with NAFLD with 331 modest drinkers with NAFLD [35]. Modest drinkers had lower odds for fibrosis (odds ratio [OR] 0.56; 95% confidence interval [CI] 0.41-0.77) and ballooning hepatocellular injury (OR 0.66; 95% CI 0.48-0.92). However, prospective studies examining the effects of light or moderate alcohol consumption in patients with NAFLD are lacking.

Hepatocellular carcinoma — Hepatocellular carcinoma (HCC) is associated with cirrhosis due to NAFLD. In a systematic review of 61 studies and case series of patients with NAFLD or NASH, the risk of HCC among those with cirrhosis ranged from 2.4 percent over seven years to 12.8 percent over three years [36]. Among those without cirrhosis, the risk of mortality from HCC was 0 to 3 percent after follow-up periods of up to 20 years.

As examples, individual studies found the following:

- In one report of 137 patients with NASH and advanced fibrosis, the five-year cumulative incidence of HCC was 8 percent [37].
- In a second report of 195 patients with NASH-related cirrhosis, the one-year cumulative incidence of HCC was 3 percent [38]. Patients who reported regular alcohol consumption were at increased risk for HCC compared with nondrinkers (hazard ratio 3.6).

HCC surveillance is recommended for patients with NASH-related cirrhosis. (See "Prevention of hepatocellular carcinoma and recommendations for surveillance in adults with chronic liver disease", section on 'Other causes of cirrhosis'.)

Recurrence following liver transplantation — Recurrence of NAFLD has been reported following liver transplantation [39-41]. In a series of 622 liver transplants, eight patients, all female, had features consistent with NASH pre-transplantation [41]. At a median follow-up of 15 months, six developed persistent fatty infiltration, three of whom had hepatic degeneration consistent with NASH. In two of the patients, the histologic progression from mild steatosis to steatohepatitis occurred within two years.

Mortality — Cardiovascular disease is the most common cause of death among patients with NAFLD, though patients with NASH are at increased risk for liver-related death compared with patients without NASH [13,42-44]. The association with cardiovascular disease suggests that there should be a reduced threshold for surveillance for cardiovascular disease in patients with NAFLD or NASH [45]. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Associated disorders'.)

Whether patients with NAFLD have increased overall mortality rates compared with the general population is not clear. The largest study from the United States suggests that the overall mortality rate is not increased, whereas smaller studies and studies in other populations suggest a slight increase in mortality:

- The US study examined 11,371 adults participating in NHANES III [46]. Using hepatic ultrasound and serum liver tests, NAFLD was diagnosed in 2089 participants (16 percent), and NASH was diagnosed in 426 (3 percent). There were no significant differences between participants without hepatic steatosis and participants with NAFL or NASH with regard to overall mortality (15 percent, 22 percent, and 13 percent, respectively), mortality due to cardiovascular disease (6 percent, 9 percent, and 4 percent, respectively), cancer mortality (4 percent, 8 percent, and 3 percent, respectively), or mortality due to liver disease (0.4 percent, 0.3 percent, and 0.7 percent, respectively). However, a limitation of the study is that the diagnosis of NAFLD was not based upon liver biopsy, so some patients may have been misclassified, potentially masking differences in mortality rates.

In a second study using the NHANES III data, it was noted that while overall mortality was not increased in patients with NAFLD, there was an increase in mortality among patients who were predicted to have advanced fibrosis based on noninvasive tests (NAFLD fibrosis score or FIB-4 index) compared with patients with NAFLD but no predicted fibrosis (hazard ratios of 1.8 to 2.2) [47]. The increase in mortality was due almost exclusively to cardiovascular causes. (See "Tests used for the noninvasive assessment of hepatic fibrosis", section on 'Panels of indirect markers of fibrosis'.)

- In a smaller population-based study from the US (Minnesota), 420 patients with NAFLD (diagnosed by imaging in 83 percent) had slightly lower overall survival than expected for the Minnesota general population (standardized mortality ratio of 1.34, 95% CI 1.00-1.76) [48]. Higher mortality was associated with increasing age, impaired fasting glucose, and cirrhosis.
- Higher mortality rates in patients with NAFLD were also seen in a population-based study from Sweden. Compared with the general sex- and age-matched population, overall mortality was increased in the 118 patients with biopsy-proven NAFLD or NASH (standardized mortality ratios of 1.69 and 1.86, respectively) [44]. Of the 47 deaths observed during the study in patients with NAFLD (23 with bland steatosis, 24 with NASH), most were due to cardiovascular disease (30 percent), followed by extrahepatic malignancies (28 percent), and liver disease (19 percent).

MANAGEMENT

General approach to the patient — Multiple therapies have been investigated for the treatment of nonalcoholic fatty liver disease (NAFLD). Weight loss is the only therapy with reasonable evidence suggesting it is beneficial and safe.

We recommend the following approach in patients with nonalcoholic fatty liver (NAFL) or NASH:

- Weight loss for patients who are overweight or obese: Options to promote weight loss include lifestyle modifications and, for patients who are candidates, bariatric surgery. A reasonable goal for many patients is to lose 0.5 to 1 kg/week (1 to 2 lb/week). Pharmacologic therapy can be used to aid with weight loss in patients who fail to achieve weight loss goals through diet and exercise alone. (See 'Weight loss' below and 'Other pharmacologic therapies' below and "Obesity in adults: Overview of management" and "Obesity in adults: Drug therapy".)
- Hepatitis A and B vaccinations should be given to patients without serologic evidence of immunity. Additional vaccines recommended for patients with chronic liver disease include pneumococcal vaccination and standard immunizations recommended for the population in general (eg, influenza, diphtheria, tetanus boosters) (figure 1 and figure 2). (See "Immunizations for patients with chronic liver disease", section on 'Vaccines in chronic liver disease'.)
- Treatment of risk factors for cardiovascular disease: Patients with NAFLD are at increased risk for cardiovascular disease and often have multiple cardiovascular disease risk factors. Management of patients with NAFLD includes optimization of blood glucose control in patients with diabetes and treatment of hyperlipidemia. Statin therapy has been shown to be safe in patients with NAFLD [49]. (See "Initial management of blood glucose in adults with type 2 diabetes mellitus" and "Treatment of lipids (including hypercholesterolemia) in secondary prevention", section on 'Statins' and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Associated disorders'.)
- In general, we do not suggest using pharmacologic agents (eg, vitamin E, pioglitazone) solely for the treatment of NAFLD. However, we do suggest vitamin E at a dose of 400 int. unit/day for the subset of patients with advanced fibrosis on biopsy who do not have diabetes or coronary artery disease. (See 'Vitamin E' below.)
- We suggest that patients with NAFLD avoid all alcohol consumption. Heavy alcohol use is associated with disease progression among patients with NAFLD. Whether light to moderate alcohol consumption is harmful is not as clear. It is possible that light or moderate alcohol use may have beneficial effects on the liver [35], and there are potential cardiovascular benefits as well. However, it has not been shown that the cardiovascular benefits of moderate alcohol consumption extend to patients with NAFLD. In the absence of more definitive data, we suggest that patients with NAFLD avoid all alcohol consumption. (See 'Risk factors for progression' above and "Cardiovascular benefits and risks of moderate alcohol consumption" and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Association with other disorders'.)

Weight loss — Weight loss and increased physical activity can lead to sustained improvement in liver enzymes, histology, serum insulin levels, and quality of life in patients with NAFLD, and we recommend weight loss for all patients with NAFLD who are overweight or obese [50-54]. One of the few randomized trials of weight loss included 31 overweight and obese patients (body mass index 25 to 40 kg/m^2) with biopsy proven NASH who were assigned to a weight loss and exercise program or structured education [53]. After one year, average weight loss was higher in patients assigned to the weight loss program (9 versus 0.2 percent body weight). A higher proportion

of the participants in the weight loss group had histologic improvement (72 versus 30 percent), particularly those who achieved the study goal of loss of at least a 7 percent reduction in weight.

A reasonable goal for many patients is to lose 0.5 to 1 kg/week (1 to 2 lb/week). More rapid weight reduction may be associated with worsening of liver disease. In one study of 41 patients with morbid obesity receiving very-low calorie diets (900 kcal/day), the median weight loss after a median follow-up of 261 days was 34 kg [55]. A quarter of the patients developed slight portal fibrosis, which was associated with faster weight loss (median 0.28 kg/day for those with portal fibrosis versus 0.15 kg/day for those without portal fibrosis) [55]. This suggests that patients should avoid rapid weight loss. (See "Obesity in adults: Dietary therapy", section on 'Goals of weight loss' and "Obesity in adults: Dietary therapy", section on 'Rate of weight loss'.)

Histologic improvement has also been observed after bariatric surgery [51,56-64]. In a systematic review that included 21 observational studies of bariatric surgery in patients with NASH, an improvement in steatosis was reported in 18 studies, decreased inflammation was reported in 11, and improvement in fibrosis score was reported in 6 [65]. However, in four studies there was some worsening of fibrosis. Taken together, these data suggest that bariatric surgery is a promising approach in obese patients with NAFLD. However, given the potential for worsening fibrosis in some patients following bariatric surgery, patients should continue to have their liver function monitored closely. (See "Short-term medical outcomes following bariatric surgery", section on 'Nonalcoholic fatty liver disease (NAFLD)'.)

Pharmacologic therapies — Pharmacologic therapies have been studied for the treatment of the subset of patients with nonalcoholic steatohepatitis (NASH). However, most trials have been too short to determine an impact on important patient-centered clinical outcomes (eg, decompensated cirrhosis), instead reporting on surrogate outcomes, such as serum transaminase levels or histologic findings, often with conflicting results [66]. As a result, we do not suggest using pharmacologic agents (eg, vitamin E, pioglitazone) solely for the treatment of NASH.

Vitamin E — Vitamin E decreases oxidative stress, and initial observational studies suggested improvement in aminotransferase levels in patients with NASH who received vitamin E [67]. However, subsequent randomized trials reached variable conclusions [68-75], with the largest trial suggesting a benefit in patients who do not have diabetes who received 800 int. units/day [70,76]. However, observational studies have raised concern over a possible increase in all-cause mortality with high-dose vitamin E supplementation (>400 int. unit/day). We typically treat patients with advanced fibrosis on biopsy who do not have diabetes or coronary artery disease with 400 int. unit/day to avoid the increased all-cause mortality associated with 800 int. unit/day, although data supporting this approach are lacking. (See "Vitamin supplementation in disease prevention", section on 'All-cause mortality'.)

A meta-analysis that included five randomized trials deemed to be of high-quality found no histologic benefits with vitamin E, though there was significant heterogeneity among the studies with respect to the formulation of vitamin E used, the patient population, the duration of treatment, and the addition of lifestyle modifications [66].

The largest randomized trial included in the meta-analysis (Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH; PIVENS) did suggest a benefit with vitamin E. The trial included 247 adults with NASH without diabetes who were randomly assigned to pioglitazone (30 mg daily), vitamin E (800 int. units daily), or placebo for 96 weeks [70]. Patients treated with vitamin E were more likely to have improvement in their global histology score compared with patients who received placebo (43 versus 19 percent). By comparison, histologic improvement was not significantly different with pioglitazone compared with placebo, although there were significant differences in some histologic features such as hepatic steatosis and lobular inflammation. Patients receiving vitamin E or placebo gained less weight than those receiving pioglitazone. A subsequent report from the trial found that among patients receiving vitamin E, improvements in alanine aminotransferase levels were associated with decreases in the NAFLD score, but not in the fibrosis score [76]. (See 'NAFLD activity score' above.)

We suggest vitamin E at a dose of 400 int. unit/day for patients with advanced fibrosis on biopsy who do not have diabetes or coronary artery disease, though a joint guideline issued in 2012 by the American Association for the Study of Liver Diseases, the American Gastroenterological Association, and the American College of Gastroenterology recommends a higher dose of vitamin E (800 mg daily) as first-line pharmacotherapy for nondiabetic patients with biopsy-proven NASH (not just advanced fibrosis) [77]. We reserve the use of vitamin E to those with advanced fibrosis because, while vitamin E appears to be beneficial, we believe additional studies are required before recommending it more broadly.

Insulin-sensitizing agents — The use of insulin-sensitizing agents in the treatment of NAFLD is based upon the role insulin resistance plays in the development of NAFLD. Whereas the thiazolidinediones have been shown to improve histologic parameters in patients with NASH, metformin has not. However, thiazolidinediones are associated with significant side effects and are thus not routinely used for the treatment of NASH. (See "Pathogenesis of nonalcoholic fatty liver disease", section on 'Insulin resistance'.)

Thiazolidinediones — Thiazolidinediones, including pioglitazone and rosiglitazone, are insulin-sensitizing agents that improve liver biochemical and histologic parameters in patients with NASH [68,70,78-83]. However, their use is associated with adverse events, including weight gain, painful swollen legs, and heart failure. In addition, it is likely that long-term treatment is required to achieve a clinically important benefit because the improvements seen with thiazolidinediones may reverse if the drugs are stopped [78]. Our approach is to use thiazolidinediones for the treatment of NASH only in patients with type 2 diabetes who are otherwise candidates for treatment with a thiazolidinedione. (See "Initial management of blood glucose in adults with type 2 diabetes mellitus" and "Thiazolidinediones in the treatment of diabetes mellitus", section on 'Safety'.)

The effect of thiazolidinediones on histologic parameters in NASH was examined in a meta-analysis of four randomized trials that compared thiazolidinediones with placebo in 334 patients with NASH [84]. The analysis found that compared with placebo, thiazolidinediones were more likely to improve hepatic histologic parameters such as ballooning degeneration (odds ratio [OR] 2.1), lobular inflammation (OR 2.6), and steatosis (OR 3.4). Improvement in fibrosis was not seen when all thiazolidinediones were examined, but when the analysis was limited to three studies that used pioglitazone, there was a significant improvement in fibrosis among patients treated with pioglitazone compared with placebo (OR 1.7).

Metformin — Metformin lowers blood glucose by decreasing hepatic gluconeogenesis, stimulating glucose uptake by muscle, and increasing fatty acid oxidation in adipose tissue. However, it does not appear to be effective for the treatment of NASH.

The effectiveness of metformin for the treatment of NASH was evaluated in a meta-analysis that included three randomized trials of metformin with histologic data available both before and after treatment [85]. There was no difference between the patients who received metformin and the control patients with regard to histologic response (steatosis, ballooning, inflammation, or fibrosis), changes in alanine aminotransferase levels, or changes in body mass index.

Other pharmacologic therapies — Numerous other drugs have been examined for the treatment of NASH. While some have shown initial promise, none has been studied sufficiently to recommend its use as a primary treatment for NASH.

Orlistat — Orlistat is a gastrointestinal lipase inhibitor used in the treatment of obesity and type 2 diabetes mellitus. Studies of orlistat as a treatment for NASH have reached variable conclusions [86-88]. We suggest using orlistat when needed as an adjunct for weight loss, but not as a primary treatment for NASH. (See 'General approach to the patient' above and "Obesity in adults: Drug therapy", section on 'Orlistat'.)

Some studies suggest orlistat may be effective in the treatment of NASH independent of its effect on weight loss, whereas others suggest its benefit is only through weight loss:

- A pilot trial in 44 patients with NASH randomly assigned patients to treatment with orlistat or placebo [86]. Both groups also participated in a weight loss program. A similar amount of weight loss was seen in both groups, but a reduction in ultrasound-assessed hepatic steatosis was only seen in the orlistat group. Serum aminotransferases declined in both groups, but did so to a greater extent with orlistat (48 versus 26 percent reduction from baseline).
- A biochemical and histologic benefit from treatment with orlistat was seen in a case series of 14 obese patients with NASH [87]. Improvements in steatosis were related to the degree of weight loss, whereas changes in inflammation and fibrosis were independent of weight loss.
- No benefit on liver histology, insulin resistance, or liver biochemical tests was observed in a randomized trial involving 50 patients with NASH [88]. However, in subgroup analyses, those who lost ≥5 percent of body weight over nine months had improved insulin resistance, and those who lost ≥9 percent of body weight also achieved improved liver histology.

There has been some concern that orlistat may be associated with hepatic inflammation. However, in patients taking orlistat, liver test abnormalities appear to be as likely to occur in the 90 days before starting the drug as in the period after its initiation [89,90]. This suggests that the liver test abnormalities may be related to the NAFLD itself, and not the orlistat.

Ursodeoxycholic acid — Ursodeoxycholic acid (UDCA) may have antiapoptotic and anti-inflammatory effects in the liver [91]. A potential benefit of UDCA in the treatment of NASH was suggested in a pilot study of 40 patients [92] and in studies that combined UDCA with vitamin E [71,93]. However, larger randomized trials have failed to show a benefit [94,95]. As an example, in a randomized trial of 185 patients with biopsy-proven NASH treated with UDCA or placebo, there was no significant difference in overall liver histology between the two groups after 18 months of therapy [95].

Probucol — Probucol is a lipid lowering agent with antioxidant properties. It was studied for the treatment of NASH in a randomized trial with 30 patients with biopsy-proven NASH [96]. Patients were assigned to receive probucol 500 mg daily for six months

or placebo. Patients in the probucol group had a larger change in alanine aminotransferase level than patients in the control group (-57.5 versus -0.6 int. unit/L). In addition, more patients in the probucol group achieved normal aminotransferase levels than controls (50 versus 0 percent). However, the effect on liver histology was not assessed. Probucol is not available in the United States.

Betaine — Betaine is a normal component of the metabolic cycle of methionine, which has a protective effect against steatosis in animal models. Favorable results in a pilot study [97] prompted a randomized controlled trial involving 55 patients who received oral betaine or placebo for one year [98]. Thirty-four patients in the study underwent liver biopsy. While hepatic steatosis improved in the betaine group, there was no significant effect on markers of hepatic inflammation or oxidative stress. Thus, the benefit of betaine therapy remains uncertain.

Losartan — Angiotensin II is involved in the pathogenesis of hepatic fibrosis and enhances iron deposition and insulin resistance. A pilot study of the angiotensin II receptor antagonist losartan in seven patients with NASH suggested a benefit on blood markers of hepatic fibrosis and serum aminotransferase levels [99]. Further studies are needed. (See "Emerging therapies for hepatic fibrosis".)

Atorvastatin — Pilot studies found a benefit from atorvastatin on aminotransferase levels in patients with NAFLD [100,101]. The use of atorvastatin was then examined in a secondary analysis of a trial looking at the effect of atorvastatin, vitamin C, and vitamin E on the development of cardiovascular events in healthy adults [102]. Two of the exclusion criteria for the study were the presence of diabetes and serum aminotransferases >1.5 times the upper limit of normal. At baseline, 80 patients had NAFLD based upon imaging criteria. After a mean of 3.6 years of follow-up, fewer patients in the treatment arm still had NAFLD compared with the placebo arm (34 versus 70 percent; adjusted odds ratio 0.36, 95% CI 0.16-0.83).

However, the conclusions that can be drawn from the trial are limited because patients did not receive atorvastatin alone, only in combination with vitamin E and C, because the diagnosis of NAFLD was based upon imaging criteria and not histology, and because the exclusion criteria (diabetes or elevated aminotransferases) limit its generalizability.

Pentoxifylline — Pentoxifylline inhibits production of tumor necrosis factor-alpha, which has been hypothesized to contribute to the progression of NASH. Biochemical improvement, and in some cases histologic improvement, was described in several pilot studies [103-106]. However, in one of the studies [103], 9 of 20 patients dropped out due to side-effects (primarily nausea).

A subsequent trial randomly assigned 55 patients with biopsy-confirmed NASH to pentoxifylline 400 mg three times per day or placebo [107]. After one year, patients treated with pentoxifylline were more likely than those treated with placebo to show a reduction in the histologic NAFLD activity score of at least two points (39 versus 14 percent) (see 'NAFLD activity score' above). Pentoxifylline was associated with improvements in steatosis, lobular inflammation, and liver fibrosis scores. Three patients receiving pentoxifylline had to decrease their medication dose from three times daily to twice daily because of nausea, which resulted in adequate symptom control.

A smaller randomized trial was unable to show a difference between pentoxifylline and placebo with regard to aminotransferase levels or histologic findings, though patients who received pentoxifylline did show improvement in serum aminotransferases and the histologic findings of steatosis and cellular ballooning compared with their baseline values [108].

Omega-3 fatty acids — Studies have suggested a benefit of omega-3 fatty acids in animals and humans with NAFLD or NASH [109-117]. In a meta-analysis of nine studies with 355 patients, treatment with omega-3 fatty acids was associated with improvement in hepatic steatosis as well as aspartate aminotransferase levels [118]. There was also a trend toward improvement in alanine aminotransferase levels. When the analysis was restricted to data from randomized trials, only hepatic steatosis continued to show improvement with omega-3 fatty acid treatment.

Patients with cirrhosis — The management of cirrhosis due to NAFLD is similar to that for cirrhosis due to other causes and includes management of portal hypertension, screening for hepatocellular carcinoma, and consideration of liver transplantation for patients with decompensated cirrhosis. A general approach to the management of patients with cirrhosis is presented elsewhere. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis" and "Patient selection for liver transplantation".)

Follow-up liver biopsy — During follow-up, some patients will require a liver biopsy. In patients who have never had a liver biopsy, or who had a liver biopsy that showed steatosis but not steatohepatitis, we obtain a liver biopsy if the physical examination or laboratory findings suggest progressive liver disease. Findings suggestive of progressive liver disease include:

- Peripheral stigmata of chronic liver disease (suggestive of cirrhosis)
- Splenomegaly (suggestive of cirrhosis)
- Cytopenias (suggestive of cirrhosis)
- Serum ferritin >1.5 times the upper limit of normal (suggestive of NASH and advanced fibrosis)

- Age >45 years with associated obesity or diabetes (increased risk of advanced fibrosis)

In patients who had a baseline liver biopsy that showed NASH and who have a stable or improving physical examination and laboratory findings, we repeat a liver biopsy in five to seven years to assess disease progression. We obtain a liver biopsy sooner if there is evidence of worsening liver disease.

WHEN TO REFER — We suggest that patients with steatohepatitis on biopsy be followed by a hepatologist. Patients with nonalcoholic fatty liver without steatohepatitis can often be followed by a primary care physician, provided the diagnosis is clear. However, if the patient develops significant aminotransferase elevations (twice the upper limit of normal) or evidence of cirrhosis, we suggest referral to a hepatologist for further evaluation and management.

Patients who develop cirrhosis and have complications (eg, ascites, variceal bleeding) or a model for end-stage liver disease (MELD) score ≥10 (calculator 1 and calculator 2) should be referred for a liver transplantation evaluation. (See "Patient selection for liver transplantation".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Nonalcoholic fatty liver disease, including nonalcoholic steatohepatitis (NASH) (The Basics)")
- Beyond the Basics topics (see "Patient information: Nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Multiple therapies have been investigated for the treatment of nonalcoholic fatty liver disease (NAFLD). Weight loss is the only therapy with sufficient evidence suggesting it is beneficial and safe. (See 'Weight loss' above.)
- We recommend weight loss for overweight and obese patients (**Grade 1B**). In addition to its other health benefits, weight loss, either through lifestyle modifications or bariatric surgery, has been associated with histologic improvement in patients with NAFLD. A reasonable goal for many patients is to lose 0.5 to 1 kg/week (1 to 2 lb/week). Orlistat can be used to aid with weight loss in patients who fail to achieve weight loss goals through diet and exercise alone. (See 'Weight loss' above and 'Other pharmacologic therapies' above.)
- Patients with chronic liver disease, including NAFLD, require vaccinations for hepatitis A and B if they are not already immune, the pneumococcal vaccine, and standard age-appropriate vaccinations (figure 1 and figure 2). (See "Immunizations for patients with chronic liver disease", section on 'Vaccines in chronic liver disease'.)
- We recommend that all patients avoid heavy alcohol consumption (**Grade 1A**). Heavy alcohol use is associated with alcoholic liver disease and numerous other adverse consequences, including cancers of the mouth and esophagus and injuries due to accidents. In patients with or at risk for NAFLD, heavy alcohol use is associated with hepatic steatosis, hepatic injury, and fibrosis progression. (See 'Risk factors for progression' above and "Alcohol use disorder: Epidemiology, pathogenesis, clinical manifestations, adverse consequences, and diagnosis".)
- We suggest that patients with NAFLD refrain from any alcohol consumption (**Grade 2C**). Data are mixed regarding the risks and benefits of light or moderate alcohol consumption among patients with NAFLD, with some studies suggesting harm with alcohol consumption of one to two drinks per day. (See 'Risk factors for progression' above and 'General approach to the patient' above.)
- Patients with NAFLD are at increased risk for cardiovascular disease and often have multiple cardiovascular disease risk factors. Management of patients with NAFLD includes optimization of blood glucose control in patients with diabetes and treatment of hyperlipidemia. Statin therapy has been shown to be safe in patients with NAFLD. (See "Initial management of blood glucose in adults with type 2 diabetes mellitus" and "Treatment of lipids (including hypercholesterolemia) in secondary prevention", section on

'Statins' and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Associated disorders'.)

- We suggest vitamin E for patients with advanced fibrosis on biopsy who do not have diabetes or coronary artery disease (**Grade 2C**). Limited evidence supports a benefit with up to 800 int. units/day of vitamin E in patients without diabetes, but some observational studies suggest a possible increase in all-cause mortality with higher-dose vitamin E (800 int. units/day). As a result, we typically treat with 400 int. unit/day, although data supporting this approach are lacking. (See 'Vitamin E' above.)
- We suggest not using thiazolidinediones primarily for the treatment of NASH (**Grade 2B**). Thiazolidinediones improve histologic parameters in patients with NASH, but likely need to be used long-term and their use has been associated with serious adverse events, including heart failure. Using a thiazolidinedione is reasonable in patients who are candidates for thiazolidinedione treatment for type 2 diabetes. (See 'Thiazolidinediones' above and "Initial management of blood glucose in adults with type 2 diabetes mellitus", section on 'Thiazolidinediones'.)
- Patients with NASH-related cirrhosis should undergo screening for hepatocellular carcinoma. (See "Prevention of hepatocellular carcinoma and recommendations for surveillance in adults with chronic liver disease".)

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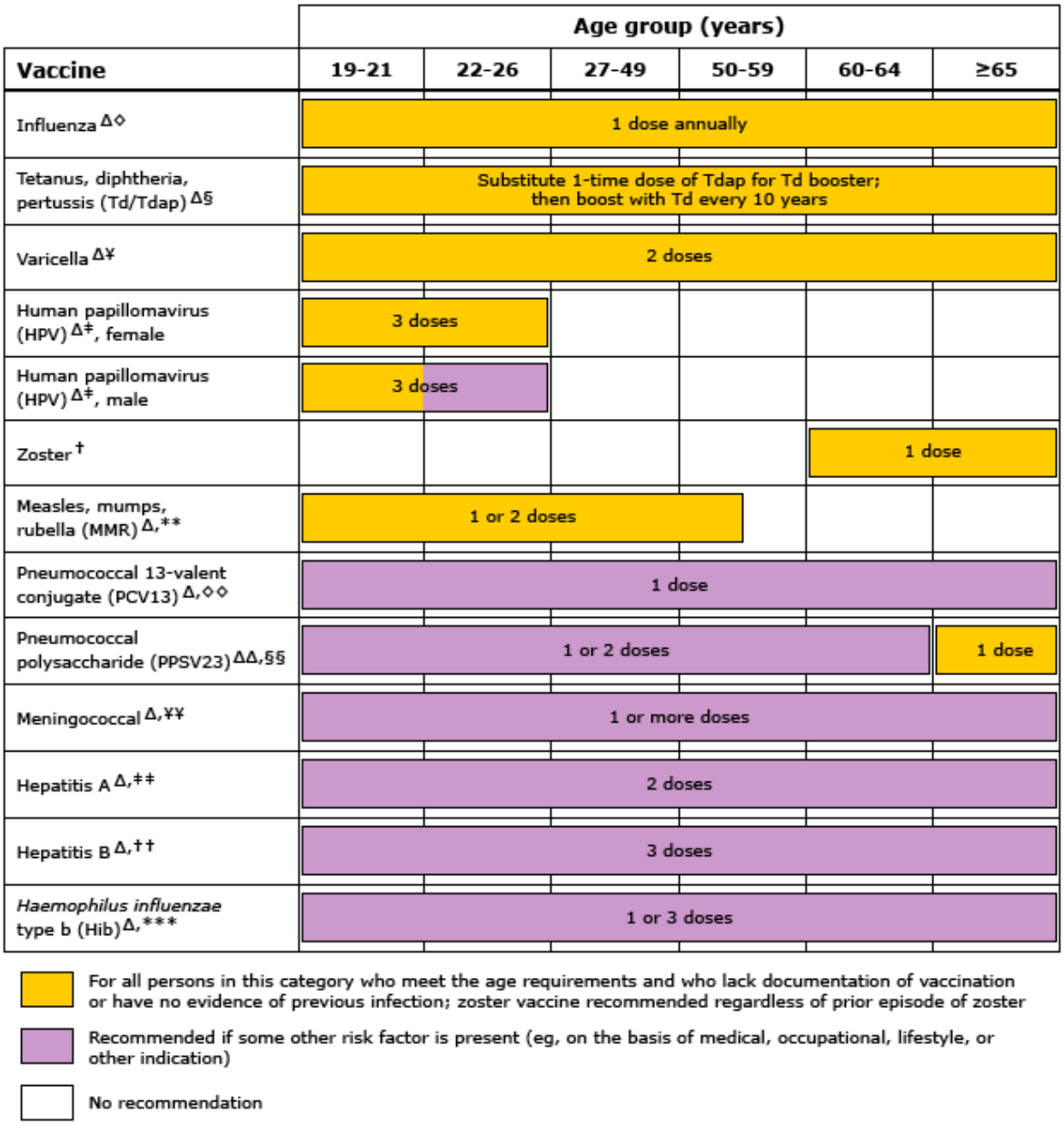
Topic 3600 Version 33.0

GRAPHICS

Recommended adult immunization schedule, by vaccine and age group* - United States, 2014



NOTE: These recommendations **must** be read with the footnotes that follow containing number of doses, intervals between doses, and other important information. The recommendations in this schedule were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), American College of Obstetricians and Gynecologists (ACOG), and American College of Nurse-Midwives (ACNM).

* **Additional information**

- Additional guidance for the use of the vaccines described in this supplement is available at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- Information on vaccination recommendations when vaccination status is unknown and other general

immunization information can be found in the General Recommendations on Immunization at www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm.

- Information on travel vaccine requirements and recommendations (eg, for hepatitis A and B, meningococcal, and other vaccines) is available at http://wwwnc.cdc.gov/travel/destinations/list.
- Additional information and resources regarding vaccination of pregnant women can be found at http://www.cdc.gov/vaccines/adults/rec-vac/pregnant.html.
- Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available at www.vaers.hhs.gov or by telephone, 800-822-7967.
- Information on how to file a Vaccine Injury Compensation Program claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382. To file a claim for vaccine injury, contact the US Court of Federal Claims, 717 Madison Place, NW, Washington, DC 20005; telephone, 202-357-6400.

Δ Covered by the Vaccine Injury Compensation Program.

◇ **Influenza vaccination**

- Annual vaccination against influenza is recommended for all persons aged six months or older.
- Persons aged six months or older, including pregnant women and persons with hives-only allergy to eggs, can receive the inactivated influenza vaccine (IIV). An age-appropriate IIV formulation should be used.
- Adults aged 18 to 49 years can receive the recombinant influenza vaccine (RIV) (FluBlok). RIV does not contain any egg protein.
- Healthy, nonpregnant persons aged 2 to 49 years without high-risk medical conditions can receive either intranasally administered live, attenuated influenza vaccine (LAIV) (FluMist), or IIV. Healthcare personnel who care for severely immunocompromised persons (ie, those who require care in a protected environment) should receive IIV or RIV rather than LAIV.
- The intramuscularly or intradermally administered IIV are options for adults aged 18 to 64 years.
- Adults aged 65 years or older can receive the standard-dose IIV or the high-dose IIV (Fluzone High-Dose).

§ **Tetanus, diphtheria, and acellular pertussis (Td/Tdap) vaccination**

- Administer one dose of Tdap vaccine to pregnant women during each pregnancy (preferred during 27 to 36 weeks' gestation) regardless of interval since prior Td or Tdap vaccination.
- Persons aged 11 years or older who have not received Tdap vaccine or for whom vaccine status is unknown should receive a dose of Tdap followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter. Tdap can be administered regardless of interval since the most recent tetanus or diphtheria-toxoid containing vaccine.
- Adults with an unknown or incomplete history of completing a three-dose primary vaccination series with Td-containing vaccines should begin or complete a primary vaccination series including a Tdap dose.
- For unvaccinated adults, administer the first two doses at least four weeks apart and the third dose 6 to 12 months after the second.
- For incompletely vaccinated (ie, less than three doses) adults, administer remaining doses.
- Refer to the Advisory Committee on Immunization Practices (ACIP) statement for recommendations for administering Td/Tdap as prophylaxis in wound management (see footnote *).

¥ **Varicella vaccination**

- All adults without evidence of immunity to varicella (as defined below) should receive two doses of single-antigen varicella vaccine or a second dose if they have received only one dose.
- Vaccination should be emphasized for those who have close contact with persons at high risk for severe disease (eg, healthcare personnel and family contacts of persons with immunocompromising conditions) or are at high risk for exposure or transmission (eg, teachers; child care employees; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; and international travelers).
- Pregnant women should be assessed for evidence of varicella immunity. Women who do not have

evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility. The second dose should be administered four to eight weeks after the first dose.

- Evidence of immunity to varicella in adults includes any of the following:
  - Documentation of two doses of varicella vaccine at least four weeks apart;
  - US-born before 1980, except healthcare personnel and pregnant women;
  - History of varicella based on diagnosis or verification of varicella disease by a healthcare provider;
  - History of herpes zoster based on diagnosis or verification of herpes zoster disease by a healthcare provider; or
  - Laboratory evidence of immunity or laboratory confirmation of disease.

‡ **Human papillomavirus (HPV) vaccination**

- Two vaccines are licensed for use in females, bivalent HPV vaccine (HPV2) and quadrivalent HPV vaccine (HPV4), and one HPV vaccine for use in males (HPV4).
- For females, either HPV4 or HPV2 is recommended in a three-dose series for routine vaccination at age 11 or 12 years and for those aged 13 through 26 years, if not previously vaccinated.
- For males, HPV4 is recommended in a three-dose series for routine vaccination at age 11 or 12 years and for those aged 13 through 21 years, if not previously vaccinated. Males aged 22 through 26 years may be vaccinated.
- HPV4 is recommended for men who have sex with men through age 26 years for those who did not get any or all doses when they were younger.
- Vaccination is recommended for immunocompromised persons (including those with HIV infection) through age 26 years for those who did not get any or all doses when they were younger.
- A complete series for either HPV4 or HPV2 consists of three doses. The second dose should be administered four to eight weeks (minimum interval of four weeks) after the first dose; the third dose should be administered 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of at least 12 weeks).
- HPV vaccines are not recommended for use in pregnant women. However, pregnancy testing is not needed before vaccination. If a woman is found to be pregnant after initiating the vaccination series, no intervention is needed; the remainder of the three-dose series should be delayed until completion of pregnancy.

† **Zoster vaccination**

- A single dose of zoster vaccine is recommended for adults aged 60 years or older regardless of whether they report a prior episode of herpes zoster. Although the vaccine is licensed by the US Food and Drug Administration (FDA) for use among and can be administered to persons aged 50 years or older, ACIP recommends that vaccination begin at age 60 years.
- Persons aged 60 years or older with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication, such as pregnancy or severe immunodeficiency.

** **Measles-mumps-rubella (MMR) vaccination**

Adults born before 1957 are generally considered immune to measles and mumps. All adults born in 1957 or later should have documentation of one or more doses of MMR vaccine unless they have a medical contraindication to the vaccine or laboratory evidence of immunity to each of the three diseases. Documentation of provider-diagnosed disease is not considered acceptable evidence of immunity for measles, mumps, or rubella.

Measles component:

- A routine second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who:
  - Are students in postsecondary educational institutions;
  - Work in a healthcare facility; or
  - Plan to travel internationally.
- Persons who received inactivated (killed) measles vaccine or measles vaccine of unknown type during 1963 to 1967 should be revaccinated with two doses of MMR vaccine.

Mumps component:

- A routine second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is

recommended for adults who:
- Are students in a postsecondary educational institution;
- Work in a healthcare facility; or
- Plan to travel internationally.

- Persons vaccinated before 1979 with either killed mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection (eg, persons who are working in a healthcare facility) should be considered for revaccination with two doses of MMR vaccine.

Rubella component:

- For women of childbearing age, regardless of birth year, rubella immunity should be determined. If there is no evidence of immunity, women who are not pregnant should be vaccinated. Pregnant women who do not have evidence of immunity should receive MMR vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility.

Healthcare personnel born before 1957:

- For unvaccinated healthcare personnel born before 1957 who lack laboratory evidence of measles, mumps, and/or rubella immunity or laboratory confirmation of disease, healthcare facilities should consider vaccinating personnel with two doses of MMR vaccine at the appropriate interval for measles and mumps or one dose of MMR vaccine for rubella.

◇◇ **Pneumococcal conjugate (PCV13) vaccination**

- Adults aged 19 years or older with immunocompromising conditions (including chronic renal failure and nephrotic syndrome), functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants who have not previously received PCV13 or PPSV23 should receive a single dose of PCV13 followed by a dose of PPSV23 at least eight weeks later.
- Adults aged 19 years or older with the aforementioned conditions who have previously received one or more doses of PPSV23 should receive a dose of PCV13 one or more years after the last PPSV23 dose was received. For adults who require additional doses of PPSV23, the first such dose should be given no sooner than eight weeks after PCV13 and at least five years after the most recent dose of PPSV23.
- When indicated, PCV13 should be administered to patients who are uncertain of their vaccination status history and have no record of previous vaccination.
- Although PCV13 is licensed by the US Food and Drug Administration for use among and can be administered to persons aged 50 years or older, ACIP recommends PCV13 for adults aged 19 years or older with the specific medical conditions noted above.

ΔΔ **Pneumococcal polysaccharide (PPSV23) vaccination**

- When PCV13 is also indicated, PCV13 should be given first (see footnote ◇◇).
- Vaccinate all persons with the following indications:
  - All adults aged 65 years or older;
  - Adults younger than 65 years with chronic lung disease (including chronic obstructive pulmonary disease, emphysema, and asthma), chronic cardiovascular diseases, diabetes mellitus, chronic renal failure, nephrotic syndrome, chronic liver disease (including cirrhosis), alcoholism, cochlear implants, cerebrospinal fluid leaks, immunocompromising conditions, and functional or anatomic asplenia (eg, sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, splenic dysfunction, or splenectomy [if elective splenectomy is planned, vaccinate at least two weeks before surgery]);
  - Residents of nursing homes or long-term care facilities; and
  - Adults who smoke cigarettes.
- Persons with immunocompromising conditions and other selected conditions are recommended to receive PCV13 and PPSV23 vaccines. See footnote ◇◇ for information on timing of PCV13 and PPSV23 vaccinations.
- Persons with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis.
- When cancer chemotherapy or other immunosuppressive therapy is being considered, the interval between vaccination and initiation of immunosuppressive therapy should be at least two weeks. Vaccination during chemotherapy or radiation therapy should be avoided.

- Routine use of PPSV23 vaccine is not recommended for American Indians/Alaska Natives or other persons younger than 65 years unless they have underlying medical conditions that are PPSV23 indications. However, public health authorities may consider recommending PPSV23 for American Indians/Alaska Natives who are living in areas where the risk for invasive pneumococcal disease is increased.
- When indicated, PPSV23 vaccine should be administered to patients who are uncertain of their vaccination status and have no record of vaccination.

§§ **Revaccination with PPSV23**

- One-time revaccination five years after the first dose of PPSV23 is recommended for persons aged 19 through 64 years with chronic renal failure or nephrotic syndrome, functional or anatomic asplenia (eg, sickle cell disease or splenectomy), or immunocompromising conditions.
- Persons who received one or two doses of PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years or later if at least five years have passed since their previous dose.
- No further doses of PPSV23 are needed for persons vaccinated with PPSV23 at or after age 65 years.

¥¥ **Meningococcal vaccination**

- Administer two doses of quadrivalent meningococcal conjugate vaccine (MenACWY [Menactra, Menveo]) at least two months apart to adults of all ages with functional asplenia or persistent complement component deficiencies. HIV infection is not an indication for routine vaccination with MenACWY. If an HIV-infected person of any age is vaccinated, two doses of MenACWY should be administered at least two months apart.
- Administer a single dose of meningococcal vaccine to microbiologists routinely exposed to isolates of *Neisseria meningitidis*, military recruits, persons at risk during an outbreak attributable to a vaccine serogroup, and persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic.
- First-year college students up through age 21 years who are living in residence halls should be vaccinated if they have not received a dose on or after their 16th birthday. MenACWY is preferred for adults with any of the preceding indications who are aged 55 years or younger as well as for adults aged 56 years or older who (a) were vaccinated previously with MenACWY and are recommended for revaccination, or (b) for whom multiple doses are anticipated. Meningococcal polysaccharide vaccine (MPSV4 [Menomune]) is preferred for adults aged 56 years or older who have not received MenACWY previously and who require a single dose only (eg, travelers).
- Revaccination with MenACWY every five years is recommended for adults previously vaccinated with MenACWY or MPSV4 who remain at increased risk for infection (eg, adults with anatomic or functional asplenia, those with persistent complement component deficiencies, or microbiologists).

‡‡ **Hepatitis A vaccination**

- Vaccinate any person seeking protection from hepatitis A virus (HAV) infection and persons with any of the following indications:
  - Men who have sex with men and persons who use injection or noninjection illicit drugs;
  - Persons working with HAV-infected primates or with HAV in a research laboratory setting;
  - Persons with chronic liver disease and persons who receive clotting factor concentrates;
  - Persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A; and
  - Unvaccinated persons who anticipate close personal contact (eg, household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. (See footnote * for more information on travel recommendations.) The first dose of the two-dose hepatitis A vaccine series should be administered as soon as adoption is planned, ideally two or more weeks before the arrival of the adoptee.
  - Single-antigen vaccine formulations should be administered in a two-dose schedule at either 0 and 6 to 12 months (Havrix), or 0 and 6 to 18 months (Vaqta). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer three doses at 0, 1, and 6 months; alternatively, a four-dose schedule may be used, administered on days 0, 7, and 21 to 30 followed by a booster

dose at month 12.

†† **Hepatitis B vaccination**

- Vaccinate persons with any of the following indications and any person seeking protection from hepatitis B virus (HBV) infection:
  - Sexually active persons who are not in a long-term, mutually monogamous relationship (eg, persons with more than one sex partner during the previous six months); persons seeking evaluation or treatment for a sexually transmitted disease (STD); current or recent injection drug users; and men who have sex with men;
  - Healthcare personnel and public safety workers who are potentially exposed to blood or other infectious body fluids;
  - Persons with diabetes who are younger than age 60 years as soon as feasible after diagnosis; persons with diabetes who are age 60 years or older at the discretion of the treating clinician based on the likelihood of acquiring HBV infection, including the risk posed by an increased need for assisted blood glucose monitoring in long-term care facilities, the likelihood of experiencing chronic sequelae if infected with HBV, and the likelihood of immune response to vaccination;
  - Persons with end-stage renal disease, including patients receiving hemodialysis, persons with HIV infection, and persons with chronic liver disease;
  - Household contacts and sex partners of hepatitis B surface antigen–positive persons, clients and staff members of institutions for persons with developmental disabilities, and international travelers to countries with high or intermediate prevalence of chronic HBV infection; and
  - All adults in the following settings: STD treatment facilities, HIV testing and treatment facilities, facilities providing drug abuse treatment and prevention services, healthcare settings targeting services to injection drug users or men who have sex with men, correctional facilities, end-stage renal disease programs and facilities for chronic hemodialysis patients, and institutions and nonresidential day care facilities for persons with developmental disabilities.
- Administer missing doses to complete a three-dose series of hepatitis B vaccine to those persons not vaccinated or not completely vaccinated. The second dose should be administered one month after the first dose; the third dose should be given at least two months after the second dose (and at least four months after the first dose). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, give three doses at 0, 1, and 6 months; alternatively, a four-dose Twinrix schedule, administered on days 0, 7, and 21 to 30 followed by a booster dose at month 12 may be used.
- Adult patients receiving hemodialysis or with other immunocompromising conditions should receive one dose of 40 mcg/mL (Recombivax HB) administered on a three-dose schedule at 0, 1, and 6 months or two doses of 20 mcg/mL (Engerix-B) administered simultaneously on a four-dose schedule at 0, 1, 2, and 6 months.

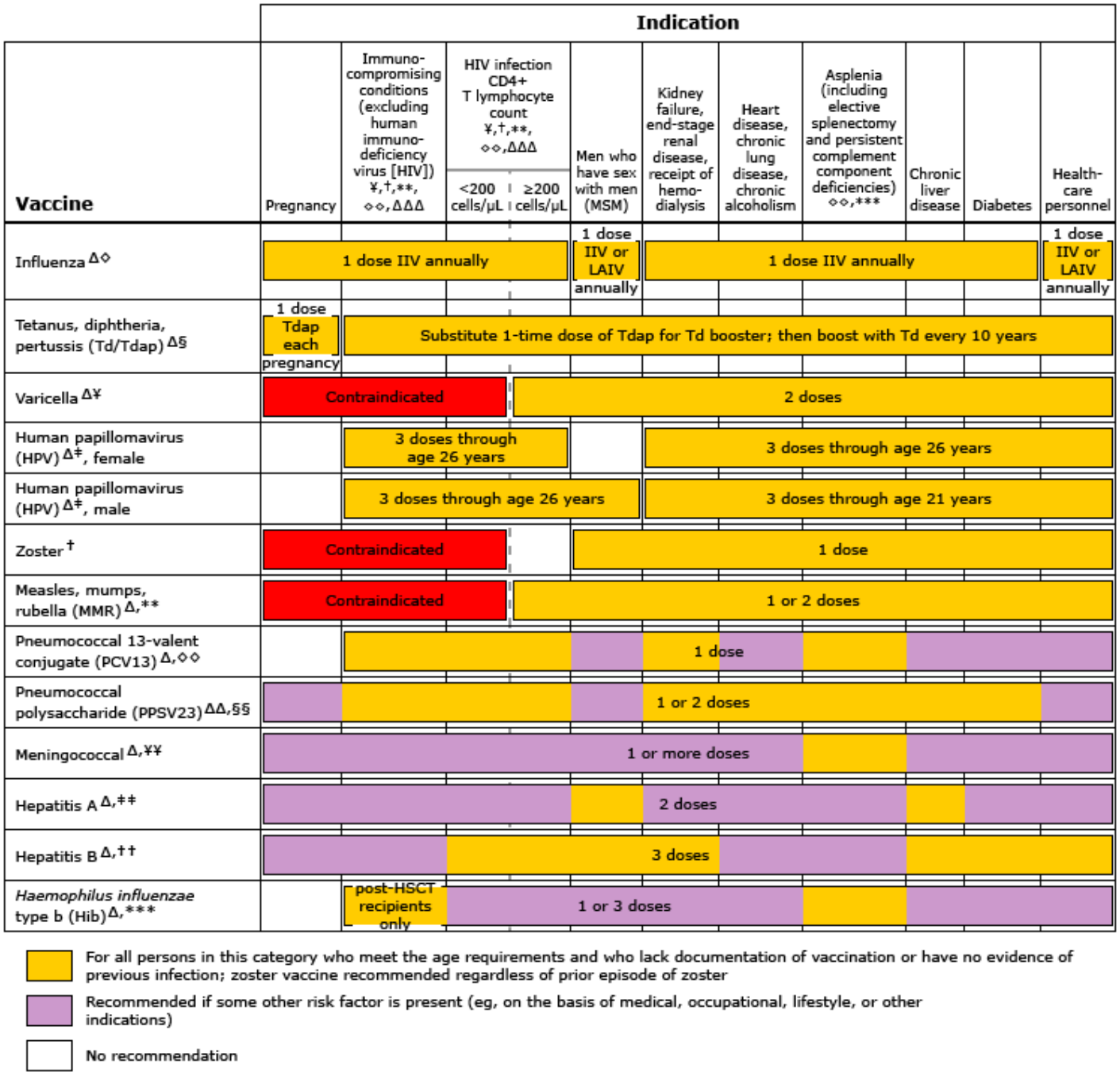
*** ***Haemophilus influenzae*** **type b (Hib) vaccination**

- One dose of Hib vaccine should be administered to persons who have functional or anatomic asplenia or sickle cell disease or are undergoing elective splenectomy if they have not previously received Hib vaccine. Hib vaccination 14 or more days before splenectomy is suggested.
- Recipients of a hematopoietic stem cell transplant should be vaccinated with a three-dose regimen 6 to 12 months after a successful transplant, regardless of vaccination history; at least four weeks should separate doses.
- Hib vaccine is not recommended for adults with HIV infection since their risk for Hib infection is low.

Reproduced from: Advisory Committee on Immunization Practices (ACIP). Adult immunization schedules, United States 2014. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/hcp/adult.html (Accessed on February 11, 2014).

Graphic 82634 Version 10.0

Recommended vaccinations indicated for adults based on medical and other indications* - United States, 2014



NOTE: These recommendations **must** be read with the footnotes that follow containing number of doses, intervals between doses, and other important information. The recommendations in this schedule were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), American College of Obstetricians and Gynecologists (ACOG), and American College of Nurse-Midwives (ACNM).

* **Additional information**

- Additional guidance for the use of the vaccines described in this supplement is available at www.cdc.gov/vaccines/hcp/acip-

recs/index.html.

- Information on vaccination recommendations when vaccination status is unknown and other general immunization information can be found in the General Recommendations on Immunization at www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm.
- Information on travel vaccine requirements and recommendations (eg, for hepatitis A and B, meningococcal, and other vaccines) is available at http://wwwnc.cdc.gov/travel/destinations/list.
- Additional information and resources regarding vaccination of pregnant women can be found at http://www.cdc.gov/vaccines/adults/rec-vac/pregnant.html.
- Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available at www.vaers.hhs.gov or by telephone, 800-822-7967.
- Information on how to file a Vaccine Injury Compensation Program claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382. To file a claim for vaccine injury, contact the US Court of Federal Claims, 717 Madison Place, NW, Washington, DC 20005; telephone, 202-357-6400.

Δ Covered by the Vaccine Injury Compensation Program.

◇ **Influenza vaccination**

- Annual vaccination against influenza is recommended for all persons aged six months or older.
- Persons aged six months or older, including pregnant women and persons with hives-only allergy to eggs, can receive the inactivated influenza vaccine (IIV). An age-appropriate IIV formulation should be used.
- Adults aged 18 to 49 years can receive the recombinant influenza vaccine (RIV) (FluBlok). RIV does not contain any egg protein.
- Healthy, nonpregnant persons aged 2 to 49 years without high-risk medical conditions can receive either intranasally administered live, attenuated influenza vaccine (LAIV) (FluMist), or IIV. Healthcare personnel who care for severely immunocompromised persons (ie, those who require care in a protected environment) should receive IIV or RIV rather than LAIV.
- The intramuscularly or intradermally administered IIV are options for adults aged 18 to 64 years.
- Adults aged 65 years or older can receive the standard-dose IIV or the high-dose IIV (Fluzone High-Dose).

§ **Tetanus, diphtheria, and acellular pertussis (Td/Tdap) vaccination**

- Administer one dose of Tdap vaccine to pregnant women during each pregnancy (preferred during 27 to 36 weeks' gestation) regardless of interval since prior Td or Tdap vaccination.
- Persons aged 11 years or older who have not received Tdap vaccine or for whom vaccine status is unknown should receive a dose of Tdap followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter. Tdap can be administered regardless of interval since the most recent tetanus or diphtheria-toxoid containing vaccine.
- Adults with an unknown or incomplete history of completing a three-dose primary vaccination series with Td-containing vaccines should begin or complete a primary vaccination series including a Tdap dose.
- For unvaccinated adults, administer the first two doses at least four weeks apart and the third dose 6 to 12 months after the second.
- For incompletely vaccinated (ie, less than three doses) adults, administer remaining doses.
- Refer to the Advisory Committee on Immunization Practices (ACIP) statement for recommendations for administering Td/Tdap as prophylaxis in wound management (see footnote *).

¥ **Varicella vaccination**

- All adults without evidence of immunity to varicella (as defined below) should receive two doses of single-antigen varicella vaccine or a second dose if they have received only one dose.
- Vaccination should be emphasized for those who have close contact with persons at high risk for severe disease (eg, healthcare personnel and family contacts of persons with immunocompromising conditions) or are at high risk for exposure or transmission (eg, teachers; child care employees; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; and international travelers).
- Pregnant women should be assessed for evidence of varicella immunity. Women who do not have evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility. The second dose should be administered four to eight weeks after the first dose.
- Evidence of immunity to varicella in adults includes any of the following:
  - Documentation of two doses of varicella vaccine at least four weeks apart;
  - US-born before 1980, except healthcare personnel and pregnant women;

- History of varicella based on diagnosis or verification of varicella disease by a healthcare provider;
- History of herpes zoster based on diagnosis or verification of herpes zoster disease by a healthcare provider; or
- Laboratory evidence of immunity or laboratory confirmation of disease.

‡ **Human papillomavirus (HPV) vaccination**

- Two vaccines are licensed for use in females, bivalent HPV vaccine (HPV2) and quadrivalent HPV vaccine (HPV4), and one HPV vaccine for use in males (HPV4).
- For females, either HPV4 or HPV2 is recommended in a three-dose series for routine vaccination at age 11 or 12 years and for those aged 13 through 26 years, if not previously vaccinated.
- For males, HPV4 is recommended in a three-dose series for routine vaccination at age 11 or 12 years and for those aged 13 through 21 years, if not previously vaccinated. Males aged 22 through 26 years may be vaccinated.
- HPV4 is recommended for men who have sex with men through age 26 years for those who did not get any or all doses when they were younger.
- Vaccination is recommended for immunocompromised persons (including those with HIV infection) through age 26 years for those who did not get any or all doses when they were younger.
- A complete series for either HPV4 or HPV2 consists of three doses. The second dose should be administered four to eight weeks (minimum interval of four weeks) after the first dose; the third dose should be administered 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of at least 12 weeks).
- HPV vaccines are not recommended for use in pregnant women. However, pregnancy testing is not needed before vaccination. If a woman is found to be pregnant after initiating the vaccination series, no intervention is needed; the remainder of the three-dose series should be delayed until completion of pregnancy.

† **Zoster vaccination**

- A single dose of zoster vaccine is recommended for adults aged 60 years or older regardless of whether they report a prior episode of herpes zoster. Although the vaccine is licensed by the US Food and Drug Administration (FDA) for use among and can be administered to persons aged 50 years or older, ACIP recommends that vaccination begin at age 60 years.
- Persons aged 60 years or older with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication, such as pregnancy or severe immunodeficiency.

** **Measles-mumps-rubella (MMR) vaccination**

Adults born before 1957 are generally considered immune to measles and mumps. All adults born in 1957 or later should have documentation of one or more doses of MMR vaccine unless they have a medical contraindication to the vaccine or laboratory evidence of immunity to each of the three diseases. Documentation of provider-diagnosed disease is not considered acceptable evidence of immunity for measles, mumps, or rubella.

Measles component:

- A routine second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who:
  - Are students in postsecondary educational institutions;
  - Work in a healthcare facility; or
  - Plan to travel internationally.
- Persons who received inactivated (killed) measles vaccine or measles vaccine of unknown type during 1963 to 1967 should be revaccinated with two doses of MMR vaccine.

Mumps component:

- A routine second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who:
  - Are students in a postsecondary educational institution;
  - Work in a healthcare facility; or
  - Plan to travel internationally.
- Persons vaccinated before 1979 with either killed mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection (eg, persons who are working in a healthcare facility) should be considered for revaccination with two doses of MMR vaccine.

Rubella component:

- For women of childbearing age, regardless of birth year, rubella immunity should be determined. If there is no evidence of immunity, women who are not pregnant should be vaccinated. Pregnant women who do not have evidence of immunity should receive MMR vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility.

Healthcare personnel born before 1957:

- For unvaccinated healthcare personnel born before 1957 who lack laboratory evidence of measles, mumps, and/or rubella immunity or laboratory confirmation of disease, healthcare facilities should consider vaccinating personnel with two doses of MMR vaccine at the appropriate interval for measles and mumps or one dose of MMR vaccine for rubella.

◇◇ **Pneumococcal conjugate (PCV13) vaccination**

- Adults aged 19 years or older with immunocompromising conditions (including chronic renal failure and nephrotic syndrome), functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants who have not previously received PCV13 or PPSV23 should receive a single dose of PCV13 followed by a dose of PPSV23 at least eight weeks later.
- Adults aged 19 years or older with the aforementioned conditions who have previously received one or more doses of PPSV23 should receive a dose of PCV13 one or more years after the last PPSV23 dose was received. For adults who require additional doses of PPSV23, the first such dose should be given no sooner than eight weeks after PCV13 and at least five years after the most recent dose of PPSV23.
- When indicated, PCV13 should be administered to patients who are uncertain of their vaccination status history and have no record of previous vaccination.
- Although PCV13 is licensed by the US Food and Drug Administration for use among and can be administered to persons aged 50 years or older, ACIP recommends PCV13 for adults aged 19 years or older with the specific medical conditions noted above.

ΔΔ **Pneumococcal polysaccharide (PPSV23) vaccination**

- When PCV13 is also indicated, PCV13 should be given first (see footnote ◇◇).
- Vaccinate all persons with the following indications:
  - All adults aged 65 years or older;
  - Adults younger than 65 years with chronic lung disease (including chronic obstructive pulmonary disease, emphysema, and asthma), chronic cardiovascular diseases, diabetes mellitus, chronic renal failure, nephrotic syndrome, chronic liver disease (including cirrhosis), alcoholism, cochlear implants, cerebrospinal fluid leaks, immunocompromising conditions, and functional or anatomic asplenia (eg, sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, splenic dysfunction, or splenectomy [if elective splenectomy is planned, vaccinate at least two weeks before surgery]);
  - Residents of nursing homes or long-term care facilities; and
  - Adults who smoke cigarettes.
- Persons with immunocompromising conditions and other selected conditions are recommended to receive PCV13 and PPSV23 vaccines. See footnote ◇◇ for information on timing of PCV13 and PPSV23 vaccinations.
- Persons with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis.
- When cancer chemotherapy or other immunosuppressive therapy is being considered, the interval between vaccination and initiation of immunosuppressive therapy should be at least two weeks. Vaccination during chemotherapy or radiation therapy should be avoided.
- Routine use of PPSV23 vaccine is not recommended for American Indians/Alaska Natives or other persons younger than 65 years unless they have underlying medical conditions that are PPSV23 indications. However, public health authorities may consider recommending PPSV23 for American Indians/Alaska Natives who are living in areas where the risk for invasive pneumococcal disease is increased.
- When indicated, PPSV23 vaccine should be administered to patients who are uncertain of their vaccination status and have no record of vaccination.

§§ **Revaccination with PPSV23**

- One-time revaccination five years after the first dose of PPSV23 is recommended for persons aged 19 through 64 years with chronic renal failure or nephrotic syndrome, functional or anatomic asplenia (eg, sickle cell disease or splenectomy), or immunocompromising conditions.
- Persons who received one or two doses of PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years or later if at least five years have passed since their previous dose.
- No further doses of PPSV23 are needed for persons vaccinated with PPSV23 at or after age 65 years.

¥¥ **Meningococcal vaccination**

- Administer two doses of quadrivalent meningococcal conjugate vaccine (MenACWY [Menactra, Menveo]) at least two months apart to adults of all ages with functional asplenia or persistent complement component deficiencies. HIV infection is not an indication for routine vaccination with MenACWY. If an HIV-infected person of any age is vaccinated, two doses of MenACWY should be administered at least two months apart.

- Administer a single dose of meningococcal vaccine to microbiologists routinely exposed to isolates of *Neisseria meningitidis*, military recruits, persons at risk during an outbreak attributable to a vaccine serogroup, and persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic.
- First-year college students up through age 21 years who are living in residence halls should be vaccinated if they have not received a dose on or after their 16th birthday. MenACWY is preferred for adults with any of the preceding indications who are aged 55 years or younger as well as for adults aged 56 years or older who (a) were vaccinated previously with MenACWY and are recommended for revaccination, or (b) for whom multiple doses are anticipated. Meningococcal polysaccharide vaccine (MPSV4 [Menomune]) is preferred for adults aged 56 years or older who have not received MenACWY previously and who require a single dose only (eg, travelers).
- Revaccination with MenACWY every five years is recommended for adults previously vaccinated with MenACWY or MPSV4 who remain at increased risk for infection (eg, adults with anatomic or functional asplenia, those with persistent complement component deficiencies, or microbiologists).

‡‡ **Hepatitis A vaccination**

- Vaccinate any person seeking protection from hepatitis A virus (HAV) infection and persons with any of the following indications:
  - Men who have sex with men and persons who use injection or noninjection illicit drugs;
  - Persons working with HAV-infected primates or with HAV in a research laboratory setting;
  - Persons with chronic liver disease and persons who receive clotting factor concentrates;
  - Persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A; and
  - Unvaccinated persons who anticipate close personal contact (eg, household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. (See footnote * for more information on travel recommendations.) The first dose of the two-dose hepatitis A vaccine series should be administered as soon as adoption is planned, ideally two or more weeks before the arrival of the adoptee.
  - Single-antigen vaccine formulations should be administered in a two-dose schedule at either 0 and 6 to 12 months (Havrix), or 0 and 6 to 18 months (Vaqta). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer three doses at 0, 1, and 6 months; alternatively, a four-dose schedule may be used, administered on days 0, 7, and 21 to 30 followed by a booster dose at month 12.

†† **Hepatitis B vaccination**

- Vaccinate persons with any of the following indications and any person seeking protection from hepatitis B virus (HBV) infection:
  - Sexually active persons who are not in a long-term, mutually monogamous relationship (eg, persons with more than one sex partner during the previous six months); persons seeking evaluation or treatment for a sexually transmitted disease (STD); current or recent injection drug users; and men who have sex with men;
  - Healthcare personnel and public safety workers who are potentially exposed to blood or other infectious body fluids;
  - Persons with diabetes who are younger than age 60 years as soon as feasible after diagnosis; persons with diabetes who are age 60 years or older at the discretion of the treating clinician based on the likelihood of acquiring HBV infection, including the risk posed by an increased need for assisted blood glucose monitoring in long-term care facilities, the likelihood of experiencing chronic sequelae if infected with HBV, and the likelihood of immune response to vaccination;
  - Persons with end-stage renal disease, including patients receiving hemodialysis, persons with HIV infection, and persons with chronic liver disease;
  - Household contacts and sex partners of hepatitis B surface antigen–positive persons, clients and staff members of institutions for persons with developmental disabilities, and international travelers to countries with high or intermediate prevalence of chronic HBV infection; and
  - All adults in the following settings: STD treatment facilities, HIV testing and treatment facilities, facilities providing drug abuse treatment and prevention services, healthcare settings targeting services to injection drug users or men who have sex with men, correctional facilities, end-stage renal disease programs and facilities for chronic hemodialysis patients, and institutions and nonresidential day care facilities for persons with developmental disabilities.
- Administer missing doses to complete a three-dose series of hepatitis B vaccine to those persons not vaccinated or not completely vaccinated. The second dose should be administered one month after the first dose; the third dose should be given at least two months after the second dose (and at least four months after the first dose). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, give three doses at 0, 1, and 6 months; alternatively, a four-dose Twinrix

schedule, administered on days 0, 7, and 21 to 30 followed by a booster dose at month 12 may be used.

- Adult patients receiving hemodialysis or with other immunocompromising conditions should receive one dose of 40 mcg/mL (Recombivax HB) administered on a three-dose schedule at 0, 1, and 6 months or two doses of 20 mcg/mL (Engerix-B) administered simultaneously on a four-dose schedule at 0, 1, 2, and 6 months.

*** ***Haemophilus influenzae*** **type b (Hib) vaccination**

- One dose of Hib vaccine should be administered to persons who have functional or anatomic asplenia or sickle cell disease or are undergoing elective splenectomy if they have not previously received Hib vaccine. Hib vaccination 14 or more days before splenectomy is suggested.
- Recipients of a hematopoietic stem cell transplant should be vaccinated with a three-dose regimen 6 to 12 months after a successful transplant, regardless of vaccination history; at least four weeks should separate doses.
- Hib vaccine is not recommended for adults with HIV infection since their risk for Hib infection is low.

ΔΔΔ **Immunocompromising conditions**

- Inactivated vaccines generally are acceptable (eg, pneumococcal, meningococcal, and inactivated influenza vaccine) and live vaccines generally are avoided in persons with immune deficiencies or immunocompromising conditions. Information on specific conditions is available at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.

Reproduced from: Advisory Committee on Immunization Practices (ACIP). Adult immunization schedules, United States 2014. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/hcp/adult.html (Accessed on February 11, 2014).

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Disclosures

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