Opportunities for pharmacists in vaccinating higher-risk populations

Carolyn Whiskin, RPh, BScPhm, NCMP ; Nora Cutcliffe, MSc, PhD

Need for vaccination in higher-risk populations

Populations at higher risk for infection encompass^{1,2}:

1. Adults over 65 years of age
2. High-risk individuals with immunocompromising conditions, including those related to disease (such as cancer, human immunodeficiency virus [HIV] or sickle cell anemia), surgical procedures (such as tissue transplants or splenectomy) and immunosuppressive medications (biologic or nonbiologic therapies)
3. At-risk individuals who are immunocompetent but have 1 or more comorbid medical conditions, such as chronic heart disease, chronic obstructive pulmonary disease (COPD) or other chronic lung disease and diabetes

Individuals in each of these populations have greater vulnerability to infection than individuals in the general “healthy” population, due to decline or aberrations in immune system function.^{3,4} While the need for vaccination in higher-risk populations is well acknowledged³ and recommended by the National Advisory Committee on Immunization (NACI),¹ vaccination of these groups—particularly for immunocompromised patients—continues to be an area of uncertainty for many primary care clinicians. Questions regarding which vaccines to administer, the efficacy and timing of vaccine administration with respect to timing of immune-compromising treatments, along with disease-specific concerns (e.g., potential flares in patients with autoimmune disease), all contribute to such uncertainty. These ambiguities have caused many higher-risk patients to rely on their specialists³ to either administer the vaccines themselves or provide specific directives to the primary care provider. However, surveys indicate that even among specialists who consider vaccination important, it may not be given the attention it deserves.⁵

Pharmacists uniquely poised to play sentinel role

To help address the unmet need for vaccinating higher-risk individuals, pharmacists are well positioned to both recommend and administer vaccinations, particularly as scope of practice continues to expand across Canada. Notably, while many vaccinations are Schedule II, as per the National Association of Pharmacy Regulatory Authorities (NAPRA) Guidelines (and can thus be given without a physician’s prescription), some pharmacists have obtained medical directives to initiate Schedule I vaccinations independently. Pharmacists also have a unique opportunity to play a “sentinel role” in identifying patients at increased risk of infection, as multiple points of contact (e.g., for prescription refills) provide opportunities to evaluate an individual’s vaccination status (Table 1). In this context, vaccination checklists can be very helpful in guiding decisions for vaccines that may be delivered at the pharmacy (depending on product availability and potential funding) or in other health care settings.^{5,6} For all higher-risk populations, the *minimum* requirement is to follow NACI guidelines for adult vaccinations, including tetanus every 10 years, annual influenza vaccination, herpes zoster vaccination at age 50 and pneumococcal vaccination for adults ≥ 65 years.⁷

Adults over 65 years

The rationale for vaccination in older adults is well documented, primarily based on waning of immune system function as observed with aging, a process known as *immunosenescence*.^{3,8} While individuals over 65 years have increased susceptibility to infections and their complications, vaccination rates in this population are suboptimal. The 2016 adult National Immunization Coverage Survey demonstrates that among adults ≥ 65 years, only 65% received influenza vaccine and only 42% received 1 dose of a pneumococcal vaccine.⁹ Both vaccination rates fell well under the national goals of 80% coverage. Herpes

zoster (HZ) vaccine coverage is also very low, estimated at 8% in adults ≥ 60 years from 2009 to 2013 in Alberta, where the vaccine is not publicly funded.¹⁰

To protect older adults against influenza, 2 vaccines tailored specifically to address declining immune function are currently licensed in Canada: high-dose trivalent inactivated vaccine (HD-TIV; Fluzone High-Dose) and adjuvanted trivalent inactivated vaccine (aTIV; Fludax). Standard-dose TIV and quadrivalent inactivated vaccine (QIV) formulations are also available and can be administered to adults ≥ 65 years. At the programmatic level, NACI currently recommends that any of these 4 vaccines should be used, whereas at an individual level, NACI currently recommends that HD-TIV should be offered over standard-dose TIV to persons ≥ 65 years.¹¹

Individual jurisdictions make annual decisions regarding specific influenza vaccines (and quantities) to be distributed through publicly funded programs at physician and public health clinics, pharmacies and long-term care facilities. While pharmacy access to publicly funded HD-TIV and aTIV has been relatively limited across Canada to date,^{12,13} it is anticipated that pharmacist provision of these enhanced vaccines will expand in the future. Since influenza vaccination protects older adults against influenza and related complications,^{14,15} including frailty, disabilities, cardiovascular events, hospitalization and even death, pharmacists have a tremendous opportunity to reduce influenza and its adverse outcomes.

For immunocompetent adults ≥ 65 years, pneumococcal vaccination with the polysaccharide vaccine PNEU-P-23 (Pneumovax 23) is recommended by NACI.¹⁶ More recent recommendations for pneumococcal vaccination with the conjugate vaccine PNEU-C-13 (Pneumovax 13) in series with PNEU-P-23, as well as HZ vaccination in older adults, are covered elsewhere in this special section.

High-risk individuals: Immunocompromising conditions

In general, immunocompromised persons are more susceptible to vaccine-preventable infections and may have severe infections.¹⁷ Yet vaccination rates in high-risk immunocompromised individuals are currently suboptimal.^{3,18} For example, in patients awaiting transplant, who will be on lifelong immunosuppressive treatment, rates of vaccination are reported to be low. Among 362 waitlisted kidney transplant patients in the United States, only 55% of patients had completed vaccination for influenza, 35.9% for pneumococcus, 6.9% for HZ and 2.5% for tetanus, thus demonstrating a significant gap between recommendations and vaccine uptake in clinical practice among this high-risk population.¹⁹

For influenza vaccination, the role of HD-TIV in immunocompromised individuals is being investigated,²⁰ more recently including patients with rheumatoid arthritis (RA). In a randomized controlled trial of RA patients on immunosuppressive medications, immune response to vaccination was consistently higher

in the HD-TIV arm (vs the standard-dose TIV arm), with no increase in disease activity observed in this cohort.²¹

It is important to consider that immune-compromising treatments may potentially affect the effectiveness of the influenza vaccine. A recent Korean study of stable RA patients on methotrexate (MTX) compared the immune response when MTX was withheld for 2 weeks after administering the influenza vaccine.²² Results indicated a significant increase in antibody titres compared to not withholding MTX. Although the primary concern related to withholding MTX is risk of flare, in this study of well-controlled patients, flare rates were the same for patients whose MTX was withheld vs the control arm. Further research is required to assess the impact of withholding MTX on immunogenicity outcomes following influenza vaccination in individuals for whom RA is less well controlled. At present, withholding MTX is a judgement call made by rheumatologists for individual RA patients.

With regard to pneumococcal vaccination, patients with immunocompromising conditions have the highest risk of both invasive pneumococcal disease (IPD) and community-acquired pneumonia (CAP).² Vaccination should be initiated in these high-risk individuals as soon as the risk(s) are identified, often well before age 65. Since PNEU-P-23 and PNEU-C-13 are not live vaccines, they may be given at any time while on immunosuppressive therapy. However, the ideal time to vaccinate is 2 weeks before initiating such treatment, since immune protection is generally established 2 weeks after vaccination.

NACI recommends the use of PNEU-C-13 in immunocompromised adults ≥ 18 years, including hematopoietic stem cell transplant (HSCT), HIV and other immunocompromising conditions (asplenia, sickle cell disease, congenital immunodeficiencies, immunosuppressive therapy, malignant neoplasms and solid organ or islet cell transplant).²³ In these high-risk populations, PNEU-C-13 is to be given first, followed 8 weeks (or more) later by PNEU-P-23 to obtain optimal protection against 23 pneumococcal serotypes. Further details regarding dosing, sequencing and timing of PNEU-C-13 and PNEU-P-23 vaccination for specific high-risk populations are provided in the NACI statement.²³ For many of these patient groups, public funding programs are currently in place in several Canadian jurisdictions to cover vaccination with PNEU-C-13 in series with PNEU-P-23, although vaccination occurs primarily through physician and/or public health clinics.

For HZ, the risk of infection increases with age; NACI currently recommends vaccination of all adults ≥ 50 years.²⁴ In immunocompromised populations, the risk of HZ is greater than that of the immunocompetent population at ages much lower than 50, particularly for patients with HSCT, lupus and RA.²⁵ Given the evidence of increased risk in younger adults with immunocompromising conditions, many specialists are considering vaccination against HZ before the age of 50. However, both HZ vaccines licensed in Canada are only indicated for adults ≥ 50 years. The

TABLE 1 Touch points for vaccination in pharmacy practice

All higher-risk populations	
During influenza vaccination	<ul style="list-style-type: none"> While patients complete screening questions prior to influenza vaccination, an adult vaccination checklist can be reviewed.⁶ This provides an annual opportunity for multiple vaccines to be updated beyond influenza.
During a medication review	<ul style="list-style-type: none"> Many provinces offer compensation to pharmacists for annual medication reviews, with the opportunity for shorter follow-up appointments that may include review of an adult vaccination checklist. This can be particularly helpful in identifying and proactively vaccinating patients with immunocompromising and chronic conditions (including diabetes and chronic obstructive pulmonary disease).
When dispensing a medication for infection	<ul style="list-style-type: none"> When an antibiotic is dispensed for a bacterial respiratory infection, this provides a teachable moment to have the patient return for vaccination once the infection has resolved. Pharmacists can schedule a reminder call 3 to 4 weeks later to book a vaccination consult or, at minimum, send a referral note to the primary care provider. For viral conditions such as herpes zoster (HZ), an episode of HZ in itself offers immune protection for a minimum of 1 year. The National Advisory Committee on Immunization suggests vaccination with recombinant subunit zoster vaccine 1 year after a herpes zoster outbreak.²⁴ Pharmacists can set a reminder to contact the patient at that time for a vaccination consult.
Immunosuppressed populations	
Prior to initiating chemotherapy	<ul style="list-style-type: none"> Patients will often inform their pharmacist of a cancer diagnosis before treatment is initiated. This presents an opportunity to update adult vaccinations.
While on an organ transplant list	<ul style="list-style-type: none"> Patients with impaired organ function (liver/kidney/heart) awaiting transplant will receive immunosuppressive treatment for life after receiving the transplant. As soon as becoming aware of a patient in this situation, the pharmacist should ensure adult vaccines are updated.
Prior to initiating an immunosuppressive treatment for rheumatoid arthritis	<ul style="list-style-type: none"> Patients presenting with a prescription for disease-modifying antirheumatic drugs (such as methotrexate, leflunomide or biologic therapies) should have their adult vaccinations updated prior to treatment initiation. Wherever possible, allow 2 weeks for immune response before starting immunosuppressive therapy.

recombinant subunit zoster vaccine, RZV (Shingrix), is nonlive and therefore is considered safe for immunocompromised populations and also offers higher protection than the live attenuated zoster vaccine, LZV (Zostavax II). Notably, since the efficacy of RZV has not been studied in patients with autoimmune diseases, the potential risk of flare of their condition has not been assessed. NACI guidelines nonetheless suggest use of RZV for this population.²⁴

To assist in implementing NACI and other available guidelines and to fill an unmet need in vaccinating immunocompromised individuals, pharmacists have taken a lead role in developing practical tools to improve vaccination coverage. For example, protocols have been published⁵ and other resources have been developed by pharmacists²⁶ (and jointly with other specialists²⁷) for vaccinating patients receiving immunosuppressant therapy. National vaccination guidelines have also been published in 2019 by a group of multidisciplinary Canadian physicians for patients taking immunosuppressive

therapies, including synthetic disease-modifying antirheumatic drugs (DMARDs) and biologics, for treatment of autoimmune and inflammatory diseases.^{18,28} These guidelines serve to inform and encourage communication among specialists, family physicians, pharmacists and other immunizers on issues regarding safety and efficacy of vaccines in patients taking immunosuppressive therapies.

At-risk individuals: Chronic conditions

Immunocompetent individuals with 1 or more chronic medical conditions, including chronic heart disease, COPD, asthma or other chronic lung disease, diabetes and other chronic conditions, are at increased risk of infectious disease.^{2,3} However, these at-risk populations generally remain underimmunized. As 1 example, in Canadian adults 18 to 64 years with a chronic medical condition, influenza vaccine coverage was reported at 39%, well below the national goal of 80% (2017/18).²⁹

BOX 1 Key points for higher-risk populations

1. For adults ≥ 65 years, pharmacists should play a lead role in increasing vaccine access and optimizing vaccination rates, particularly for influenza and pneumococcal vaccines. This role is anticipated to expand as more vaccines (e.g., HD-TIV, aTIV and PNEU-C-13) become available (and/or are publicly funded) specifically through pharmacies.
2. Pharmacists are uniquely positioned to identify patients with immunocompromising and chronic conditions (i.e., through medication reviews or other touch points) and can thus help improve vaccination coverage in these vulnerable populations.
 - Response to vaccination decreases with age and may be blunted in these populations at an earlier age than the general population, so early vaccination is prudent.
3. For immunocompromised patients specifically:
 - Proactive assessment of vaccination status and early administration of required vaccines (e.g., upon identifying high-risk status or prior to immunosuppressive therapy) can prevent later infectious complications.
 - All nonlive vaccines can be administered to high-risk individuals who are taking immunosuppressive therapies. Where possible, ideal timing is 14 or more days prior to treatment initiation for maximum benefit. When a biologic treatment is being discontinued, 3 half-lives after stopping therapy is also a good time to vaccinate to achieve maximum benefit.²⁷
 - Live vaccines should generally not be administered in patients taking immunosuppressive treatments, although there may be some exceptions when live vaccinations could be appropriate under the guidance of a specialist in immunodeficiency.
 - Live vaccines should be administered a minimum of 2 weeks (ideally 4 weeks) prior to starting immunosuppressive therapy, since live virus exposure is most predominant 2 weeks after administering a live vaccine but can linger up to 4 weeks.²⁸
 - For patients already on immunosuppressive therapy who need a live vaccine, immunosuppressive treatment interruption will be required and will vary based on the therapy used.^{27,28}
 - Corticosteroids are immunosuppressive and may blunt vaccination benefit. For example, prednisone doses ≥ 10 mg per day may blunt responses to influenza vaccination, while doses ≥ 20 mg per day may blunt responses to pneumococcal and other vaccinations. Waiting until prednisone is weaned to < 20 mg per day (or < 10 mg per day prior to influenza vaccination) may enhance the immune response.²⁸

For pneumococcal disease specifically, a retrospective analysis of US claims data showed that at-risk adults with ≥ 2 concurrent comorbid conditions had incidence rates that were as high as or higher than rates observed in high-risk adults with immunocompromising conditions.² This phenomenon of “risk stacking” was observed for adults aged 18 to 49, 50 to 64 and ≥ 65 years. These data support the conclusion that pneumococcal vaccination should not be limited to adults ≥ 65 years; vaccination should also be offered to younger adults (< 65 years) with chronic conditions. Current NACI guidelines recommend the use of PNEU-P-23 in these populations.²³

Recognizing the need for increased protection in more vulnerable populations, disease-specific guidelines, including Diabetes Canada’s 2018 Clinical Practice Guidelines³⁰ and Health Quality Ontario’s 2018 Quality Standards for patients with COPD³¹ (including those on immunosuppressive corticosteroids), have been developed for certain at-risk groups. These guidelines underscore the importance of influenza vaccination in patients with diabetes and COPD, while emphasizing their need for earlier pneumococcal vaccination than in the general “healthy” population. For adults with various chronic

conditions, public programs for pneumococcal vaccination vary across the country. However, the newer PNEU-C-13 vaccine should be offered (in series with PNEU-P-23) to these at-risk individuals, for additional protection against pneumococcal disease, particularly CAP.

Integrating vaccination into pharmacy practice

Health care practitioners should aim to provide personalized vaccination plans for higher-risk populations, depending on individual medical status, treatment programs, and immunological potential.⁴ As frontline clinicians, pharmacists should vaccinate higher-risk patients and seize the opportunity to advocate, facilitate and ultimately vaccinate these susceptible populations to prevent infectious disease.⁵ Table 1 presents examples of touch points for vaccination of higher-risk patients in pharmacy practice. Particularly for patients on immunosuppressive therapies, aggressive approaches to vaccination are required to help achieve the desired outcome of disease modification. Box 1 summarizes key points for pharmacists in proactively immunizing higher-risk populations. ■

C. Whiskin is a pharmacist with Charlton Health Inc., Hamilton, and N. Cutcliffe is a BioPharma Consultant in Toronto, Ontario. Contact hugapharmacist@hotmail.com.

Declaration of Conflicting Interests: The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding: The authors received no financial support for the research, authorship and/or publication of this article.

ORCID iD: Carolyn Whiskin <https://orcid.org/0000-0002-3360-5028>

References

- Public Health Agency of Canada (PHAC). *Canadian immunization guide: part 3—vaccination of specific populations*. September 1, 2016. Available: www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations.html (accessed Apr. 17, 2019).
- Shea KM, Edelsberg J, Weycker D, et al. Rates of pneumococcal disease in adults with chronic medical conditions. *Open Forum Infect Dis* 2014;1(1):ofu024.
- Doherty M, Schmidt-Ott R, Santos JJ, et al. Vaccination of special populations: protecting the vulnerable. *Vaccine* 2016;34(52):6681-90.
- Ferreira I, Isenberg D. Vaccines and biologics. *Ann Rheum Dis* 2014;73(8):1446-54.
- Whiskin C, Haaland D, Bensen W, Brown V. A call to action for adult vaccination: immunocompromised patients at increased risk. *Can Rheumatol Assoc J* 2014;24(1):10-3a.
- Whiskin Consulting. *Adult Vaccination Checklist*. Hamilton & District Pharmacists' Association; 2018. Hamilton, Ontario.
- Public Health Agency of Canada (PHAC). *Canadian immunization guide: part 3—vaccination of specific populations, immunization of adults*. February 21, 2018. Available: www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-2-immunization-of-adults.html (accessed Apr. 16, 2019).
- Haq K, McElhaney JE. Immunosenescence: influenza vaccination and the elderly. *Curr Opin Immunol* 2014;29:38-42.
- Public Health Agency of Canada (PHAC). *Vaccine uptake in Canadian adults: highlights from the 2016 adult National Immunization Coverage Survey (aNICS)*. March 6, 2019. Available: www.canada.ca/en/services/health/publications/healthy-living/2016-vaccine-uptake-canadian-adults-survey.html (accessed Apr. 1, 2019).
- Liu XC, Simmonds KA, Russell ML, Svenson LW. Herpes zoster vaccine (HZV): utilization and coverage 2009-2013, Alberta, Canada. *BMC Public Health* 2014;14:1098.
- Vaudry W, Zhao L, Stirling R, on behalf of the National Advisory Committee on Immunization (NACI). Summary of the NACI Seasonal Influenza Vaccine Statement for 2018-2019. *Can Commun Dis Rep* 2018;44(6):123-8. Available: www.canada.ca/en/public-health/services/reports-publications/canada-com-municable-disease-report-ccdr/monthly-issue/2018-44/issue-6-june-7-2018/article-1-summary-influenza-2018-2019.html (accessed Apr. 1, 2019).
- Canadian Healthcare Network. *Enhancing flu-ency for your 65+ patients*. Webinar presentation Slides, September 20, 2018. Available: www.canadianhealthcarenetwork.ca/pharmacists/seniors-health-influenza/learning/webinar-sept-20-enhancing-flu-ency-for-your-65-patients-42683 (accessed Apr. 1, 2019).
- McRae C. *Canadian Healthcare Network, 2018-2019 flu vaccine programs by province/territory*. October 26, 2018. Available: www.canadianhealthcarenetwork.ca/healthcarenetwork/seniors-health-influenza/interactive-map-flu-vaccine-programs-by-province-and-territory-37557 (accessed Apr. 1, 2019).
- McElhaney JE, Zhou X, Talbot HK, et al. The unmet need in the elderly: how immunosenescence, CMV infection, co-morbidities and frailty are a challenge for the development of more effective influenza vaccines. *Vaccine* 2012;30(12):2060-7.
- Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med* 2018;378(4):345-53.
- National Advisory Committee on Immunization (NACI). *Update on the use of 13-valent pneumococcal conjugate vaccine (PNEU-C-13) in addition to 23-valent pneumococcal polysaccharide vaccine (PNEU-P-23) in immunocompetent adults 65 years of age and older—Interim Recommendation*. October 2016. Available: <https://www.canada.ca/en/public-health/services/publications/healthy-living/update-use-of-13-valent-pneumococcal-conjugate-vaccine-pneu-c-13-in-addition-to-23-valent-pneumococcal-polysaccharide-vaccine-pneu-p-23-immunocompetent-adults-65-years-and-older-interim-recommendation.html> (accessed Sept. 19, 2019).
- Public Health Agency of Canada (PHAC). *Canadian immunization guide: part 3—vaccination of specific populations, immunization of immunocompromised persons*. May 2018. Available: www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons.html (accessed Apr. 1, 2019).
- Papp KA, Haraoui B, Kumar D, et al. Vaccination guidelines for patients with immune-mediated disorders taking immunosuppressive therapies: executive summary. *J Rheumatol* 2019;46(7):751-4.
- Lee DH, Boyle SM, Malat G, Sharma A, Bias T, Doyle AM. Low rates of vaccination in listed kidney transplant candidates. *Transplant Infect Dis* 2016;18(1):155-9.
- Robertson CA, DiazGranados CA, Decker MD, Chit A, Mercer M, Greenberg DP. Fluzone(R) high-dose influenza vaccine. *Exp Rev Vaccines* 2016;15(12):1495-505.
- Colmegna I. *Efficacy of high-dose versus standard-dose influenza vaccine in seropositive rheumatoid arthritis patients*. Abstract 837, American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (ARHP) Annual Meeting 2018, October 20-24, 2018, Chicago. Available: <https://acr.confex.com/acr/2018/meetingapp.cgi/Person/60160> (accessed Apr. 1, 2019).
- Park JK, Lee YJ, Shin K, et al. Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2018;77(6):898-904.
- National Advisory Committee on Immunization (NACI). Statement on the use of conjugate pneumococcal vaccine—13 valent in adults (Pneu-C-13). *Can Communicable Dis Rep* 2013;39:ACS-5.
- National Advisory Committee on Immunization (NACI). *Updated recommendations on the use of herpes zoster vaccines*. August 30, 2018. Available: <https://www.canada.ca/en/services/health/publications/healthy-living/updated-recommendations-use-herpes-zoster-vaccines.html> (accessed Sept. 19, 2019).
- Yanni EA, Ferreira G, Guennec M, et al. Burden of herpes zoster in 16 selected immunocompromised populations in England: a cohort

study in the Clinical Practice Research Datalink 2000-2012. *BMJ Open* 2018;8(6):e020528.

26. Charlton A. *Vaccines and immune modifying/immunosuppressant agents: common questions and answers*. University of Alberta PharmD Research. November 2018. Division of Rheumatology, Cumming School of Medicine, University of Calgary, Calgary.

27. Alberta Rheumatology. *Vaccinations when taking DMARDs or biologics, 2019*. Available: <https://albertarheumatology.com/vaccinations/> (accessed Apr. 16, 2019).

28. Papp KA, Haraoui B, Kumar D, et al. Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. *J Cutan Med Surg* 2019;23(1):50-74.

29. Public Health Agency of Canada (PHAC). *Seasonal influenza vaccine coverage in Canada, 2017-2018, January 2019*. Available: http://publications.gc.ca/collections/collection_2019/aspc-phac/HP40-198-2018-eng.pdf (accessed Apr. 16, 2019).

30. Husein N, Chetty A. 2018 Clinical practice guidelines: influenza, pneumococcal, hepatitis B and herpes zoster vaccinations. *Can J Diabetes* 2018;42(suppl 1):S142-S4.

31. Health Quality Ontario. *Quality standards, chronic obstructive pulmonary disease, care in the community for adults*. 2018. Available: www.hqontario.ca/Portals/0/documents/evidence/quality-standards/qs-chronic-obstructive-pulmonary-disease-quality-standard-en.pdf (accessed Apr. 20, 2019).