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Gastroenterology for Geriatric Patients (S Katz and A Afzali, Section Editors)

Vaccination in the Elderly and IBD

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Abstract

Purpose of review Significant gaps in knowledge and utilization of vaccinations exist among practitioners providing care for patients with IBD. This review is intended to update the reader on best practices for vaccination within the IBD population with a specific focus on the elderly.
Recent findings Advances in IBD therapeutics have recently increased the number of immunosuppressive therapies available to practitioners. Differences in mechanisms of action of these medications have led to differential implications pertaining to vaccination strategies. Additionally, new vaccines, including the recombinant zoster vaccine, have recently become available for the use in the IBD population.
Summary Given the prominent role the IBD provider plays in the management of patients with IBD, a clear understanding of best practices is essential. This review provides a framework for the integration of optimal vaccination strategies for practitioners caring for adult and elderly patients with IBD.

Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, represent a large health burden globally. In western countries, the burden of inflammatory bowel disease remains large as prevalence has stabilized at over 0.3%, while newly industrialized countries such as Asia, South America, and Africa are seeing accelerating incidence in the twenty-first century [1]. With the rising global increase of IBD along with the

growing number of elderly, the number of older patients with IBD is also expected to grow, and exist in two separate groups: elderly patients with long-standing IBD who were first diagnosed at a younger age and elderly patients with late-onset IBD [2]. Approximately 10–15% of cases of IBD are diagnosed in patients aged > 60 years, and 10–30% of the IBD population are aged > 60 years [3, 4].

Consistent with the experience in other chronic disease states, patients with IBD have poorer receipt of preventive healthcare than patients seen in a primary care setting, including vaccinations [5•]. This may be particularly true among young, otherwise healthy patients with IBD for whom the gastroenterologist may be the sole healthcare provider. Indeed, the comfort level with providing preventive maintenance and knowledge of best practices are highly variable among IBD practitioners [6–8].

Older patients with IBD present several unique challenges, including the implementation of routine health maintenance and vaccination. Immune function likely wanes with advancing age, possibly due to a phenomenon termed immunosensescence [9]. It is well known that vaccine uptake rates are sub-optimal in patients with IBD. However, not only are older patients at a greater risk for severe and preventable infections, but they also demonstrate poorer response rates to vaccinations than younger patients [10•]. Furthermore, immunosuppressive medications, including immunomodulators, biologic agents, and small molecule therapies, are being used more often and earlier in the treatment of inflammatory bowel diseases [11, 12]. These medications are both associated with increased risk of infection as well as potentially reduced immunogenic response to vaccinations [12–14].

This review is intended to update the reader on recent advances in knowledge pertaining to vaccination within the IBD population, with a particular emphasis on the elderly population.

Routine vaccination within the general adult and elderly population

The Advisory Committee on Immunization Practices (ACIP) is made up of medical and public health experts who develop recommendations on the use of vaccines in the USA. The CDC publishes updated ACIP recommendations regarding immunization schedules in the general adult population on its website [15], which stands as public health guidance for the safe use of vaccines. Table 1 lists the current recommendations for vaccinations in the general (non-pregnant) adult population, as well as specific recommendations for adults over ages 50 and 65. In addition to age, other factors that affect vaccine recommendations include pregnancy, environmental exposures, and immunocompromising conditions; the particulars of how each of these factors may affect vaccine recommendations will be discussed briefly but non-comprehensively below.

Children over the age of 6 months and adults of every age are recommended to receive an annual inactivated or recombinant influenza vaccine. Adults may also receive the influenza live attenuated vaccine, although this is not currently recommended after age 50. Influenza vaccination is most effective when administered prior to the onset of influenza circulation in the community, which in general occurs in October, with a peak incidence from December to February [16]. The tetanus, diphtheria, acellular pertussis (TDaP) vaccine is recommended to be received as a one-time dose, with a tetanus, diphtheria (Td) booster to be administered every 10 years thereafter, and with every pregnancy in women. Non-pregnant adults born in or after 1957 should receive either one or two doses of the measles, mumps, rubella (MMR) vaccine and two doses of the varicella vaccine if born in or after 1980. Both MMR and varicella are live

Table 1. Current vaccine recommendations in adults and special concerns for those with IBD

	Vaccine	Recommendation	Special concerns in IBD population
All adults	**Influenza**	Annually	Do not use intranasal
	MenB	2–3 doses (depending on the vaccine and indication)	Anatomic or functional asplenia, pregnancy
	TDP	1 dose, then TD booster every 10 years	
	Hib	1 or 3 doses (depending on the indication)	
	HPV	2–3 doses recommended through age 26 for women and age 21 for men	Recommended through age 26 if immunosuppressed (3 doses) or age 45 based on shared decision
	HepA	2–3 doses depending on the vaccine	
	HepB	2–3 doses depending on the vaccine	
	MenACWY	1–2 doses (depending on indication), then booster every 5 years if risk remains	Anatomic or functional asplenia, college, military, or travel
	MMR	1 dose for most adults born after 1957; 2 doses recommended in certain populations	Avoid in immunosuppressed
	Varicella	2 doses (if born later than 1980)	Avoid in immunosuppressed
Age > 50	**Zoster**	2 doses recombinant (preferred) or one dose live	Avoid live vaccine if immunosuppressed
Age > 65	*PCV13*	1 dose (if not previously satisfied)	Age 19–64 if immunosuppressed
	PPSV23	1 dose	Age 19–64 if immunosuppressed

Italic means non-live. Bold means live and non-live versions. Bold italics means live

vaccines and therefore contraindicated during pregnancy, as well as in patients with immunocompromising conditions.

In addition to the above, young adults are also recommended to receive vaccination for human papillomavirus. The current recommendation is that vaccination with the 9-valent HPV vaccine (9vHPV; Gardasil 9) should be given routinely at age 11 or 12 (of if high risk as early as age 9) and in females age 13 to 26, and in males age 13 to 21 if not previously administered. [17] Patients under the age of 15 at the time of vaccination should receive two doses of 9vHPV and those older than 15 require a third dose. Men who have sex with men, transgender persons, and persons with immunocompromising conditions should also be vaccinated from age 22 to 26 if not previously received. The ACIP has recently approved two new recommendations for the HPV vaccine: "catch up" doses are approved in males up to age 26, and any adult age 27 to 45 may receive the HPV vaccine based on a shared decision-making approach between healthcare provider and patient if the benefits are perceived to be sufficient [18]. However, at the time of publication of this review, these recommendations have not been formally released by the ACIP.

At-risk young adults, including asplenic patients and patients living in close quarters (e.g., first-year college students, military recruits), may also benefit from the receipt of meningococcal vaccination. Other vaccines that can be administered to at-risk adults include hepatitis A, hepatitis B, *Haemophilus*

influenzae type B, and pneumococcal pneumonia. In particular, pneumococcal vaccination should occur in adults between ages 19 and 64 with certain chronic medical conditions (including lung, liver, or non-hypertension heart disease; diabetes; and other immunocompromising conditions) as well as in adults with a history of alcoholism or cigarette smoking.

Adults over the age of 50 are recommended to receive the recently approved recombinant zoster vaccine (Shingrix®) in two doses, though vaccination may also be administered via the zoster live vaccine in a one-time dose after the age of 60. Immunocompetent adults over the age of 65 should also receive one dose of the pneumococcal conjugate vaccine (PCV13), followed at least 1 year later by the pneumococcal polysaccharide vaccine (PPSV23).

Vaccination guidelines in patients with IBD

A thorough infectious and vaccination history should be obtained from patients as a part of the initial outpatient IBD office encounter. When possible, appropriate vaccination should be undertaken early, prior to the initiation of immunosuppressive therapy. Vaccination guidelines in patients with IBD are available from the American College of Gastroenterology (ACG) [19]. In general, adherence to age-appropriate vaccination schedules (as published by the ACIP and Infectious Disease Society of America (IDSA) [20]) is recommended, although delaying some vaccinations may be necessary to facilitate timely administration of immunosuppressive therapy. The Crohn's and Colitis Foundation (www.crohnscolitisfoundation.org) recommendations largely mirror the guidelines of the ACG, stating that adults with IBD should generally follow the same vaccination schedules as the general population, but live virus vaccines should be avoided in patients receiving immunomodulators and/or anti-TNF therapy.

Several potential concerns arise regarding the vaccination of patients with IBD. IBD activity does not appear to be adversely affected by vaccination, with low rates of post-vaccine exacerbations observed in several studies, consistent with the background rate of relapse [21, 22], and numerous other reports have not attributed vaccination with significant rates of IBD- and non-IBD-related adverse events [23].

A well-documented concern is the low rate of medically appropriate vaccinations among patients with IBD [24–28], and gastroenterologists exhibit poor knowledge and comfort level in this area. Several factors may play a role in preventing optimal vaccination, including identifying which provider is responsible for performing health maintenance in vaccination, lack of availability of vaccines within gastroenterology practices as compared with a primary care setting, the lack of primary care physicians in many IBD patients, concerns about reimbursement for vaccines, and lack of knowledge among providers of best practices (Fig. 1). In many cases, vaccines recommended for immunosuppressed patients will not be covered by insurance plans due to age criteria pertaining to the general population. In other chronic disease populations, consultation with an infectious disease specialist has been associated with increased adherence to recommended immunization schedules [29].

A second theoretical concern is infection following vaccination within the immunosuppressed population with IBD. Currently, the ACG deems all non-live vaccines safe to be administered to patients regardless of

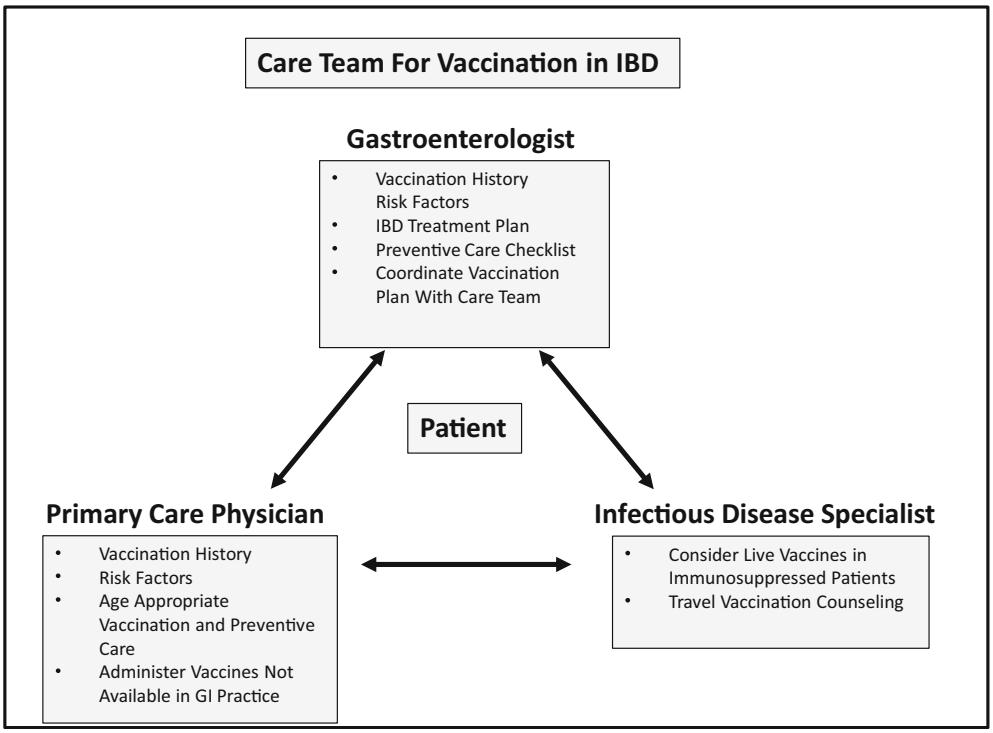

Fig. 1. Roles of care team members in optimizing vaccination for patients with IBD.

immunosuppression status [19]. Administration of any live vaccine warrants caution among patients receiving immunosuppression, but the risk of infection is dependent on medication type and context of use (monotherapy vs. combination therapy). The most common live vaccines considered within the IBD population are the MMR, varicella, and the live herpes zoster vaccine (Zostavax). Immunosuppression in patients with IBD is defined as listed in Table 2 [30]. In general, live vaccines should precede the initiation of immunosuppressive therapy by at least 4 weeks, but the risks of infection versus delays in treatment must be carefully considered, often in consultation with an infectious disease specialist.

Risk of infection has been observed to be greater with anti-TNF monotherapy as compared with thiopurine monotherapy, and highest with combination therapy [13•, 31]. The ACG guidelines [19••] differentiate between "low-level" and "high-level" immunosuppression, with the latter category comprising biologic therapy with TNF antagonists, natalizumab, and ustekinumab therapy. These guidelines were issued prior to the FDA approval of tofacitinib, but it is presumed that this and other JAK inhibitors represent high-level immunosuppression. Conversely, the use of the $\alpha_4\beta_7$ integrin antagonist vedolizumab is considered low-level immunosuppression by most authorities.

Influenza represents a significant risk of morbidity and mortality within patients with chronic illness, especially within those on immunosuppressive therapy. While vaccination annually is recommended for all individuals above 6 months of age [32], it is especially important for patients with IBD and their

Table 2. Definitions of immunosuppression. Modified from Gisbert JP and Chaparro M. *Nat Rev Gastroenterol Hepatol.* 2013;10:277-285 (Ref. [30])

Conventional definition
Treatment with steroids (prednisone equivalent > 20 mg per day, or 2 mg/kg per day if < 10 kg, for 2 weeks or more, and within 3 months of stopping
Ongoing treatment with effective doses of thiopurines or discontinuation within the previous 3 months
Treatment with methotrexate or discontinuation within the previous 3 months
Treatment with anti-TNF agents or discontinuation within the previous 3 months
Significant protein-calorie malnutrition
Proposed updates
Treatment with ustekinumab or discontinuation within the previous 3 months
Treatment with tofacitinib or discontinuation within the previous 4 weeks
Vedolizumab used in combination with an immune modulator

household contacts to receive immunization. The inactivated trivalent vaccine active against influenza A and B is preferred over other vaccines [33], and the ACIP recently advised against use of the live attenuated intranasal influenza vaccine for all populations. Similarly, per the ACG preventive care guidelines [19••], close contacts of immunosuppressed patients should avoid the intranasal live vaccine.

In addition to the potential infectious risks of live vaccines within the immunosuppressed IBD population, the immunogenicity of non-live vaccines may also be impacted by type of medication, with combination immune modulator and biologic therapy leading to the lowest response rates. However, studies of efficacy of vaccination within this population have yielded mixed results.

In a study of 73 patients with IBD and non-immunity to HBV, response to HBV vaccination was lower in patients older than 26 years of age (baseline characteristics of patients were age 29.9 ± 12.3 years) [34]. Multiple studies have shown an association between TNF antagonist medications and impaired response to HBV vaccination in IBD patients [35•, 36, 37]. Among different agents within the anti-TNF class, little data exist with respect to efficacy, although infliximab may be associated with lower rates of seroconversion [35•, 38].

For MMR vaccination, a prospective study was carried out including 122 patients (age range 19–76 years), of whom more than half were on immunosuppressant therapy [39]. Age > 50 was associated with lower measles titers. However, in a another study evaluating MMR vaccine response in which median time since immunization was over 200 months, IBD patients on various immunosuppressive medications sustained antibody concentrations comparable with healthy controls [40].

Multiple studies have demonstrated that combination thiopurine and tumor necrosis antagonist therapy leads to an impaired immunologic response to influenza vaccination [21, 22, 41–49]; however, the blunted response is likely still sufficient to confer a protective benefit [50•].

In a recent study looking at 2007–2016 registry data, maternal immunosuppression was not associated with lower rates of infant response to tetanus or HiB vaccines compared with unexposed infants of mothers with IBD [51]. However, given the materno-fetal placental transfer of many biologics within the third trimester, detectable biologic levels may be detected in infant blood for several months after birth [52]. Therefore, due to a theoretical concern for infection, all live vaccinations should be deferred for a minimum of 6 months after birth and the gastroenterologist should personally discuss the risks and benefits of live vaccination with the pediatrician to coordinate optimal timing of these vaccines.

Because of the abovementioned issues with decreased immune response to vaccination, accelerated or double-dose vaccination regimens may be used to increase efficacy and has been suggested for HBV [36], influenza [47], and DPT. [53, 54] In most cases, these regimens are effective in developing immunogenicity to the intended target.

Travel to regions with high rates of endemic infection, including yellow fever and typhoid, remains a concern for patients on high-level immune suppression. The oral typhoid and injectable yellow fever vaccine are both live, and vaccination is only advised for patients after a wash out period of up to 3 months. Additionally, immunosuppressive therapy should continue to be withheld for 4 weeks following vaccination with these agents. Such logistical difficulties present a challenge to the safe travel of patients with IBD, and consultation with an infectious disease travel medicine specialist should be undertaken for patients traveling to high-risk areas. The non-live injectable typhoid vaccine is preferable for these patients. Inadvertent yellow fever vaccine administration has been reported in two instances in patients receiving TNF antagonists [55, 56]. In each of these, the patient did contract self-limited fever and transaminase abnormalities but the true risk of this vaccine among immunosuppressed individuals remains unknown.

Specific issues pertaining to elderly patients With IBD

As previously stated, vaccine efficacy is lower for the elderly than for younger individuals. In addition, older patients have an increased incidence of certain infections and are more likely to experience worse outcomes. Advanced age has been shown to be a risk factor for opportunistic infections among patients with IBD [57]. While immunosuppressive therapies are associated with an increased risk for infections, data from a large retrospective cohort study analyzing patients receiving combination thiopurine and TNF antagonist therapy did not identify age > 65 as an additional risk factor for infection [58]. A recent retrospective analysis of 63,759 patients with IBD from the Truven database demonstrated that those above the age of 65 were specifically at an increased risk of sepsis and pneumonia, but not other types of infection as compared with patients aged 18–64 [59]. Of special concern within the elderly population are pneumococcal pneumonia and herpes zoster infections, which will be discussed in more detail.

Pneumoccoccus

Patients with IBD are at increased risk of pneumonia [31] as well as related mortality and hospitalization [60]. A large cohort study found that IBD patients

were specifically at increased risk of invasive pneumococcal pneumonia [61•]. Currently, vaccination against pneumococcal pneumonia includes the 13-valent pneumococcal conjugate vaccine (PCV13, Prevnar-13), and 23-valent pneumococcal polysaccharide vaccine (PPSV23, Pneumovax), both of which are recommended for patients on immunosuppressive therapy, regardless of age.

Multiple studies in adults with IBD have shown decreased immune responses to PPSV23 [62, 63] when on combination therapy with thiopurines and an anti-TNF agent. In contrast, monotherapy with anti-TNF biologic affects vaccine responses to a lesser degree [23].

A study of 141 patients found while generally safe and well tolerated the sequential vaccination schedule of PCV13 followed by PPSV23 produced lower immunogenicity rates in those patients receiving immunosuppressive drugs (especially combination therapy) when compared with controls [64]. Given the potential for increased risk of both infection and lymphoma among elderly patients receiving combination therapy [65], providers should be especially vigilant for treatment-related complications within this population.

Herpes zoster

Herpes zoster results from a reactivation of latent VZV infection within the sensory ganglia, and age is the major risk factor for both incidence [66] as well as severity and likelihood of complications [67]. Patients receiving immunosuppressive therapy are at increased risk of zoster infection, and this is highest among patients receiving combination TNF antagonist and thiopurine therapy [58]. In a large retrospective study of veterans (mean age 70 and 65 in the control and IBD groups, respectively), multivariate analysis revealed that patients older than 60 and on combination therapy (thiopurines + anti-TNF) were at highest risk for developing herpes zoster at almost 2% per year [68]. IBD itself was a risk factor for herpes zoster when compared with controls, and within IBD patients, age, thiopurine or combination therapy, recency of and cumulative use of prednisone, and IBD flare were all independent risk factors for herpes zoster.

A large Canadian study also found that patients with IBD were at increased risk of herpes zoster compared with controls [69]; however, there was no difference in vaccination rates (live attenuated herpes zoster vaccine) for those aged 60 to 80 years. IBD patients receiving the vaccine were less likely than controls to be on thiopurines and anti-TNF, likely due to the contraindication of live vaccines while on these therapies. In 2008, the CDC issued a statement that therapy with medications causing low-level immune suppression for various conditions, including IBD, was not a contraindication for administration of the live attenuated herpes zoster vaccine. Large studies have suggested that the live attenuated herpes zoster vaccine is effective in reducing rates of herpes zoster in patients on anti-TNF therapy [70, 71].

Recent data on vaccination in IBD

Most of the data reported above pertains to patients receiving therapy with more established immunosuppressive therapies. Few data exist with regard to efficacy or risks of vaccination while on therapy with newer immunosuppressive agents, including the anti-integrin vedolizumab, anti-IL 12/23 biologics (ustekinumab), or JAK inhibitors (tofacitinib).

Vedolizumab is a therapy for Crohn's disease and ulcerative colitis approved by the FDA in 2014 following the GEMINI clinical trial program [72, 73]. It is a humanized monoclonal antibody that selectively targets the $\alpha_4\beta_7$ integrin interaction with MAdCAM-1, preventing leukocyte migration to the gastrointestinal tract, limiting off-target toxicity and systemic infection risk. Given its favorable risk profile observed in the GEMINI trials and real-world cohorts [74, 75] as well as recent reports on comparative safety versus anti-TNF therapies [76, 77], it is frequently positioned for earlier use within the elderly population, with additional data suggesting its use is safe and effective in elderly IBD patients [78, 79]. Because of its mechanism, it is unknown whether vedolizumab may induce a different immune response to vaccines or affect the immunogenicity of oral vaccines.

A small study compared immune response to the trivalent influenza vaccine in IBD patients receiving vedolizumab, other biologics, or no immunosuppressives [80]. All 26 patients failed to meet the vaccination efficacy criteria of a 4-fold increase over baseline IgG titers. Another study on vedolizumab but without a diagnosis of IBD noted that vedolizumab did not alter the response to parenterally administered antigens but did reduce the response to oral antigens, which may be explained by its gut-specific mechanisms of action [81•]. Of note, the package insert for vedolizumab states that patients on this biologic agent may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks [82]. Caution is advised with oral vaccines among patients on vedolizumab given its mechanism of action. Given the previously stated thresholds for low- and high-level immunosuppression, it is generally agreed that for at-risk patients, if the risk of a vaccine-preventable illness is sufficient, the benefits of live vaccination likely outweigh the risks of complications in patients on vedolizumab. In instances of uncertainty, we advocate for consultation with an infectious disease specialist.

Approved in 2017, recombinant zoster vaccine (RZV, Shingrix) [83] is indicated for the prevention of herpes zoster in adults aged 50 and older (www.fda.gov). The Advisory Committee on Immunization Practices (ACIP) now recommends RZV as the preferred shingles vaccine over the zoster vaccine live (ZVL, Zostavax), which has been in use since 2006. There is a dearth of data on the effects (clinical efficacy or adverse effects) of RZV on patients with IBD. Quite recently, Reich et al. reported on 14 IBD patients who received the vaccine, of which the average age was 62 and 21% were on immunosuppressive therapy, with none experiencing an exacerbation of their IBD at an average follow-up time of 48 days [84•]. Given the significant incidence of herpes zoster infections among patients receiving therapy with tofacitinib [85–87], use of RZV is advised prior to the start of therapy, regardless of the age of the patient.

Future directions in the field include the use of vaccine adjuvants in order to boost immunogenicity within the IBD population, better understanding of specific immune pathways relating to vaccine response in the elderly and immunosuppressed populations, as well as emerging concerns pertaining to novel immune pathways affected by newer IBD therapies.

Potential strategies for increased utilization and adherence to guidelines include the use of apps, such as one found on the CDC website (https://www.cdc.gov/vaccines/schedules/hcp/schedule-app.html), or checklists [88, 89] which may help clarify vaccination needs in a manner compatible with time constraints of routine clinical practice. Additionally, care pathways such as the

creation of a multi-disciplinary immune disease vaccination clinic or incorporation of specially trained practitioners into the IBD practice may help optimize rates of adherence to guidelines.

Conclusions

The prevention of vaccine-preventable illness is an essential component of health maintenance for all patients with IBD, and this role will often fall on the gastroenterology treatment team. This is particularly critical among patients receiving immunosuppressive therapy and the elderly, where infection risk and potential concerns regarding vaccination are more significant. Given the proven safety and efficacy of available vaccines, it is essential to ensure patients and family members are adequately informed on the clear benefits of maintaining up-to-date immunizations and the risks of voluntary non-vaccination. The incorporation of clinical guidelines and routine practice aides, such as checklists and integration of experienced practitioners into the care team, can ensure the maximization of best practices.

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Authored first draft (AC, DJL), critical revisions (all), approved final draft (all).

Compliance with Ethical Standards

Conflict of Interest
Dana Lukin reports grants and personal fees from Abbvie; personal fees from Janssen, Pfizer, Prometheus, Celgene, and Salix; and educational grants from Takeda. Anthony Choi declares that he has no conflict of interest. Preston Atteberry declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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