Update on Vaccine Preventable Illness in IBD

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Objectives

To understand the care gap in the management of VPI in IBD

To review the highlights from the recent CAG CPG guidelines on VPD in IBD

To explore data in support of current recommendations for COVID-19 vaccines in IBD

Vaccine Preventable Illness in IBD

Patients with IBD may be at increased risk of some VPDs

Vaccine safety, efficacy, and appropriateness may be altered by IBD and its therapies

Fulminant or fatal infections have been reported in patient with IBD on various immunosuppressive therapies

Melmed et al., Inflamm Bowel Dis, 2009
Benchimol et al. JCAG, 2021
Jones et al. JCAG, 2021

The Evidence-Practice Gap for VPD in IBD

IBD patients have lower rates of vaccination uptake vs. general population

- Uncertainty about which provider recommends and provides vaccines
- Lack of knowledge
- Beliefs in inefficacy
- Vaccine hesitancy

IBD self-administered questionnaire at tertiary care center in US

- 86% Reported current of prior use of IS medications
- 28% reported regularly receiving flu shots
- 9% Received pneumococcal vaccine
- 28% at risk for HBV vaccinated

Melmed et al., Am J Gastro 2006

Melmed et al., Inflamm Bowel Dis, 2009

Fiore et al., ACIP 2008

Evidence to guide approach to VPD in IBD

- Previous guidelines on VPD in IBD focused only on limited data specific to IBD population

- The CAG CPG for Immunizations for Patients with IBD , through a rigorous systematic review, provided evidence-based recommendations for the administration of vaccines in adult and pediatric patients with IBD
  - Part 1: Live
  - Part 2: Inactivated

Melmed, GY et al. Am J Gastroenterol; 2006:101:134-40
Selby et al., Dig Dis Sci 2011; 56:819-24
Wasan SK et al., Inflamm Bowel Dis 2014; 20:246-50
Agarwal N. et al., Vaccine 2012;30:1413-24
Marin, AC et al., World J Gastroenterol 2015;21:11273

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CLINICAL PRACTICE GUIDELINES FOR IMMUNIZATIONS IN PATIENTS WITH IBD

Part 1 – Live Vaccines
Part 2 – Inactivated Vaccines

Benchimol EI, Jones JL, et al. Gastroenterology 2021, in press.
Benchimol EI, Jones JL, et al. Journal of the Canadian Association of Gastroenterology 2021, in press.
Jones JL, Benchimol EI et al. Gastroenterology 2021, in press
Jones JL, Benchimol EI, et al. Journal of the Canadian Association of Gastroenterology 2021, in press

Methods

- Systematic searches of published English language literature via OVIDSP from 1989 through April 12, 2019
  - Efficacy, effectiveness and safety of vaccines in IBD, other IM mediated diseases & the general population
- Per vaccine, population divided into adult and pediatric subgroups *a priori*
- Critical outcomes: mortality, VPD, serious adverse events
  - *Immunogenicity considered a surrogate outcome for efficacy*
- Certainty of evidence (CoE) rated according to the GRADE approach
  - When available CDC-ACIP, WHO-GRADE evidence-profile tables in the general population reviewed & incorporated into overall GRADE assessment

Methods

- Key questions developed through iterative process & voted on by multidisciplinary panel
  - Strong recommendation: most patients should receive the recommended course of action
  - Conditional: different choices will be appropriate for different patients

- Anonymous voting
  - Consensus on direction ≧ 75% (yes / no)
  - Consensus on strength ≧ 75% (strong / conditional)
    - Strong = *we recommend*
    - Conditional = *we suggest*
  - PICO question with no consensus → no recommendation

RECOMMENDATIONS: Good Clinical Practice Statements

- **Recommendation 1:** Complete review of patient's immunization history should be performed at diagnosis, and regular intervals by IBD care providers.
- **Recommendation 2:** All appropriate vaccinations should be given ASAP, ideally prior to initiation of immunosuppressive therapy.
- **Recommendation 3:** In patients who require urgent immunosuppressive therapy, treatment should **not be delayed** in order to provide vaccinations.

Part 1. LIVE VACCINES

- Examples:
  - MMR (measles-mumps-rubella)
  - Varicella (chicken pox)
  - Infant rotavirus vaccine
  - Nasal spray influenza vaccine

- **Should be given, unless on immunosuppressive medications**

MMR & Varicella

MMR vaccine recommended for both pediatric and adult patients with IBD NOT on immunosuppressive therapy but NOT for those using IS medications (conditional)
Varicella vaccine is recommended for pediatric patients with IBD NOT on IS therapy but not for those on IS therapy (conditional)
Varicella vaccine is conditionally favored for adults with IBD not on IS therapy. Varicella vaccine is NOT recommended in adults on IS therapy

Measles, Mumps, and Rubella (MMR)

- MMR susceptible: no documented vaccine, lab confirmed infection, lab evidence immunity – *NACI*
- For pediatric patients on IS, CDC and NACI recommend no live vaccine if IS therapy equivalent to
  - ≧ 2 mg/kg/day or 20 mg/day prednisone ≧ 14 days
  - *Conditional and dependent on incidence / prevalence of disease and immunization*
- Sparse data outside childhood schedule
  - Similar safety & efficacy data
  - *not downgraded for indirectness in adults NOT on IS therapy*

Varicella (VZV)

- Varicella susceptible: No documented immunization with 2 doses of varicella containing vaccine, or lab evidence of immunity –*NACI*
- CoE Safety & effectiveness moderate (Peds)
  - Not downgraded from moderate in pediatric population NOT on IS
  - Downgraded from low to very low (indirectness) in peds on IS
- CoE effectiveness high in general population
  - IBD downgraded from high to low due to indirectness (observational studies suggest reduced immunogenicity)
- CoE Safety & Effectiveness (Adults)
  - Effectiveness downgraded from low to very low (indirectness and imprecision)

Infants Born to Mothers Using Biologic Therapies

- ***No recommendation:*** *In infants born of mothers using biologic therapies, the consensus group could not make a recommendation for or against giving live vaccines in the first 6 months of life.*

  - *GRADE for PICO: very low-certainty of evidence. Vote on PICO question: uncertain/neutral, 67%; no, 33%*

Part 2: INACTIVATED VACCINES

- Herpes zoster (shingles)
- Hepatitis B
- Influenza
- Human papilloma virus (HPV)
- Haemophilus influenza type b (Hib)
- Pneumococcus
- Meningococcus
- Tetanus, diphtheria and pertussis (TDaP)

Inactivated Vaccines

- Consensus was reached on 15 of 20 questions
- Most recommendations were congruent with current CDC and NACI recommendations with a few exceptions
- Consensus was not reached, and recommendations were not made for 5 statements due to lack of evidence
  - Need for double dose hepatitis B vaccine
  - Timing of influenza immunization in patients on biologics
  - Administration of Pneumococcal and meningococcal vaccines in adults without risk factors
  - Administration of HPV vaccines in patients age 27-45 years

Inactivated Vaccines

- ***In unimmunized pediatric patients with IBD, older than 5 years of age, we suggest Haemophilus influenzae type b (Hib) vaccine be given.*** GRADE: Conditional recommendation, low-certainty of evidence. Vote on PICO question: yes, 100%
- ***In unimmunized adult patients with IBD, we suggest Haemophilus influenzae type b (Hib) vaccine be given.*** Conditional recommendation, very low-certainty of evidence. Vote on PICO question: yes, 78%; uncertain/neutral, 22%
- ***In unimmunized adult patients with IBD without a risk factor for hepatitis B infection, we suggest hepatitis B vaccine be given.*** GRADE: Conditional recommendation, low-certainty of evidence. Vote on PICO question: yes, 100%

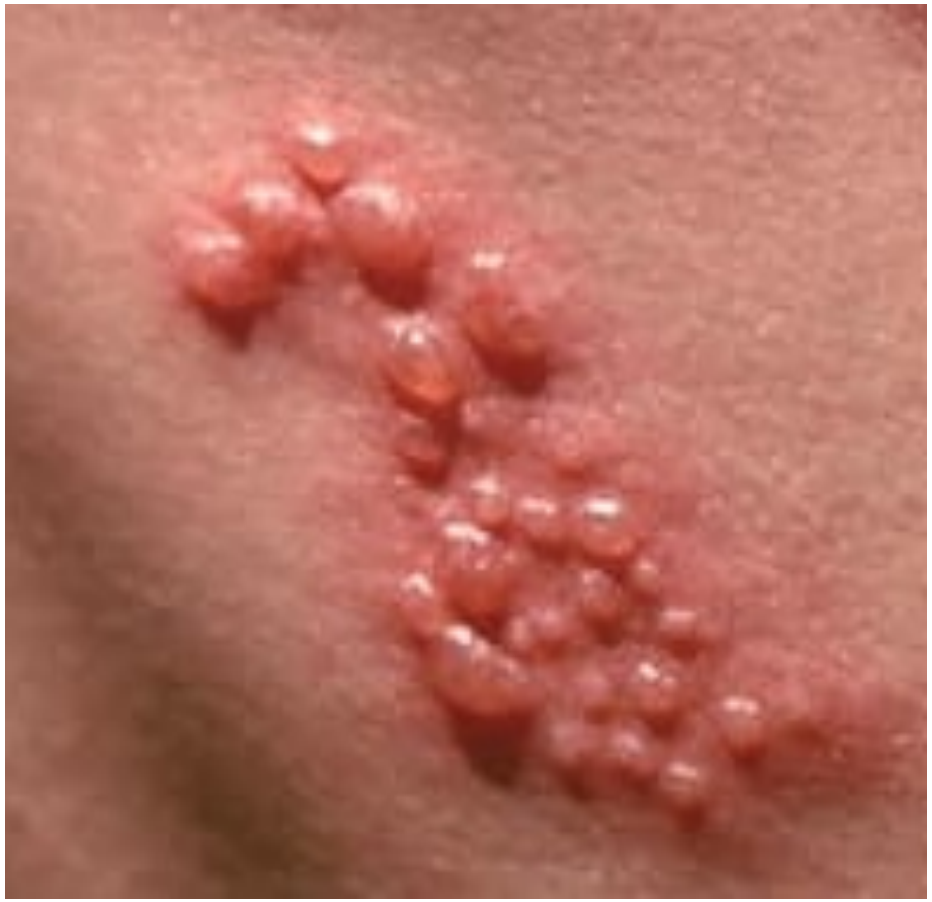
Inactivated Vaccines

- ***In adult patients with IBD on immunosuppressive therapy, we suggest pneumococcal vaccines be given.*** GRADE: Conditional recommendation, low-certainty of evidence. Vote on PICO question: yes, 100%

- ***In male patients with IBD age 9 to 26, we suggest HPV vaccine be given.*** GRADE: Conditional recommendation, very low-certainty of evidence. Vote on PICO question: yes, 100%

HERPES ZOSTER (SHINGLES)

- 9 cohort studies show IBD patients at increased risk of shingles (1.2-1.8 times)
- **Increased risk with age**
- Some medications increase the risk:
  - Immunosuppressives, including anti-TNF
  - Tofacitinib (Xeljanz)



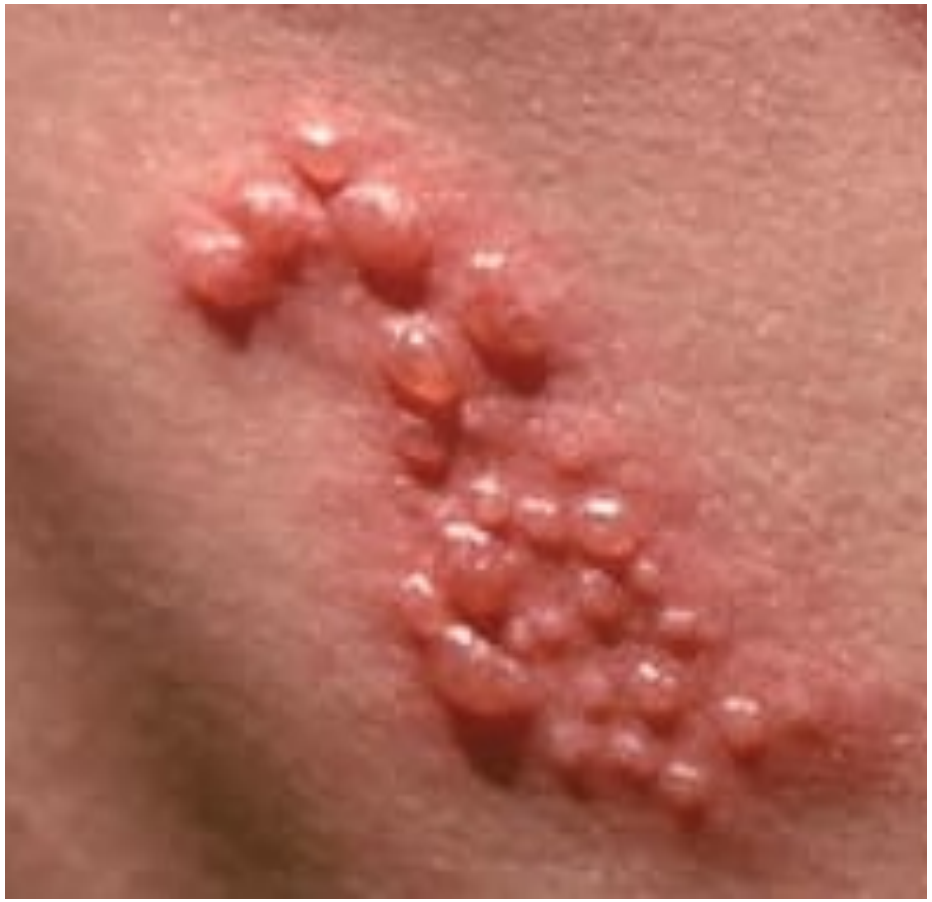
HERPES ZOSTER (SHINGLES)

In adult patients ≥50 years

- **we recommend recombinant zoster vaccine be given** *(moderate CoE)*

In adult patients with IBD <50 years

- **we suggest recombinant zoster vaccine be given** *(low CoE)*



INFLUENZA

- 2 studies examined risk of influenza in IBD patients:
  - IBD patients **28% more likely to get influenza**
  - Higher rate of **hospitalization** for influenza (5.4% vs. 1.85%)
  - 86% higher risk of hospitalization in patients with UC

- Despite this, low immunization rates in IBD patients
  - **28% of American adults ever vaccinated** (Melmed, Am J Gastorenterol, 2006)
  - **50% of Alberta children ever vaccinated** (deBruyn, Inflamm Bowel Dis, 2012)
  - **28% of German adults vaccinated in 2008** (Teich, Dtsch Arztebl Int, 2011)

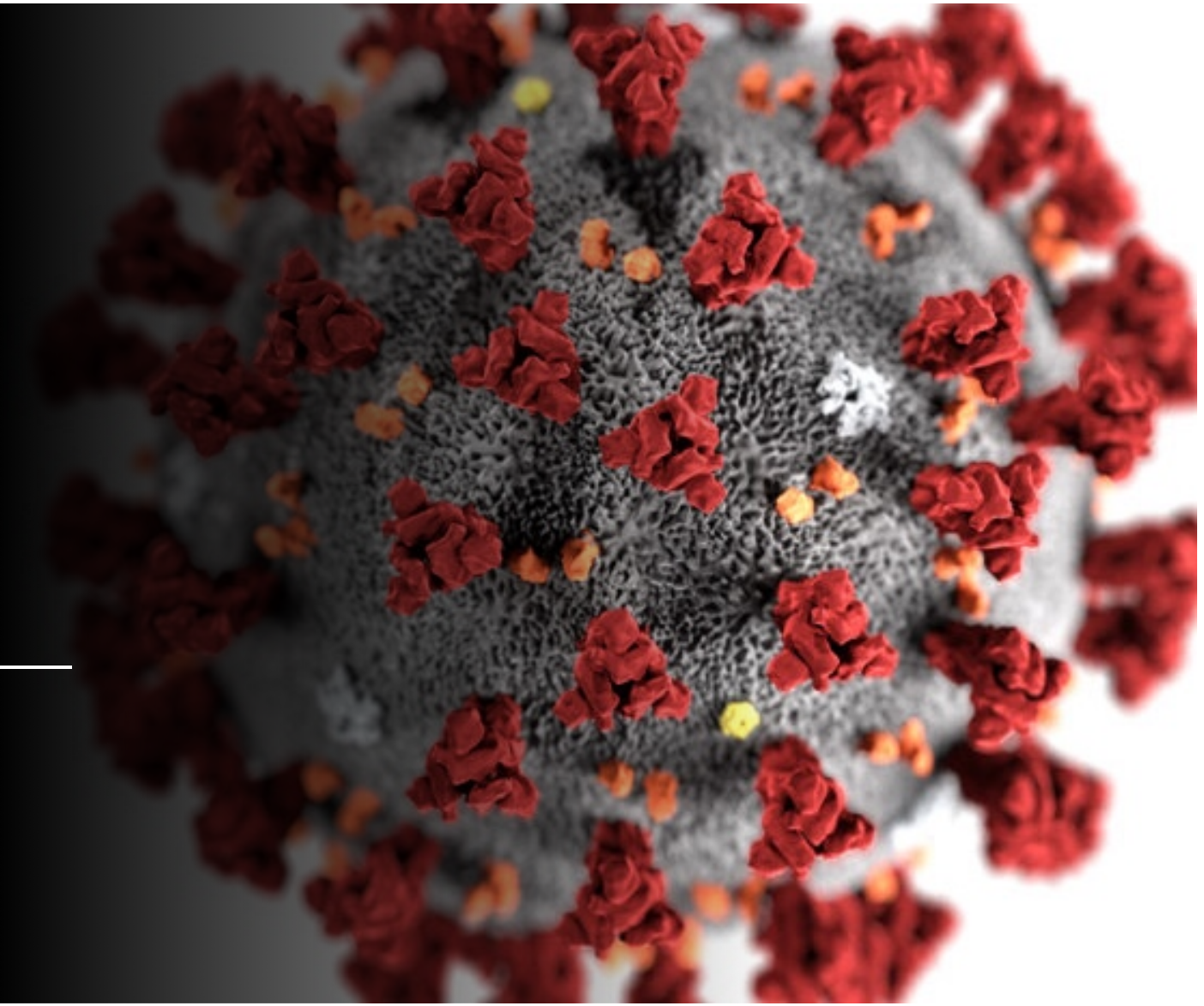
INFLUENZA

- In **pediatric** patients with IBD,
  - **we recommend influenza vaccine be given.**

- In all adult patients with IBD
  - **we recommend influenza vaccine be given.**

  - *CoE not downgraded in older adults (≧65) because ILI deemed a critical outcome*

COVID-19



Leading article

SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting

Corey A Siegel ,[1] Gil Y Melmed,[2] Dermot PB McGovern,[2] Victoria Rai,[3,4] Florian Krammer,[5] David T Rubin ,[3] Maria T Abreu,[6] Marla C Dubinsky ,[7] on behalf of the International Organization for the Study of Inflammatory Bowel Disease (IOIBD)

BACKGROUND

The COVID-19 pandemic has claimed the lives of nearly 2 million people worldwide.[1] Following rapid sequencing of SARS-CoV-2, pharmaceutical companies and academic institutions rapidly generated vaccine candidates on the back of a variety of both established and novel vaccine platforms.[2–4] Vaccines accelerated at unprecedented pace to phase 3 development, and in December 2020, two mRNA vaccines and one inactivated vaccine were authorised for use in a number of countries. Additional vaccine platforms and candidates are in late stages of phase 3 testing.[5] Prioritisation of vaccine access is generally determined by regional health authorities on the basis of risk of SARS-CoV-2 exposure and risk of developing complications from COVID-19 in order to equitably protect and promote global public well-being.[6–8]

IBD, including Crohn's disease and ulcerative colitis, are characterised by chronic intestinal inflammation due to immune dysregulation. IBD is often treated with immune-modifying therapies including corticosteroids, immunomodulators, biologic agents including monoclonal antibody inhibitors of tumour necrosis factor (TNF) alpha, interleukin 12/23, integrins and small molecules such as Janus kinase (JAK) inhibitors. Prior studies have evaluated the safety and effectiveness of various vaccines in patients with IBD, with specific focus on the impact of immune-modifying therapies on serologic responses. In general, non-live vaccines are considered safe in patients with IBD regardless of IBD therapy, although those on specific types of immune-modifying treatments at the time of vaccination may have reduced vaccine immune responses.[9–11] In spite of decreased efficacy associated with immune-modifying medication, most vaccines are broadly recommended for those with IBD.[12–17] Patients with immune conditions (including IBD) were excluded from the SARS-CoV-2 vaccine clinical development programmes,[18] and novel vaccine platforms not previously studied in IBD populations are now authorised in many countries. Therefore, many questions regarding the safety and effectiveness of SARS-CoV-2 vaccination in patients with IBD have emerged with urgent clinical relevance.

The International Organization for the Study of Inflammatory Bowel Disease (IOIBD) is a global organisation of clinician researchers dedicated to the study and management of IBD. There are currently 60 active members and 32 senior members of IOIBD representing 27 countries. In March 2020, IOIBD rapidly developed recommendations for the clinical management of patients with IBD during the COVID-19 pandemic.[19] Now that vaccinations are available, this group reconvened to develop specific recommendations pertaining to the use of SARS-CoV-2 vaccines in IBD populations.

METHODS

We used the modified Delphi method to develop consensus statements regarding SARS-CoV-2 vaccination for patients with IBD.[20] The main characteristics of this technique include expert opinion with anonymous voting on statements, iterations with controlled feedback of group opinion and statistical aggregation of the group response.[19]

A consensus meeting was planned for 18 December 2020. The invitees for this meeting included the membership of IOIBD and additional content experts including an IBD specialist with expertise in vaccinations (GM) and a vaccinologist (FK) with expertise in vaccine development and immune responses to vaccines. Prior to this planned meeting, a questionnaire was developed by authors (CS, GM, MD, DM, MA, DR) to include statements in domains that impact clinical decisions around vaccination for the IBD population. The domains included general issues of vaccines and IBD; risk of COVID-19 to patients with IBD and need for SARS-CoV-2 vaccination; efficacy and safety of the various SARS-CoV-2 vaccines for patients with IBD; timing of when to receive SARS-CoV-2 vaccination; the influence of IBD medications on the decision and timing for SARS-CoV-2 vaccination and prioritisation of patients with IBD for SARS-CoV-2 vaccination. Forty-four statements were created and participants were asked to respond to each statement on a scale from 1 to 10 (1=do not agree at all and 10=agree completely). A priori rules determined that a statement would be accepted if at least 75% of participants scored the statement between 7 and 10. If a 75% consensus was not achieved, it would be discussed during the live meeting, followed by a second round of voting. Statements that were accepted in the first round but had a SD ≥2 or had a proportion of responses between 75% and 77% were also reviewed and voted on a second time if there was particular concern from the participants. If the second round of voting during the live meeting did not achieve consensus of 75% or higher of the respondents, then the statement was not accepted.

The questionnaire was sent electronically using Google Forms (Menlo Park, California, USA) to all voting participants on 11 December 2020. A literature review was provided to the participants prior to the meeting including evidence directly relevant for proposed statements. These included Grading of Recommendations, Assessment, Development and Evaluations

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COVID-19 Vaccination in Patients with Inflammatory Bowel Disease: Communiqué from the Canadian Association of Gastroenterology

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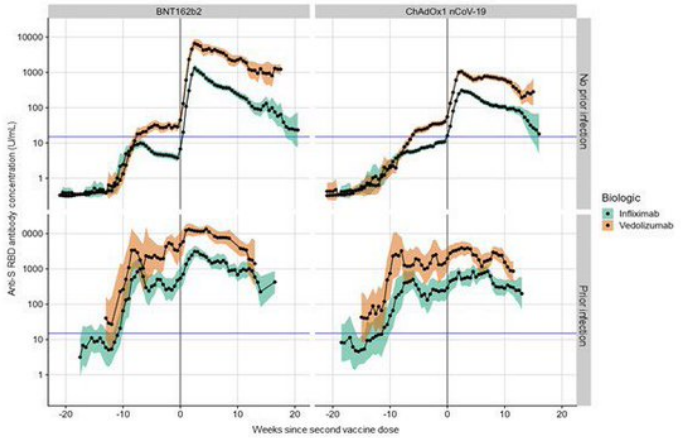
This manuscript has been submitted for publication in the *Journal of the Canadian Association of Gastroenterology*

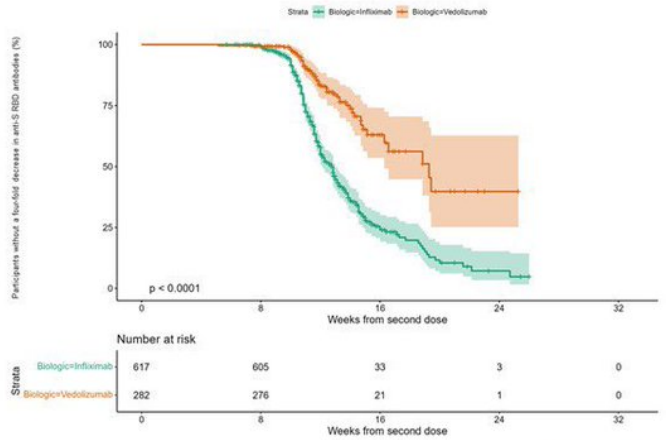
Rapid Knowledge Generation and Dissemination

CLARITY IBD

Covid-19 vaccine-induced antibodies are attenuated and decay rapidly in infliximab treated patients

- **Anti-SARS-CoV-2 spike (S) RBD antibodies** were **reduced 4-5 fold** following two doses of **BioNTech/Pfizer and Oxford/AstraZeneca SARS-CoV-2 vaccines** in **infliximab** (n=2052) compared to **vedolizumab**-treated patients (n = 925)
- Age ≥ 60 years, immunomodulator use, Crohn's disease, and smoking were also associated with **lower**, whilst non-white ethnicity and prior SARS-CoV-2 infection were associated with **higher** anti-S RBD concentrations
- **Infliximab** was independently associated with anti-SARS-CoV-2 antibody **non-persistence** (HR 2.95 (95% CI 2.17 - 4.02), p < 0.0001)

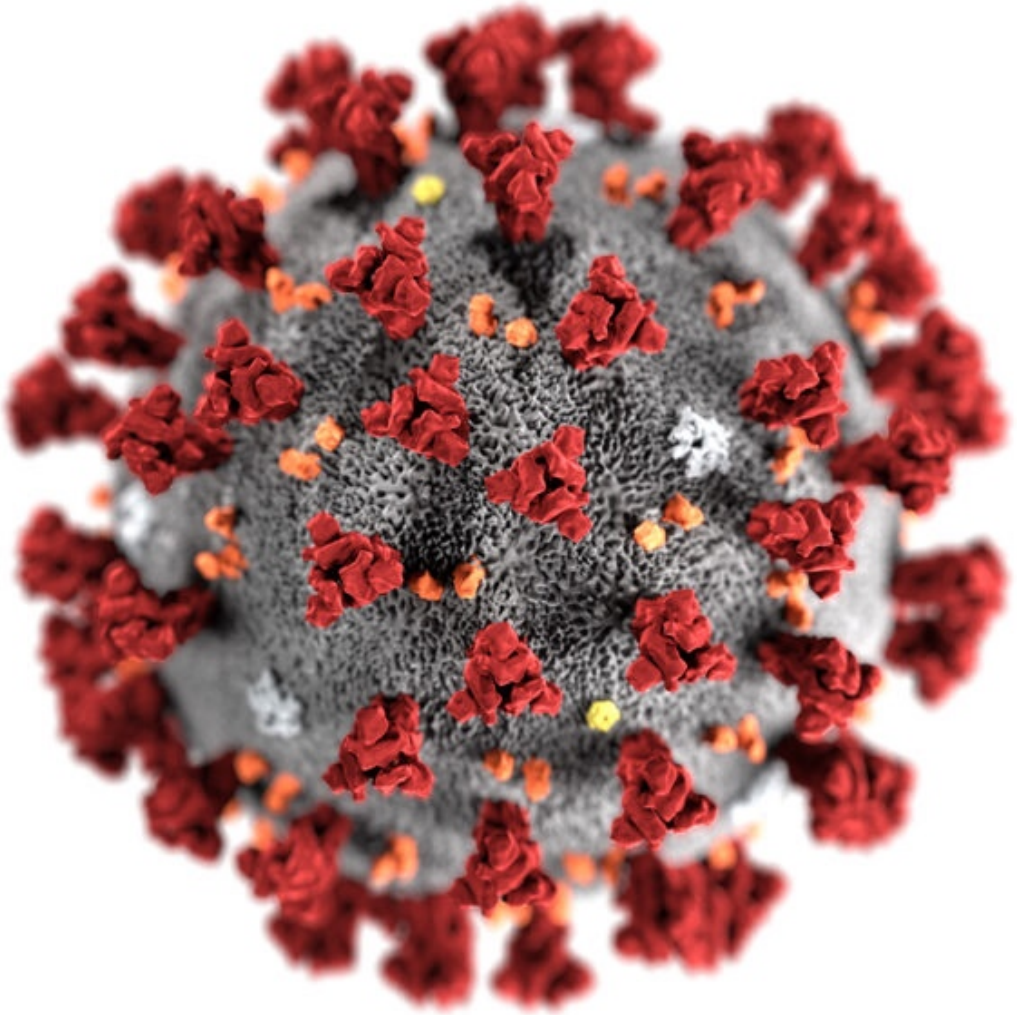




Lin S, Kennedy NA, Saifuddin A, Muñoz Sandoval D, et al. 2021. PREPRINT available at Research Square doi:10.21203/rs.3.rs-755879/v1

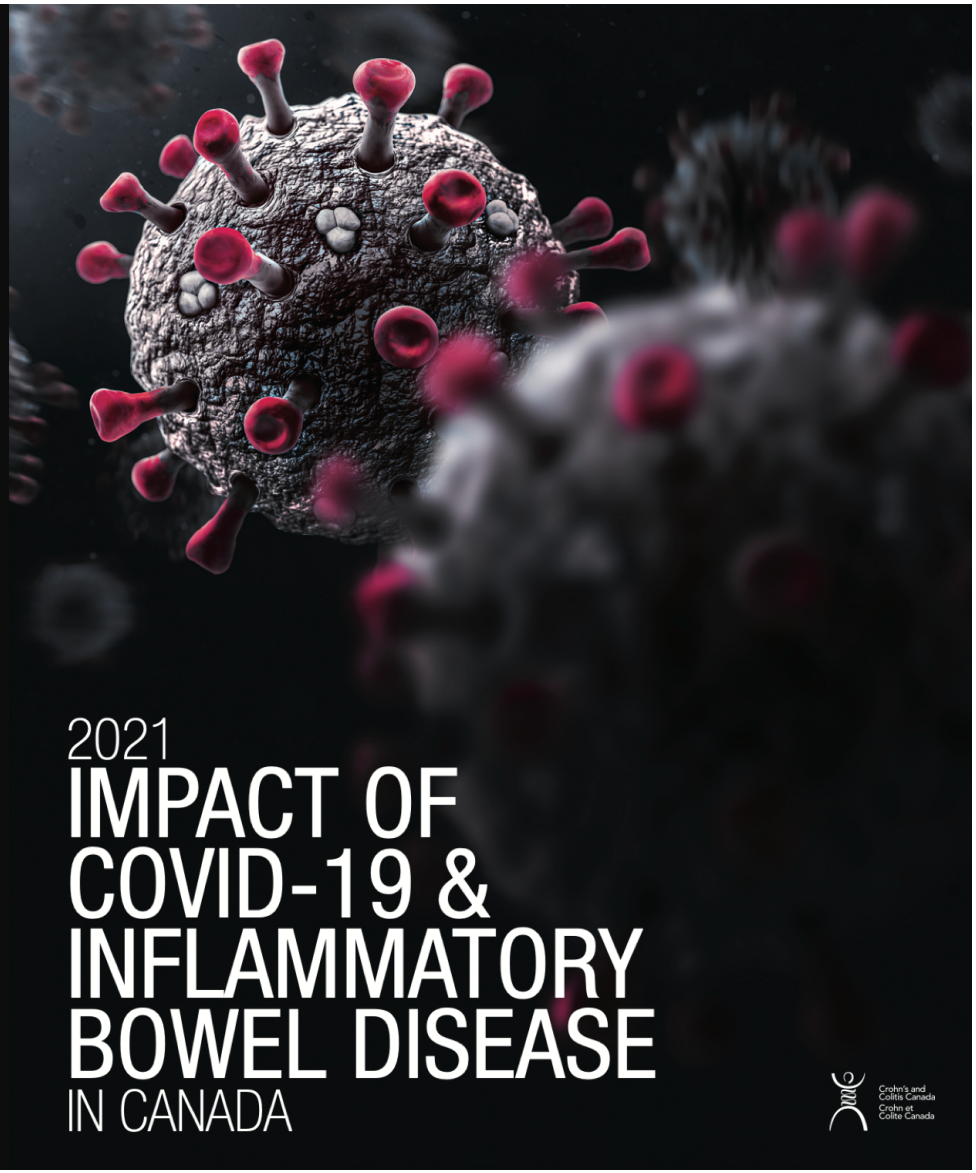
COVID-19 Vaccines and IBD

- PREVENT-COVID study (not peer reviewed)
  - BC
- ICARUS study (pre-print and not peer reviewed)
  - International
  - Mt Sinai, US



CCC COVID-19 & IBD Task Force

- Evidence Informed Information and advocacy
  - COVID-19
  - Vaccines
  - Back to school
  - Navigating clinic visits
  - Diet & Nutrition
  - Wellbeing
- COVID-19 Impact Report



COVID-19 Vaccination Recommendations

We recommend that all IBD patients receive the COVID-19 vaccine as soon as possible (unless advised otherwise by their doctor)

We recommend that people with IBD who are receiving medications that suppress their immune system (systemic corticosteroids, thiopurines, methotrexate, and biologics) have **access to booster COVID-19 vaccines** between 14–18 weeks after their second vaccine dose.

While COVID-19 vaccines continue to be studied, **those with IBD, regardless of vaccination, should practice physical distancing, wear a mask, use good hand hygiene**, and follow the recommendations of the COVID-19 & IBD Task Force and national public health authorities.

We strongly encourage employers and schools to **consider mandatory vaccination policies** so as to minimize the risk of serious and deadly COVID-19 in people living with Crohn's disease and ulcerative colitis.

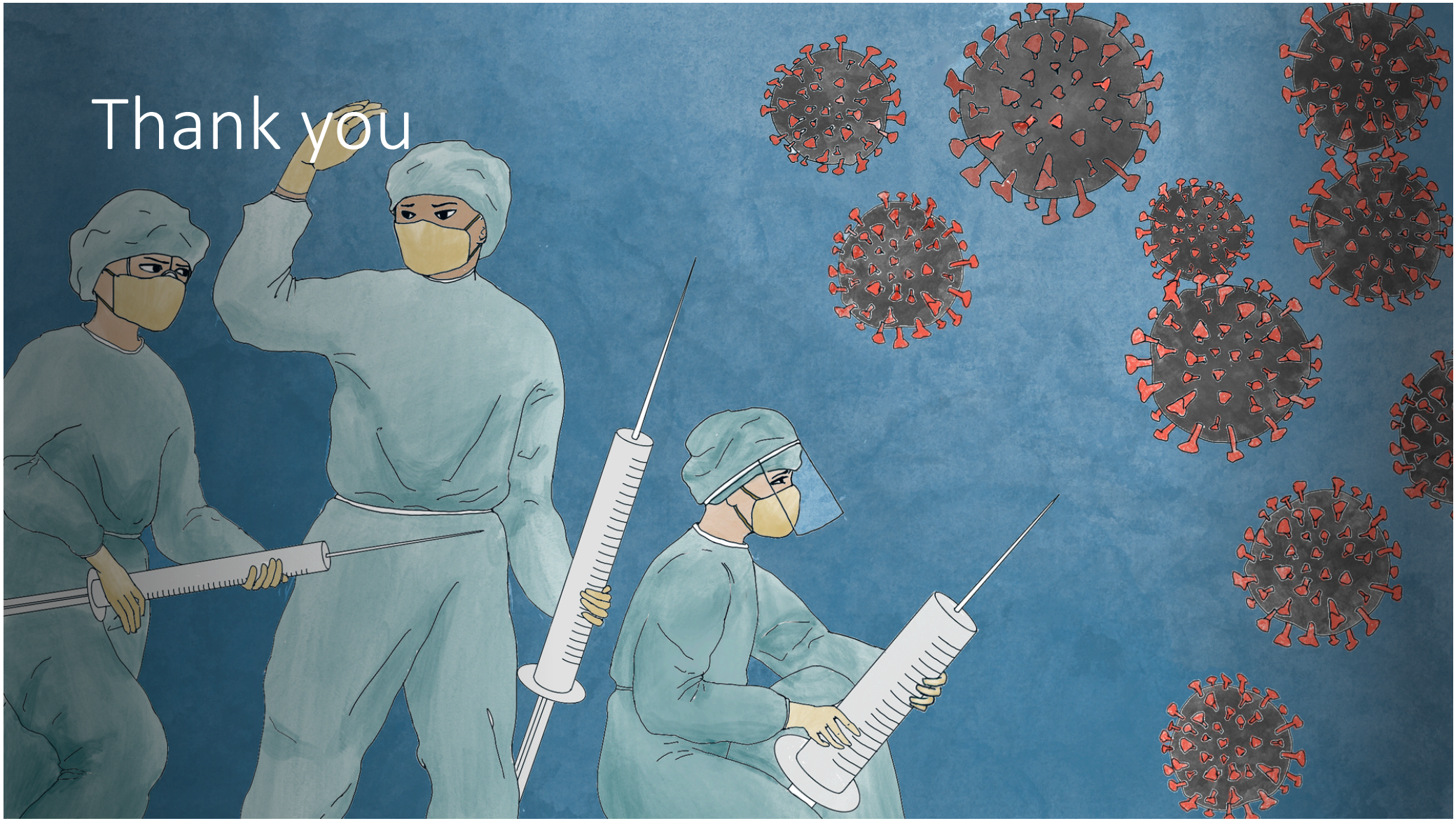
COVID-19 & IBD Task Force, CCC. Last updated Sept 14, 2021.

Summary & Future Directions

Management of VPI has high clinical relevance in clinical practices & for persons living with IBD

Further research relating to best strategies for implementation of evidence-based guidelines relating to management of VPI is needed

As further evidence emerges, recommendations and health policy will evolve in relation to management of VPI in IBD


Thank you