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A Vaccination Primer for Rheumatologists

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Vaccinations have been one of the most important scientific achievements of modern medicine; yet, they are undervalued and underutilized. Directly attributed to vaccines is the substantial decline in the number of cases, hospitalizations, deaths, and health-care costs associated with vaccine-preventable diseases. In the last decade, several new vaccines were introduced: rotavirus, quadrivalent meningococcal conjugate (MCV), herpes zoster (HZV), pneumococcal conjugate (PCV), human papillomavirus vaccines (HPV), and the tetanus, diphtheria, and acellular pertussis vaccine (DTaP) for adults, bringing the number of diseases targeted by U.S. immunization policy to 17. The Centers for Disease Control and Prevention (CDC) estimated that the PCV had prevented 211,000 serious pneumococcal infections and 13,000 deaths between 2000–2008¹. In addition, HZV was shown to reduce the incidence of disease by 55% in a real-world clinical practice setting of 303,000 healthy community dwelling adults aged 60 and older². Yet, despite evidence of the impact and benefits of vaccinations, clinicians are not adequately vaccinating their patients according to guidelines.

Approximately 45,000 adults die each year from vaccine-preventable diseases, the majority from influenza³. The most significant barrier to vaccination coverage identified by the Centers for Disease Control is lack of knowledge about these vaccines among adult patients and providers³. In this review, we will address common questions and barriers to vaccination as it pertains to the practicing rheumatologist with excerpts from the recently published Advisory Committee on Immunization Practices* (ACIP) 2011 guidelines.

1. What vaccines should my immunosuppressed patients receive? Patients who have primary or secondary altered immunocompetence (AI) are at great risk for infections. The degree to which immunosuppressive drugs cause clinically significant immunodeficiency generally is dose related and varies by drug. The ACIP advises these patients receive

the inactivated influenza vaccine and age-appropriate polysaccharide-based vaccines: PCV, MCV, and Haemophilus influenza B (Hib). All inactivated vaccines can be administered safely to persons with AI whether the vaccine is a killed whole-organism or a recombinant, subunit, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine. The usual doses and schedules of inactivated vaccines can be found at www.cdc.gov/vaccines/recs/schedules/downloads/adult/adult-schedule.pdf. **Of note, severe complications have been reported following vaccination with live, attenuated viral and bacterial vaccines among persons with AI; these vaccines (MMR, varicella, live attenuated influenza vaccine, HZV, yellow fever, oral typhoid, BCG, and rotavirus) are contraindicated in those who are significantly immunosuppressed (the ACIP specifically identified those who are receiving TNF α antagonists or prednisone \geq 20 mg/day for greater than two weeks) due to concern for uninhibited replication of the virus or bacteria.**

2. My rheumatoid arthritis patient worries about getting shingles; at what level of immunosuppression is it safe to give the zoster vaccine? Approximately one in three persons will develop zoster during their lifetime, resulting in an estimated 1 million episodes in the United States annually. The risk for post-herpetic neuralgia is 10–18%, eye involvement can occur in 10–25% of zoster episodes, and approximately 3% of patients with zoster are hospitalized; many of these episodes involved persons with immunocompromising conditions⁴. HZV is indicated for adults over age 50 yrs.

In 2006, the ACIP issued its first statement on the use of a live attenuated vaccine for the prevention of zoster in AI patients. It stated that HZV is best administered at least 14 days before initiation of immunosuppressive therapy or three months after immunosuppression has been stopped as the safety and efficacy of live, attenuated vaccines administered concurrently

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Update on TNF inhibitor-induced Psoriasis

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Four of the five currently marketed TNF inhibitors (TNFi) have chronic moderate to severe plaque psoriasis as an indication. The efficacy of this TNFi therapy in psoriasis has been tainted by hundreds of cases of new onset psoriasis or worsening of psoriasis in patients receiving anti-TNF therapy. This observation has been linked to all marketed TNF agents and been reported in adults and children with rheumatoid arthritis, spondylarthritis, psoriasis and Crohn's disease more so than ulcerative colitis¹⁻⁴. The etiology of this event is unknown.

Harrison et al examined the frequency of de novo psoriasis among the 9826 TNFi and 2880 DMARD treated RA patients in the British Society of Rheumatology Biologics Registry between January 2001 – July 2007². They found 25 new onset psoriasis patients on TNFi, but none amongst those treated with DMARD therapy. The frequency of this adverse event was estimated to be 1 per 1000 person-years of TNFi exposure. Those who developed psoriasis (n=13) in the first 6 months had more severe psoriasis or palmoplantar pustulosis, and of those who discontinued the TNFi, 75% showed improvement.

In considering all reported cases, the anatomic distribution of lesions did not deviate from the expected psoriasis pattern. Interestingly, 40-50% presented as pustular psoriasis or palmoplantar pustulosis. Plaque psoriasis is less frequent (20-40%), with fewer cases of either scalp or erythrodermic psoriasis. Worsening of psoriasis and/or new onset palmoplantar pustulosis has been reported in patients under treatment for chronic plaque-type psoriasis⁵.

The age, sex and profile of those affected reflect the populations' being treated. Moreover, many of these patients were well controlled and were receiving concomitant DMARDs when they developed psoriasis. The FDA alerted clinicians in 2009 by detailing 69 cases of new onset psoriasis (from the Adverse Event Reporting system), including 17 pustular and 15 palmoplantar cases, in patients using TNF blockers for treatment of autoimmune and rheumatic conditions other than psoriasis and psoriatic arthritis. Hospitalization was reported in 12/69 cases.

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with recombinant human immune mediators and immune modulators are unknown. Based on expert opinion, therapy with low-doses of methotrexate (<0.4 mg/Kg/week), azathioprine (<3.0 mg/Kg/day), or 6-mercaptopurine (<1.5 mg/Kg/day) are not considered sufficiently immunosuppressive to create vaccine safety concerns and are not contraindications for zoster vaccine use⁴. The amount of systemic corticosteroids and the duration of administration needed to suppress the immune system of an otherwise immunocompetent person are not well defined. Corticosteroid therapy usually is not a contraindication to administering live-virus vaccine if: **1)** short term (i.e., <14 days); **2)** a low to moderate dose (<20 mg of prednisone or equivalent per day); **3)** long-term, alternate-day treatment with short-acting preparations; **4)** maintenance physiologic doses (replacement therapy); or **5)** topical (skin or eyes), inhaled, or by intraarticular, bursal, or tendon injection. If higher doses of steroids are used (≥20 mg/day for more than two weeks), it is recommended to wait a month after the immunosuppression before a live vaccine is given. Ultimately, whether or not a patient should receive live vaccines should be determined by the treating physician.

3. Are household contacts able to receive live vaccines without impacting my patient who is immunosuppressed? Household and close contacts of persons with AI should receive all age-appropriate vaccines, with the exception of live oral polio and smallpox vaccine. No special precautions are needed unless the varicella or zoster vaccine recipient has a rash after vaccination, in which case direct contact with susceptible household contacts should be avoided until the rash resolves. To minimize potential rotavirus transmission, all members of the household should employ hand hygiene measures after contact with feces of a rotavirus-vaccinated infant for at least one week. Live vaccines can be administered to otherwise eligible contacts³.

4. How many vaccines can a patient receive in one day? In other words, can they get the shingles, pneumonia, tetanus, and flu vaccines in the same day, or do they have to spread it over a period of months? With some exceptions, simultaneous administration of live and inactivated vaccines has produced seroconversion rates and rates for adverse reactions similar to those observed when the vaccines are administered separately. Any number of inactivated vaccines can be administered either simultaneously or at any time before or after a different inactivated vaccine or live vaccine; however, a 28 day minimum interval is recommended for two or more live vaccines if not administered simultaneously³.

5. A patient receiving intravenous immunoglobulin (IVIG) needs to be vaccinated—when is the optimal time for this? Antibody-containing products (e.g., whole blood, packed red blood cells, plasma, IVIG) can decrease the response to vaccinations, but they interact less with inactivated vaccines, toxoids, recombinant subunit, and polysaccharide vaccines than with live vaccines. Administering inactivated vaccines either simultaneously with or at any interval before or after receipt of an antibody-containing product should not substantially impair development of a protective antibody response. The vaccine or toxoid and antibody preparation should be administered at different sites using the standard recommended dose. Increasing the vaccine dose volume or number of vaccinations is not indicated or recommended. Live vaccines (except yellow fever vaccine, oral typhoid vaccine, and LAIV) should be delayed until the passive antibody has degraded.

6. My patient is thought to have developed vasculitis after receiving the flu vaccine. Should he be vaccinated again with any vaccine?

The only contraindication to any vaccine is a history of a severe allergic reaction (i.e., anaphylaxis) after a previous dose of vaccine or to a vaccine component. Precaution should be exercised in someone with a history of vaccine related adverse events (e.g., Guillain-Barré syndrome within 6 weeks of a previous influenza vaccination). These individuals might experience a more severe reaction to the vaccine than would have otherwise been expected; however, the risk for this is rare. Vaccinations might be indicated if the benefit of protection from the vaccine outweighs the risk for an adverse reaction³.

7. Can patients who are allergic to eggs receive the flu vaccine?

Allergy to eggs must be distinguished from allergy to influenza vaccine. Severe allergic and anaphylactic reactions can occur in response to a number of influenza vaccine components, but such reactions are rare. All

currently available influenza vaccines are prepared by inoculation of virus into chicken eggs. Hypersensitivity to eggs has been listed as a contraindication to receipt of influenza vaccine on most package inserts. However, several recent studies have documented safe receipt of the trivalent influenza vaccine (TIV) in persons with egg allergy. The ACIP recommends that persons who have experienced only hives following exposure to egg can and should receive influenza vaccine with the following additional measures: **1)** use only the inactivated influenza vaccine which should be administered by a health-care provider who is familiar with the potential manifestations of egg allergy; **2)** vaccine recipients should be observed for at least 30 minutes for signs of a reaction following administration of each vaccine dose; and, **3)** all vaccines should be administered in settings in which personnel and equipment for rapid recognition and treatment of anaphylaxis are available⁵.

8. How often should you give the pneumonia vaccine? The ACIP recommends use of the pneumococcal vaccine in persons with AI. Re-vaccination once is recommended for persons who are at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody levels, including individuals who are receiving immunosuppressive chemotherapy and long-term systemic corticosteroids—provided that five years have elapsed since receipt of the first dose of pneumococcal vaccine. The need for subsequent doses of pneumococcal vaccine is unclear. Because data are insufficient concerning the safety of pneumococcal vaccine when administered three or more times, revaccination following a second dose is not routinely recommended⁶.

This short review of the 2011 ACIP guidelines was designed to guide clinicians and to promote appropriate vaccinations in rheumatologic patients. We acknowledge that many of the ACIP recommendations for the immunosuppressed patients lack strong evidence to support their recommendations, and there are many more questions that need to be answered. More studies are needed to address the following concerns:

- Is the risk greater for the immunocompromised traveler to receive or forego live vaccines (e.g., yellow fever) when going into an endemic area?
- Do other biologics confer the same risks as the TNF antagonists to individuals who are candidates to receive live vaccines?
- Will future data support the use of some live vaccines (e.g., HZV) in patients who are immunosuppressed?
- Are vaccinations safe and effective in patients who have very active rheumatologic diseases? **DSQ**

*The ACIP is a technical advisory committee to the CDC and the US Department of Health and Human Services. The committee convenes every three-to-five years to provide updated general guidelines on vaccinations; the most recent meeting yielded the 2011 ACIP General Recommendations on Immunizations.

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Live Vaccines	Inactivated Vaccines
Mumps Measles Rubella (MMR)	Tetanus diphtheria/acellular pertussis (Td/Tdap)
Varicella Zoster vaccine (VZV)	Hepatitis A Vaccine (HAV)
Live attenuated influenza vaccine (LAIV)	Hepatitis B Vaccine (HBV)
Herpes Zoster Vaccine (HZV)	Human Papilloma Virus (HPV)
Yellow fever	Influenza A/B/H1N1 (TIV)
Oral typhoid	Meningococcal vaccine (MCV)
Bacille Calmette-Guérin (BCG)	Pneumococcal vaccine (PCV)
Rotavirus (RV)	Inactivated polio vaccine (IPV)
Adenovirus type 4, 7, oral	Rabies Vaccine
Smallpox (Vaccinia)	Typhoid polysaccharide vaccine

Source: <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833>

In the News

NSAID-related birth defects. The National Birth Defects Prevention Study examined fetal malformations among US women who received aspirin or NSAIDs by comparing 15,000 women whose babies had birth defects to 5,500 women whose babies were born without any deformities. Overall, 22.6% reported use of NSAIDs in the first trimester of pregnancy, most commonly ibuprofen, aspirin, and naproxen. Of the 29 defect groups examined, most were not associated with NSAID use. Small to moderate increased risks of oral cleft palate, neural tube defects, anophthalmia/microphthalmia, pulmonary valve stenosis, amniotic bands/limb body wall defects, and transverse limb deficiencies were seen with NSAID use. While NSAIDs use may yield a minor increase in a few specific birth defects, the risk of these events is rare (e.g. 1/5000) (Hernandez RK, et al. Am J Obstet Gynecol 2012. PMID:22196851).

Increase in opioid-related deaths. The CDC has declared opioid pain reliever (OPR) deaths to be at an epidemic level in the United States. Opioids account for nearly 74% of all prescription drug overdoses. This epidemic of prescription drug overdoses in the United States has worsened over the last decade, varies 5 fold across the US and appears to be related to wide variations in OPR prescribing. Sales of OPR quadrupled between 1999 and 2010. Enough OPR were prescribed last year to medicate every American adult with 5 mg of hydrocodone every four hours for a month. Abuse of OPR costs health insurers approximately \$72.5 billion annually in health-care costs. As of 2008, drug overdose deaths (36,450) nearly equaled the number of deaths from motor vehicle crashes (39,973), the leading cause of injury death in the United States. The report calls for physicians, insurers and prescription drug monitoring programs to take action to reduce both inappropriate and illegal prescribing. Third-party payers can limit reimbursement in ways that reduce inappropriate prescribing, discourage efforts to obtain OPR from multiple health-care providers, and improve clinical care. Changes in state laws that focus on the prescribing practices of health-care providers might reduce prescription drug abuse and overdoses while still allowing safe and effective pain treatment. (Paulozzi LJ, et al. MMWR November 4, 2011 / 60:1487-1492)

Update on TNF blockers and the risk of pediatric malignancy. The FDA announced its ongoing review of the purported association of pediatric malignancies and TNF inhibitors (TNFi). In 2009, the FDA added warnings of pediatric malignancies to the product labeling for the TNFi class based

on Medwatch and manufacturer data. In April 2011, the FDA also reported on rare occurrences of hepatosplenic T cell lymphoma in adolescents and young adults receiving TNFi with azathioprine or mercaptopurine. The FDA has established a 10-year commitment to enhanced surveillance for such malignancies by mandating manufacturers to provide expedited follow-up and annual reports of malignancies with TNFi use to the agency. Clinicians are also requested to report such cases to the Medwatch.com or the manufacturer. Data collected will include patient demographics, comorbidities, exposure to other immunosuppressive agents, indication for TNFi, duration/dose of use, cancer diagnosis (date, stage biopsy results), and malignancy treatment and outcomes. This effort will improve our understanding of malignancies in pediatric and young adult patients treated with TNFi. The data will be re-evaluated periodically by the FDA over the next ten years (FDA Drug Safety Communication 11-3-11).

Safe disposal of used needles and other “sharps”. The FDA announced a new website (<http://acr.tw/y2zoys>) for the safe disposal of needles and self-administered injectables. This measure places needle and sharps disposal a public health priority. The EPA estimates that more than 3 billion needles and other sharps are used in homes and offices in the United States each year. Improper disposal in trash cans or toilets puts sanitation workers, sewage treatment workers, janitors, housekeepers, family members and children at risk for needle stick injuries or infection with blood born viruses such as Hepatitis B and C and Human Immunodeficiency Virus (HIV). The website will help people understand the public health hazards created by improperly discarding used sharps and will educate users on how to safely dispose of them. (FDA News Release Nov. 8, 2011)

Be vigilant for unintended pregnancies. Qualitest Pharmaceuticals issued a nationwide, retail-level recall of multiple lots of oral contraceptives because of a packaging error that may result in the daily regimen for these products being incorrect, leaving women without adequate contraception, and at risk for unintended pregnancy. Select blisters were rotated 180 degrees within the card, reversing the weekly tablet orientation and making the lot number and expiry date no longer visible. Products affected by this error include: Cyclofem 7/7/7, Cyclofem 1/35, Emoquette, Gildess FE 1.5/30, Gildess FE 1/20, Orsythia, Previfem, Tri-Previfem. D\$Q

Drug Shortage Update

Drug	Reason for shortage	Estimated Availability
Acyclovir Caps and Tabs	Apotex halted manufacturing due to FDA audit, Ranbaxy reported raw materials shortage	On allocation
Dexamethasone Inj	American Regent recalled all 4mg/mL formulation due to particulate matter and discontinued 1.5,30 mL vials; APP noted that demand exceeded their supply	August 2011
Leflunomide 10, 20 mg	Apotex relaunched tablet in Aug 2011, Teva and Sandoz had raw material shortage	Apotex is releasing product as it becomes available.
Lidocaine 0.5%, 1%, 1.5%, 2%	Hospira and APP reported manufacturing delays and increasing demands	Mid-Dec 2011 to Possibly early Feb 2012
Mesna Inj	Teva has manufacturing delays, Ben Venue suspended manufacturing/distribution temporarily due to maintenance and requalification of equipment.	Unknown
Methotrexate 25 mg/mL (2,4,8,10,40 mL vials)	Hospira reported manufacturing delays, Sandoz has recalled their 2 mL and 10 mL methotrexate preservative-free vials. Ben Venue suspended manufacturing/distribution temporarily due to maintenance and requalification of equipment.	Feb 2012
Methylprednisolone tabs (4,8,16,32 mg)	Breckenridge, Sandoz and Cadista reported manufacturing delays from their supplier. Qualitest reported raw material shortage.	Qualitest has a limited supply on allocation
Metronidazole	Watson noted supply constraints, Teval discontinued product	Unknown
Trazodone 50,100,150 mg	Apotex states the shortage is due to an import ban on this product that was only recently removed	Late Dec 2011
Voltaren gel	Production delays due to manufacturing plant issues.	Unknown
Zoster Vaccine	Merck states the shortage is due to shipping delays and raw material production problems.	Zostavax is available for ordering but has shipping delays

Resolved Shortages	Date of Resolution
Acetaminophen suppository	November 2011
Cyclophosphamide injection	July 2011
Fentanyl Transdermal Patches	June 2011
Mycophenolate Mofetil oral suspension	July 2011

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Safety Signals (December 2011)

Suneet Grewal, MD and Michael Weisman, MD, Cedars Sinai Medical Center

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Update continued from cover

A retrospective report of TNFi treated patients (1998-2010) from the Mayo Clinic identified 56 patients who developed psoriasis when treated for Crohn's disease (39%) or RA (25%). Psoriasis occurred a mean of 17.1 months after TNFi initiation. And a variety of presentations were seen: plaque psoriasis (27), palmoplantar pustulosis (25), scalp psoriasis (12), generalized pustular psoriasis (7), erythrodermic psoriasis (2) or inverse psoriasis (2).

Cullen et al reported on 30 new psoriasis cases occurring in inflammatory bowel disease (IBD) patients - 80% having Crohn's and 20% with ulcerative colitis⁴. 70% were well controlled and one-third were receiving MTX or azathioprine. Two-thirds had a good response to topical corticosteroids and most of these continued the same or alternate TNFi. For those not responding to topical therapy, 2/3 ultimately stopped TNFi therapy. They identified an additional 120 IBD patients with TNFi related psoriasis and found that 41% responded favorably to topical therapy. TNFi switching occurred in 27/148 patients, but this was only successful in 15%. Overall 43% had to discontinue TNFi therapy due to psoriasis.

The time to occurrence varies amongst reports with the FDA alert stating development of psoriasis occurred with a varying duration from weeks to years after drug initiation. While Harrison and Cullen indicate a median time to onset of 5-6 months, Ko suggests a mean onset of 10.5 months and there are reports occurring 2-9 years after beginning therapy^{1,3,4}.

Management of anti-TNF drug-induced psoriasis is empiric at best. The FDA report states that a majority of patients experienced improvement of their psoriasis following discontinuation of the TNF blocker. While some series suggest that 60–75% will improve their psoriasis with TNFi discontinuation, it appears that one-third improve with continued use (with or without topical steroid) or change in TNF blocker. Cullen and Ko suggest that only 15% will respond to TNFi switching alone and 25–40% will respond to topical corticosteroids. For those with palmoplantar pustulosis or severe psoriasis, discontinuation of the TNF inhibitor is advised. [DSQ](#)

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TNF blocker Induced Psoriasis

- Incidence: Roughly 1 per 1000 pt-yrs
- Observed with all TNF inhibitors and all indications
- Pustular lesions seen in nearly 50%
- Topical steroids effective in 25–40%
- TNFi withdrawal effective in 60–75%
- TNFi switching effective in only 15%

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Dr. Cush: clinical investigator for Genentech, Pfizer, UCB, Celgene, CORRONA; consultant to Centocor, UCB, Wyeth, Amgen, Roche, BMS, Savient.

Dr. Dao: clinical investigator for Abbott, Centocor, Genentech, Biogen-Idec, UCB, Roche; National Advisory Board for GSK; speaker for Lilly.

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