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## **Herpes zoster and vaccination strategies in inflammatory bowel diseases: a practical guide**

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LG wrote the article. CR, EHC, FD, SD, SCN, and LPB critically revised the manuscript. LPB supervised the study. The manuscript was approved by all authors.

### **Conflict of interest**

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**Abstract (141 words)**

Herpes zoster is a painful dermatomal cutaneous eruption due to the reactivation of the latent varicella-zoster virus. Patients with inflammatory bowel diseases have an increased risk of shingles compared to the general population and this risk can be increased with the use of immunosuppressive therapy. Live zoster vaccine and recombinant zoster vaccine have demonstrated efficacy for the prevention of herpes zoster. The recombinant zoster vaccine seems to offer greater efficacy and long-term protection profile compared with the live zoster vaccine. However, their use in clinical practice is still unclear and updated vaccination recommendations are lacking. This review will discuss risk for shingles in patients with inflammatory bowel diseases, available vaccines, and their efficacy and safety profiles. We will also provide guidance on who, when, and how to vaccinate for herpes zoster in routine clinical practice amongst patients with inflammatory bowel diseases.

**Keywords:** Herpes zoster, shingles, herpes zoster vaccine, inflammatory bowel diseases, Zostavax®, Shingrix®

## **Introduction**

Herpes zoster (HZ), also known as shingles, is a painful dermatomal cutaneous eruption which occurs due to the reactivation of latent varicella-zoster virus (VZV)<sup>1,2</sup>. Risk of HZ increases with old age and immunodeficiency conditions and its incidence rate (IR) is approximately 1.5 to 2-fold higher in immune-mediated inflammatory diseases (IMIDs) than in the general population<sup>3-5</sup>. Inflammatory bowel diseases (IBD) are also known to carry a higher risk of HZ<sup>5,6</sup>. Corticosteroids, anti-tumor necrosis factor (anti-TNF) agents, and other biologics may increase the risk of opportunistic infections, including shingles<sup>7,8</sup>. A recent meta-analysis showed that patients with immune mediated inflammatory disorders (IMIDs) have an overall increased risk of herpes zoster after treatment with Janus kinase (JAK) inhibitors<sup>9</sup>.

Live zoster vaccine (LZV) and non-live recombinant zoster vaccine (RZV) have both demonstrated efficacy for the prevention of HZ<sup>10,11</sup>. Both are recommended in immunocompetent adults aged  $\geq 60$  years for LZV and aged  $\geq 50$  years for RZV<sup>12,13</sup>. In 2015, the American College of Rheumatology (ACR) recommended vaccination with LZV for patients with rheumatoid arthritis (RA) aged  $\geq 50$  years before initiating biologics therapy<sup>14</sup>. In 2017, the American College of Gastroenterology (ACG) also recommended vaccination with LZV for patients with IBD aged  $\geq 50$  years<sup>15</sup>. Here, we reviewed available evidence regarding HZ risk in patients with IBD, discussed the efficacy and safety of HZ vaccination, and provided guidance for routine practice.

## **Risk for herpes zoster in IBD patients**

### *Epidemiology and risk factors*

In the general population, the IR of HZ ranges from 1.2 to 4.9 cases per 1,000 person-years (py)<sup>16-18</sup>. The incidence in IMIDs is approximately 1.5 to 2-fold higher than in the general population<sup>3,4,18-20</sup>. In IBD, IR ranges from 6.67 to 9.2 cases per 1,000 py<sup>17,21,22</sup>. Marehbian et al.<sup>20</sup> also reported a higher IR of 89 cases per 10,000 py with a ratio of 1.83 compared to the general population. Patients with Crohn's disease (CD) are at higher risk of shingles than those with ulcerative colitis (UC). IR ranges from 814 to 854 versus 664 to 670 cases per 100,000 py respectively for CD and UC<sup>19,23</sup>. These results were confirmed in another study (IR 1.6 versus 1.2)<sup>6</sup>, and a meta-analysis of observational cohort studies, including more than 1,000,000 patients, reported a relative risk (RR) of 1.74 in CD and of 1.40 in UC compared to non-IBD patients<sup>24</sup>. Finally, IBD activity is also a key factor for HZ, disease flare showed a hazard ratio (HR) of 3.69 (*Table 1*)<sup>17</sup>.

One established risk factors of shingles is the increased age<sup>1,3,25</sup>. A meta-analysis of zoster infection risk found a RR of 1.65 with older age<sup>5</sup>. Regarding IBD, this age relationship is also observed in the occurrence of HZ. Gradual increase in risk is reported among over 60 years old (11.5 cases per 1000 py<sup>21</sup>, around 1,500 cases per 100,000 py<sup>19</sup>) and over 65 years old (15.48 cases per 1,000 py<sup>18</sup>, around 1200 cases per 100,000 py<sup>6</sup>). A significant increase in IR of HZ has also been noted in subjects over 45s (around 799 cases per 100,000 py<sup>6</sup>), and over 50s (11.02 cases per 1,000 py<sup>18</sup>, around 8 cases per 1,000 py<sup>21</sup>, around 1,100 cases per 100,000 py<sup>19</sup>). Furthermore, IR among those under 50s is approximately the same as the age group of the 50-60s in the general population<sup>19</sup>. A retrospective cohort study showed that in patients with IBD and IMIDs, the IRs among the 30s to 50s was similar or higher, respectively, than the corresponding rates in adults without IMIDs aged  $\geq 60$ <sup>4</sup>. In a cohort including 108,604 IBD patients, patients with HZ had significantly more comorbidities including diabetes, cardiac conditions, liver or renal diseases, and chronic pulmonary diseases<sup>19</sup>. A meta-analysis confirmed that comorbidities such as diabetes, cardiovascular,

pulmonary, and renal diseases increased the risk of HZ (RR of 1.24 to 1.41)<sup>5</sup>. Moreover, female gender had a lower risk of HZ (RR=1.19)<sup>5</sup>. Likewise, ethnicity was identified as a risk factor for shingles. Asian patients had higher rates than north America, Europe, or Latin American populations; the incidence was particularly high in Japanese and Korean populations ranging from 10.4 to 18.34 cases per 1,000 py (*Table 1*)<sup>26,27</sup>. Interestingly, a retrospective study demonstrated that IBD was ranked at the fourth position of the immunocompromising or chronic disease conditions with the highest rate of HZ, after the hematopoietic hematological transplant, hematological malignancy, and systemic lupus, in Japanese population<sup>28</sup>. An ethnic genetic susceptibility is probably responsible to explain these differences of risk.

#### *Treatment-related risk*

Two retrospective observational cohort studies showed that 5-aminosalicylic acid (ASA) use was not associated with an increased risk of HZ<sup>6,19</sup>, while a significant increase in shingles IR was found after therapy with corticosteroids (odds ratio (OR) of 1.5<sup>6</sup> and 1.73<sup>19</sup>) and thiopurines (OR of 3.1<sup>6</sup> and 1.85<sup>19</sup>). Another retrospective studies also reported an elevated risk of HZ with corticosteroids (HR of 1.27) and thiopurines (HR of 1.47) (*Table 2*)<sup>17</sup>.

Risk of shingles is also increased after treatment with anti-TNF agents. The OR ranges from 1.33 to 1.81 compared to patients with IBD not treated with anti-TNF drugs or who received 5-ASA<sup>19,20</sup>. However, in a retrospective cohort of the United States Veterans Affairs Healthcare System (VAHS), which include 54,919 patients, anti-TNF agents alone were not associated with higher risk of zoster<sup>17</sup>. Combination therapy (anti-TNF agents and thiopurines) further increases the HZ risk with OR ranging from 1.65 to 3.68 (*Table 2*)<sup>17,19,20</sup>. Colombel et al.<sup>29</sup> reviewed six major clinical trials on adalimumab comprising 3160 CD



patients. Of note, 46 cases of HZ were registered and 6 were considered severe<sup>29</sup>. In the VARSITY trial, which compared adalimumab to vedolizumab in patients with UC, IR was 4.2 per 100 py in the adalimumab group<sup>30</sup>. Although anti-TNF agents were associated with a higher risk of shingles in UC patients, there was no signal of developing severe forms of shingles with secondary bacterial infection or the requirement of an intravenous antiviral drug<sup>31</sup>.

Data concerning vedolizumab are reassuring. A retrospective study including data from six trials on vedolizumab reported an IR of 0.5 cases per 100 py<sup>32</sup>, and these findings were consistent with data from the VARSITY study (*Table 2*)<sup>30</sup>. In the GEMINI I phase III trial, only two cases of HZ were detected in the vedolizumab arm and two cases were reported in the placebo arm<sup>33</sup>. In the VAHS cohort, no HZ case was reported in IBD patients treated with vedolizumab<sup>17</sup>.

Safety data for ustekinumab are more limited. However, three major studies, CERTIFI, UNITI, and UNIFI, showed no increased risk of HZ<sup>34-36</sup>. Similarly, in a rheumatology study on psoriasis, no increased risk of shingles was found<sup>23</sup>, but additional safety studies are necessary to confirm these findings (*Table 2*).

Tofacitinib, a pan-JAK inhibitor, has been approved for the treatment of patients with refractory UC<sup>37</sup>. Tofacitinib was associated with an increased risk of HZ in both patients with RA and IBD, with an IR ranging from 3.4 to 4.1 cases per 100 py, and a dose dependent relationship (higher risk after 10 mg twice daily than 5 mg twice daily dosage) (*Table 2*)<sup>38-41</sup>. A retrospective study, which including 1,157 UC patients treated with tofacitinib from 3 studies (induction, maintenance and long-term), showed IR of 3.45 and of 4.25 per 100 py at dosage of 5 mg and 10mg twice daily, respectively<sup>38</sup>. Filgotinib and upadacitinib are selective JAK1-inhibitors currently being tested in both CD and UC and that should be available soon in routine practice. Approximately 1.3% and 1.4-2% of patients with RA developed HZ at a

daily dosage of 100 mg and 200 mg of filgotinib, respectively<sup>42,43</sup>. Importantly, no significant difference was found in the rate of adverse events (AEs) between placebo and filgotinib groups<sup>43</sup>. In a phase 2 study, HZ was detected in 3% of CD patients treated with daily dosage of 100 mg or 200 mg of filgotinib<sup>44</sup>. Recently, a phase 2b/3 trial, which explored the use of filgotinib 100 mg or 200 mg once daily in patients with UC, reported low rates of HZ (from 0.4% to 0.8%) for both induction and maintenance phases, supporting the safety profile of the drug<sup>45</sup>. Three phase 3 studies investigating the use of upadacitinib in patients with RA revealed that 0.5-1% and 1-2% of subjects receiving upadacitinib 15 mg or 30 mg once daily, developed HZ respectively<sup>46-48</sup>. In a phase 2 trial, one case of HZ was reported in CD patients receiving 12 mg (1.7%) and 24 mg (2.8%) once daily dose during the induction phase, and one case in the 24 mg (2.8%) once daily maintenance group<sup>49</sup>. In a phase 2 trial, only one case of shingles (1.8%) was identified in UC patients treated with upadacitinib 45 mg once daily during the maintenance therapy<sup>50</sup>. Further investigations are required to define whether selective JAK1-inhibitors (filgotinib and upadacitinib) are associated with a lower risk of developing HZ than tofacitinib. Immune response to HZ use JAK-signal transducer and activator of transcription (STAT) pathways, especially type I and II<sup>51</sup>. This explain why JAK-inhibitors have a strong link with shingles compared to other opportunistic infections. May be that selective JAK1-inhibitors disrupt the VZV response less than pan-JAK inhibitors.

## **Available vaccines**

*Live zoster vaccine (LZV): Zostavax<sup>®</sup>*

Zostavax<sup>®</sup>, an attenuated form of VZV, has been approved for the prevention of HZ and its complications in adults aged  $\geq 60$  years by the US Food and Drug Administration (FDA) since 2006<sup>12</sup>, and adults aged  $\geq 50$  years by the European Medicines Agency<sup>52</sup> (EMA) and the FDA<sup>53</sup> since 2008 and 2011, respectively. Instead, the US Advisory Committee on

Immunization Practices (ACIP) recommended the use of LZV since 2008 in adults aged  $\geq 60$  years<sup>12</sup>. Zostavax<sup>®</sup> cost ranges from \$134.16 (Centers for Disease Control and Prevention (CDC) price) to \$216.66 (private price) per dose<sup>54</sup>, but cost and reimbursement policy depend on individual country's healthcare system. A single dose administered subcutaneously or intramuscularly in the deltoid region is recommended and generally well tolerated<sup>10</sup>. Importantly, concomitant administration with a quadrivalent seasonal inactivated influenza vaccine (IIV4) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) is possible without loss of efficacy<sup>55,56</sup>. Contraindications to LZV include primary and acquired immunodeficiency states (acute and chronic leukemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; HIV/AIDS; cellular immune deficiencies), immunosuppressive therapy including high-dose corticosteroids, active untreated tuberculosis, and pregnancy (*Table 3*)<sup>52</sup>.

*Recombinant zoster vaccine (RZV): Shingrix<sup>®</sup>*

Shingrix<sup>®</sup> is approved for the prevention of HZ and its complications among adults aged  $\geq 50$  years by the US FDA since 2017<sup>13</sup>, and the EMA since 2018<sup>57</sup>. The US ACIP recommended it since 2018 for adults aged  $\geq 50$  years<sup>13</sup>. Shingrix<sup>®</sup> cost ranges from \$101.51 (CDC price) to \$151.51 (private price) per dose<sup>58</sup>, but its price and reimbursement depend on the country and healthcare system. To date, it is available only in the US, Canada, and China. Two doses administered intramuscularly in the deltoid region 2-6 months apart are recommended<sup>11,59</sup>. Concomitant administration with IIV4 and PPSV23 is possible without loss of efficacy<sup>60,61</sup>. RZV is also effective in case of previous vaccination with LZV in adults over 65 years old<sup>62</sup>. Main contraindications are the hypersensitivity to the active substance or to any excipient. Administration of RZV to immunocompromised subjects should be based on careful consideration of potential benefits and risks (*Table 3*)<sup>57</sup>.

## **Efficacy and safety data**

### *Efficacy data*

It has been demonstrated that a single dose of LZV was immunogenic in adults aged over 60s<sup>63</sup>. In addition, response was significantly lower in patients aged over 70s<sup>63</sup>. The Zostavax Efficacy and Safety Trial (ZEST) reported an efficacy of 69.8% to prevent HZ in adults aged 50-59 years<sup>64</sup>, while the Shingles Prevention Study (SPS) reported an efficacy of 51.3% in adults aged over 60 years and 37.6% in subjects over 70 years<sup>65</sup>. Efficacy rates based on different age groups are as follows: 69.8% in the 50-59s, 63.9% in the 60-69s and 37.6% in the over 70s<sup>64,65</sup>. Two studies found that LZV was protective for about five years<sup>66,67</sup>. However, short-term and long-term studies showed that vaccine efficacy tended to decrease in the second year, with rates of 62.0%, 48.9%, and 44.6% at year 1, 2, and 4 respectively<sup>67</sup>. Moreover, this rate decreased to 21.1% after 11 years (*Table 4*)<sup>68</sup>. A retrospective study recruiting 463,541 patients with IMIDs (RA, psoriasis, psoriatic arthritis, ankylosing spondylitis, and IBD) showed that patients vaccinated with LZV had a lower IR of HZ than unvaccinated patients during a median follow-up of 2 years<sup>69</sup>. In the VAHS cohort, including 39,983 patients, vaccination in IBD patients was associated with a significant reduction of HZ risk versus unvaccinated patients (adjusted hazard ratio of 0.54)<sup>70</sup>. Finally, Winthrop et al.<sup>71</sup> reported that LZV did not provide adequate long-term protection in a study assessing RA patients treated with tofacitinib.

Concerning RZV, immunogenicity studies showed a dose-dependent relationship, and a two-dose schedule produced 1.5 to 2.5-fold greater humoral immunity than a single dose<sup>72,73</sup>. The ZOE-50 and ZOE-70 studies reported an efficacy against HZ of 97.2% in the over 50 years and of 89.8% in the over 70 years, respectively<sup>74,75</sup>. Furthermore, vaccine efficacy did not differ between different age groups. Efficacy rates across different age groups

were as follows: 96.6 to 96.9% in the 50-59s, 94.1 to 97.4% in the 60-69s, and 89.8 to 97.9% in the over 70s<sup>74</sup>. RZV was also associated with reduced pain symptoms and risk of postherpetic neuralgia in case of breakthrough shingles<sup>76,77</sup>. Shingrix<sup>®</sup> is protective for at least four years and a minimal decline in efficacy is described during this period, with rates of 97.6% and 87.9% at one and four years, respectively (*Table 4*)<sup>75</sup>. Further data showed that responses remained substantially above the pre-vaccination level for up to nine years, and a statistical model predicted that the immune responses remained above the pre-vaccination level for up to 15 years<sup>78</sup>. In a retrospective study including 403 patients with RA and other systemic rheumatic diseases who received RZV, only three cases of HZ occurred 11 months after vaccination<sup>79</sup>. Recently, Kochhar et al. demonstrated that HZ risk was significantly lower in IBD patients receiving 2 doses of RZV compared to those who did not (OR 0.62) , but they were still at higher risk than the general population who received 2 doses(OR 3.03)<sup>80</sup>. However, the reliability of these preliminary results in RA and IBD remains to be confirmed with additional data. Long-term efficacy data in immunocompromised subjects and booster schedule are missing.

### *Safety profile*

The most frequent local and systemic AEs after LZV vaccination are injection-site reaction of mild to moderate intensity (48.3%) and headache (9.4%) (*Table 3*)<sup>64,65,81</sup>. Zostavax<sup>®</sup> can be safely used in patients treated with methotrexate, thiopurines, or low to intermediate dose of corticosteroids (<20 mg/day of prednisone or equivalent)<sup>82</sup>. Safety data about anti-TNF agents are reassuring. A retrospective study reported no case of HZ within 42 days of vaccination in 59 IBD patients who were treated with an anti-TNF agent<sup>83</sup>. Zhang et al.<sup>69</sup> also found no case of HZ within 42 days of vaccination in a large cohort of 551 patients with IMiDs (117 IBD) receiving anti-TNF drugs. On the other hand, an observational cohort

study showed an increased risk of HZ (45 per 1,000 py) in the 42 days after vaccination in patients taking immunosuppressant drugs (e.g. azathioprine, methotrexate, etanercept...) and antirejection drugs (e.g. tacrolimus, cyclosporine...) <sup>84</sup>. However, in this cohort 83.9% of patients were taking high and low dose corticosteroids either alone or combined with other immunosuppressant agents, justifying the higher risk of shingles. Interestingly, Winthrop et al. <sup>85</sup> found that patients who began tofacitinib 2-3 weeks after receiving LZV had similar immune response to those in the placebo group at week 14.

RZV demonstrated a good safety profile. Injection-site reaction of mild to moderate intensity was the most frequent AE varying from 74.1% to 81.5% of patients <sup>74,75</sup>. Myalgia, fatigue, and headache were the most common systemic reactions ranging from 1.4% to 2.4% of patients (*Table 3*) <sup>74,75</sup>. Similarly, a recent prospective study assessing IBD patients showed a 74.6% rate of local AEs and a low rate of flares (1.5%) after vaccination with RZV <sup>86</sup>. Of note, a systematic review reported that RZV had a RR of 1.79 for injection-site events when compared with LZV <sup>87</sup>. Four phase 3 studies highlighted that RZV was immunogenic and humoral responses persisted for at least 12 months after vaccination in immunocompromised adults with solid tumors on chemotherapy, post renal transplantation, hematologic malignancies, and autologous hematopoietic stem cell transplant <sup>88-91</sup>. Although the use of RZV in immunodeficiency situations seems reassuring, data on IBD patients are lacking. In addition, impact of vaccine on IBD course is unknown.

### **Who, when, and how to vaccinate patients with IBD?**

Among patients with IBD who were followed in the nationwide VAHS cohort, only 20.96% of patients were vaccinated against shingles <sup>92</sup>, and the median age at the time of vaccination was 64.9 years <sup>83</sup>. In another study, the rate of HZ vaccination was of 15.5 per 1,000 py <sup>22</sup>. These data revealed the low vaccination coverage and the delay in access to

vaccination. In IMIDs patients aged 30 to 50 years, IR of HZ was similar or higher than the corresponding IR in healthy adults aged  $\geq 60$  years<sup>4</sup>, suggesting that vaccination should be considered earlier in this population. Ethnicity may affect the risk of HZ. Asian population has a higher risk for HZ than Caucasian populations (10.4 to 18.34 cases per 1,000py)<sup>26,27</sup>, and this risk is more pronounced with tofacitinib treatment<sup>38,39,93</sup>. The SELECT-SUNRISE study, which tested upadacitinib at 30 mg once daily dosage in RA, also reported a higher risk of HZ in Japanese population compared with the non-Japanese population (6% vs 1-2%)<sup>94</sup>. In 2015, the ACR recommended vaccination with LZV for patients with RA aged  $\geq 50$  years before initiating biologics therapy or Tofacitinib<sup>14</sup>. In 2017, the ACG clinical guidelines for IBD recommended that patients over 50 years, including those immunosuppressed, should be considered for HZ vaccination<sup>15</sup>. These guidelines encourage increased access to vaccination for IBD patients. HZ is the most frequent vaccine-preventable disease in patients with IBD compared to others (e.g. pneumococcal, influenza or hepatitis)<sup>95</sup>. Vaccination with RZV appears to be better than LZV both in terms of efficacy and duration of protection<sup>87,96</sup>. Moreover, a recent cost-efficacy study comparing both vaccines demonstrated that RZV had a lower cost-efficacy ratio than LZV<sup>97</sup>. For this reason, in 2018 the US ACIP recommended RZV use rather than LZV in immunocompetent adults aged  $\geq 50$  years<sup>13</sup>.

Updated vaccination recommendations for the prevention of HZ are still lacking for patients with IBD. To guide physicians for HZ vaccination in IBD, we propose that RZV should be considered in patients aged  $\geq 50$  years with or without immunosuppressive therapies (including high dose corticosteroids ( $\geq 20$  mg/day of prednisone or equivalent), biologics, or JAK inhibitors), in adult patients before starting treatment with biologics or JAK-inhibitors (tofacitinib, upadacitinib or filgotinib) regardless of age, and in populations at high risk (Asian population, family history of zoster, comorbidities (diabetes, cardiovascular, pulmonary and renal chronic disease)) regardless of age. If RZV is not available, LZV should

be considered in patients aged  $\geq 50$  years without immunosuppressive therapies, in adult patients before starting treatment with biologics or tofacitinib regardless of age, and in populations at high risk. LZV use in patients treated with immunosuppressive therapies should be avoided. In addition, vaccination with RZV should be considered after LZV to prevent loss of protection (*Table 5*). LZV should be administered at least 3 weeks prior to commencement of immunomodulator therapy and subsequent immunization can only be administered after a 3–6 month cessation of immunosuppressive therapy<sup>8</sup>. Concerning VZV negative patients (history or serology), a retrospective study showed that incidence of HZ in vaccinated children with VZV is 5 times lower compared to children who contract wildtype VZV<sup>98</sup>. Hence, these patients should be vaccinated with VZV vaccine in order to prevent VZV infection as recommended<sup>8</sup>, but also for HZ.



**Table 1: Risk factors for herpes zoster infection**

<b>Factor</b>	<b>Risk</b>
Older age	RR 1.65 (based on a meta-analysis)
Female	RR 1.19 (based on a meta-analysis)
Comorbidities*	RR 1.24 – 1.41 (based on a meta-analysis)
Crohn’s disease	RR 1.74 (based on a meta-analysis)
Ulcerative colitis	RR 1.40 (based on a meta-analysis)
Inflammatory bowel disease	6.67 to 9.2 cases per 1,000py (based on 3 population-based studies)
Disease flare-up	HR 3.69 (based on a population-based study)
Asian population	10.4 to 18.34 cases per 1,000py (based on 2 population-based studies)

HR, hazard ratio; py; person-years; RR, relative risk;

\* Comorbidities: diabetes, cardiovascular, pulmonary and renal chronic disease;

**Table 2: Risk related to available treatment**

<b>Treatment</b>	<b>Risk</b>
5-Aminosalicylic acid	No risk (based on 2 retrospective cohort studies)
Corticosteroids	OR 1.5 – 1.73 (based on 2 retrospective cohort studies)
	HR 1.27 (based on a population-based study)
Thiopurines	OR 1.85 – 3.1 (based on 2 retrospective cohort studies)
	HZ 1.47 (based on a population-based study)

Anti-tumor necrosis factor	OR 1.33 – 1.81 (based on 2 retrospective studies)
Combination therapy	OR 1.65- 3.68 (based on 2 retrospective studies and 1 population-based study)
Vedolizumab	IR 0.5 cases per 100py (based on 1 RCT and 1 post hoc analysis from 6 trials)
Ustekinumab	Reassuring data (based on 3 randomized controlled trial and 1 review article)
Tofacitinib	IR 3.4 – 4.1 cases per 100py (based on 4 post hoc safety analysis studies)

HR, hazard ratio, IR, incidence rate; OR, odds ratio;

**Table 3: Comparison of vaccines’ characteristics**

Category	Live zoster vaccine	Recombinant zoster vaccine
<b>FDA approval</b>	2006	2017
<b>ACIP recommendation</b>	≥ 60 years	≥ 50 years
<b>Cost</b>	\$134.16 (CDC price) to \$216.66 (private price) per dose	\$101.51 (CDC price) to \$151.51 (private price) per dose
<b>Number of doses</b>	Single 0.65 ml dose	Two 0.5 ml doses
<b>Spacing between dose</b>	Not available	2-6 months
<b>Storage</b>	Freezer: -50°C to -15°C (-58°F to 5°F)	Refrigerator: 2°C to 8°C (36°F to 46°F)
<b>Administration</b>	Subcutaneous injection in deltoid	Intramuscular injection in deltoid
<b>Concomitant validated administration</b>	IIV4 and PPSV23	IIV4 and PPSV23
<b>Contraindications</b>	Primary and acquired immunodeficiency states (acute and chronic leukemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; HIV/AIDS; cellular immune deficiencies), immunosuppressive therapy including high-dose corticosteroids, active untreated tuberculosis, and pregnancy	Hypersensitivity to the active substance or any excipient
<b>Injection site reactions</b>	48.3%	74.1 to 81.5%
<b>Adverse events</b>	Headache	Myalgia, fatigue, and headache

ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; IIV4, quadrivalent seasonal inactivated influenza vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; HIV/AIDS, human immunodeficiency virus/acquired immuno-deficiency syndrome;

**Table 4: Comparison of vaccines' efficacy**

Category	Live zoster vaccine	Recombinant zoster vaccine
50 to 59 years	69.8%	96.6 - 96.9%
60 to 69 years	63.9%	94.1 - 97.4%
≥ 60 years	37.6%	89.8 - 97.9%
Year 1	62%	97.6%
Year 4	44.6%	87.9%

**Table 5: Proposed recommendations**

Vaccines	Aged ≥ 50 years without immunosuppressive therapies*	Aged ≥ 50 years under immunosuppressive therapies*	Before starting biologics or JAK inhibitors	Population at high-risk**
Recombinant zoster vaccine	Yes	Yes	Yes	Yes
Live zoster vaccine	Yes, if RZV is not available***	Should be avoided	Yes, if RZV is not available***	Yes, if RZV is not available***

\* Including high dose corticosteroids (≥20 mg/day of prednisone or equivalent), biologics, or JAK inhibitor;

\*\* Asian population, comorbidities (diabetes, cardiovascular, pulmonary and renal chronic disease);

\*\*\* Vaccination with RZV should be considered LZV to prevent loss effective protection;

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## **What You Need to Know**

**Background:** Patients with IBD have an increased risk of HZ compared to the general population and this risk can be increased with the use of immunosuppressive therapies.

**Findings:** LVZ and RZV are currently available for the prevention of HZ. RZV offer a greatest efficacy against HZ and better long-term protection than LZV. However, to date, RZV is not recommended in patients with IBD.

**Implications for patient care:** RZV should be considered as a first-line approach when it is available for HZ prevention.