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REVIEW ARTICLE

Socioeconomic Impact of Seasonal (Epidemic) Influenza and the Role of Over-the-Counter Medicines

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Abstract The substantial economic impact of influenza on society results primarily from lost work time and reduced productivity of patients and caregivers and increased use of medical resources. Additionally, since the 1980s, aging of the US population has meant rising influenza-related morbidity and mortality. According to the most current published data on this topic, in 2003 the total economic burden of influenza epidemics in the USA across all age groups was US$87.1 billion. As of February 2013, overall vaccine effectiveness for the 2012/2013 season was estimated to be 56 %. The Centers for Disease Control and Prevention's National Center for Immunization and Respiratory Diseases has concluded that more effective vaccines and vaccination strategies are needed. Moderate efficacy of the influenza vaccine, continued questions regarding the value of treatment with antivirals, and a growing self-care movement have led to increased use of over-the-counter (OTC) medicines, which play a vital role in managing symptoms associated with mild to moderate influenza and provide an estimated US$102 billion in annual savings for the US healthcare system. A primary benefit to society of using OTC medicines to manage influenza is decreased use of the healthcare system, thereby mitigating the socioeconomic burden of influenza. Considering the stresses placed on the US healthcare system and the substantial productivity losses resulting from seasonal influenza as well as the growing self-care movement, OTC medicines will play an important role in the course of future influenza epidemics.

Key Points

As of February 2013, overall vaccine effectiveness for the 2012/2013 season was estimated to be 56 %. Vaccination of patients at high risk of influenza-related complications has been shown to favorably impact morbidity and mortality. Experts agree that vaccination benefits healthy adults, but there is still no consensus on whether the benefit justifies the cost.

Controversy exists regarding the clinical efficacy and cost effectiveness of antiviral medications, both of which in the USA are neuraminidase inhibitors.

Inappropriate prescribing of antibacterials for patients with influenza costs more than US$200 million annually.

Over-the-counter (OTC) medicines provide US$102 billion in annual savings, and nearly one-third of that amount results from consumers self-treating cough/cold and influenza symptoms.

The use of OTC medicines is one aspect of a growing movement toward medical self-care and has become a tool to help individuals manage symptoms of mild to moderate illnesses and reduce the healthcare burden on the public budget.

It should be considered that OTC medicines may play an increasingly important role in mitigating the socioeconomic burden of influenza.

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1 Introduction

Influenza places a significant socioeconomic burden on individuals, families, and society [1–4]. This burden results from various direct costs (outpatient and inpatient medical care plus medications) and indirect costs (productivity losses) [2]. There are three types of influenza viruses: Type A viruses tend to have a greater effect on adults, while Type B viruses are a greater problem in children [5], but both viruses cause seasonal influenza [6]; Type C is relatively uncommon [7] and causes only mild illness [6]. Public health experts are most concerned with Type A influenza virus because new, virulent strains of Type A are usually the cause of pandemics [6]. Type A strains are subdivided into groups based on two surface proteins: hemagglutinin (H) and neuraminidase (N). Because Type A viruses can be found in humans and animals, constant animal surveillance is critical to detecting the emergence of novel viruses with pandemic potential in humans [6].

Although over-the-counter (OTC; i.e., non-prescription) medicines do not directly affect the course of influenza virus infection or reduce contagion, they may relieve some influenza-related symptoms, such as fever, headaches, and body aches [8]. Since influenza is often self-limiting, many people with mild to moderate influenza can self treat with OTC medicines, rest, and intake of extra fluids without accessing the healthcare system [9]. Considering the stresses placed on the US healthcare system [10] and the substantial productivity losses resulting from seasonal influenza [3, 7], as well as the growing self-care movement [11, 12], OTC medicines will play an important role in the course of future influenza epidemics. Among less severely ill patients, use of OTC medicines helps preserve economic productivity by reducing time absent from work [13]. However, patients who self medicate and continue working may infect co-workers.

Individuals who are at risk for influenza-related complications (see Sect. 2.1) should not use OTC medicines to delay seeking medical attention but should immediately consult their physician. Many pharmacies are exploring the use of rapid diagnostic tests and patient assessment techniques to identify patients with influenza at high risk for complications. This strategy may allow more efficient use of healthcare resources.

This article explores the socioeconomic impact of seasonal influenza in the USA and the possible role of OTC medicines, pharmacists, and the self-care movement in mitigating that impact. The focus is on adult patients.

2 Overview of Influenza in the USA

2.1 Groups Affected by Influenza

Influenza is an acute, highly contagious viral infection that causes annual epidemics. The spectrum of disease ranges from mild to moderate in the majority of the population, with severe illness and death occurring in high-risk populations. Influenza viruses can cause disease in any age group, but rates of serious illness and death are highest among those aged ≥65 years [14]. Although the elderly have immune memory, aging can reduce an individual's immune response against an influenza infection [4]. Among older subjects, those with certain underlying medical conditions are at substantially greater risk for hospitalization and complications during the influenza season than healthy adults of the same age [4].

Those at highest risk for influenza-related complications include children <2 years old; adults ≥65 years old; those with weakened immune systems; people of any age with certain medical conditions such as heart, kidney, liver, blood, or metabolic diseases [7]; and those with chronic lung disease (i.e., asthma, chronic obstructive pulmonary disease, bronchiectasis, or cystic fibrosis) [15]. Among healthy younger adults, seasonal influenza is typically not severe and requires hospitalization far less frequently than in vulnerable groups [4].

Family size is an important variable in determining the chance of infection because each member interacts with different groups and then returns to the family, increasing the risk of infection spread. Single individuals are the least likely to become infected [16].

2.2 Prevalence, Timing, and Geographic Factors

In the Northern Hemisphere, the influenza season generally runs from November to May. Timing of influenza activity is unpredictable, but in the USA the virus most commonly peaks in January or February [5, 17]. Earlier seasons are likely to result in more cases of influenza on both the regional and the national level, as well as higher morbidity and mortality [14]. Depending on virulence, vaccination rates, and ability of the year's influenza vaccine to match the circulating strains, 15 million to 61 million Americans contract influenza each year [15], or 5–20 % of the population [5]. Incidence varies greatly from year to year [4].

An analysis of disease burden performed to estimate the average annual impact of seasonal influenza was based on 2003 US population demographics and employed surveillance studies, published literature, and data from the

National Center for Health Statistics, National Hospital Discharge Survey: 1980–2001, US Census, and National Health Interview Survey, 2002 (Table 1) [2]. Results indicated annual occurrence of about 24.7 million cases of influenza (consistent with other studies [18]), approximately 31.4 million outpatient visits attributed to influenza [95 % confidence interval (CI) 22.6–43.5], and 334,185 influenza-related hospitalizations. The majority of hospitalizations and deaths occurred in individuals >65 years old [2]. A Centers for Disease Control and Prevention (CDC) study published in the *Journal of the American Medical Association* in September 2004 and based on data from 1979 to 2001, found that, on average, >200,000 people in the USA are hospitalized for seasonal influenza-related complications each year (range 158,000–431,000; estimate still used today), and there is an overall upward trend [19]. According to the American Lung Association, influenza–pneumonia was the sixth leading cause of death in people >65 years old in 2005 [5].

In a study examining national trends of influenza seasonality, data on hospitalization rates of influenza among older adults were abstracted from the Centers for Medicare & Medicaid Services for 1991–2004 [14]. The records of 248,889 influenza patients were analyzed. Across the 13 seasons, the period of highest incidence was consistently late December to early January. The peak intensity during this timeframe varied substantially, from 358 cases in the 2002/2003 season to 7,148 cases in the 1999/2000 season [14]. In terms of peak timing, Nevada, Utah, and California were the first states to experience influenza; on average, Rhode Island, New Hampshire, and Maine were the last. A west-to-east movement of influenza epidemics does appear to occur [14].

Table 1 Influenza-attributable cases leading to outpatient visits, hospitalizations, and mortality in non–high-risk patients in the USA: population-based estimates by age group[a]

Final health outcome	Cases by age group		
	18–49 years	50–64 years	65+ years
Ill but not medically attended[b]	5,191,816	1,375,732	520,756
Outpatients only	2,374,753	644,607	988,035
Hospitalized patients	31,836	39,711	67,070
Deaths	684	2,660	17,754

Data from Molinari et al. [2]

[a] The authors combined health outcome rates with US census population estimates by age group in 2003 to estimate the number of influenza cases in a year by final health outcome

[b] Individuals with clinical influenza infection who did not seek medical attention

2.3 Symptoms and Diagnosis

Although viral culture may be considered the gold standard for diagnosing influenza, it is rarely performed clinically because speed of diagnosis is critical for making treatment decisions. Instead, the diagnosis is typically based on the patient's symptoms (Table 2) and findings of a physical examination, especially during periods of peak influenza activity in the community [5, 20]. Influenza is associated with a variety of symptoms, including fever and cough/sore throat, and classic definitions vary [21–23].

Interestingly, a retrospective study of 207 inpatients with a laboratory-confirmed diagnosis of influenza found that only 60 % had fever and only 51 % had cough or sore throat [24]. Identification of a patient with influenza-like illness (ILI) when influenza activity is high (thus improving positive predictive value) can be used to diagnose influenza. ILI is defined as fever plus cough and/or sore throat absent a known cause other than influenza [22].

Additional evidence supporting a diagnosis of influenza can be gathered with a rapid influenza diagnostic test (RIDT), which is simple to perform and delivers results in ≤15 min. An RIDT can help with treatment decisions, such as whether to prescribe antiviral medications, by distinguishing respiratory illness caused by influenza from illness caused by other respiratory pathogens [20, 28]. Specificity is high (90–95 %); a positive test result obtained when influenza is present in the community can expedite the decision to treat. Similarly, during an outbreak of respiratory illness, testing can help quickly determine whether influenza viruses are the cause [29]. If they are, positive RIDT results can support decisions to promptly implement prevention and control measures [20]. However, because sensitivity is low to moderate (40–70 %) and false-negative results are common, a negative test result cannot be used to rule out influenza; thus, follow-up is essential. Also, the test appears to be better at detecting influenza in children than in adults [29].

Cost efficacy of RIDT in the clinical setting depends on the probability that the patient has influenza and the drug to be used for treatment. Generally speaking, when influenza is probable, empiric treatment is the best strategy regardless of the drug used [30–32]. In a recent study, clinical judgment emerged as the most cost-effective strategy for adults when influenza comprised 30 % of seasonal ILI cases. Second was reverse transcriptase–polymerase chain reaction (RT-PCR); third was point-of-care (rapid) testing [33]. According to the CDC, however, RT-PCR is not available for most outpatients and emergency department patients, and results are not timely enough to inform clinical decision making [34]. Molecular testing is most appropriate for hospitalized patients if a positive test would change clinical management and is particularly useful to

Table 2 Defining influenza

Influenza symptoms	Illnesses that mimic influenza
• Patient knows exact day that flu hit [25]; symptoms start abruptly, 1–2 days after contagion [4] • Patient has headache, chills, dry cough, myalgia, exhaustion [25]; eye redness [4] • Fever is a frequent early symptom [4] • Illness lasts longer than a cold [25] • Children may experience nausea, vomiting [25]; gastrointestinal symptoms (e.g., diarrhea) are common [4] • Life-threatening complications (e.g., pneumonia) are possible, especially in frail, young, elderly, or chronically sick individuals [4, 15] • Illness is very severe in immunosuppressed individuals [4]	*Colds*: gradual arrival; runny nose, sneezing; fever absent or mild (fever is a negative predictor of rhinovirus infection in adults) [26] *Streptococcal pharyngitis*: sore throat with nasal symptoms typical of viral pharyngitis, tender unilateral adenopathy and exudate typical of streptococcal pharyngitis (severe sore throat is evidence against influenza) [26] *Acute mononucleosis*: elevated liver function test results, splenomegaly, atypical lymphocytes on peripheral smear, positive monospot test [26] *Bacterial pneumonia*: pleuritic chest pain, productive sputum (illness may be concurrent with viral pneumonia or may occur ≤2 weeks after recovery from influenza) [26] *Asthma exacerbations, chronic bronchitis, congestive heart failure* [27] *Bacterial meningitis*: clouded sensorium, prominent headache (early presentation may be confused with influenza. Influenza should show improvement within 48 h; it is associated with increased risk of invasive meningococcal disease) [26] *Encephalitis*: fever, change in mental status, stiff neck, headache [26] *Other diseases* [many relatively rare conditions can present with influenza-like symptoms (e.g., inhalational anthrax)] [26]

identify influenza virus as a cause of respiratory outbreaks in institutions [34]. Of great interest is cost efficacy of RIDT in the pharmacy setting. A study of pharmacist-provided treatment for adult pharyngitis found that pharmacist use of the rapid antigen detection test (RADT) and provision of antibacterials depending on results was more cost effective than the same care by a physician [35]. This model in all probability would hold for influenza. Under a collaborative practice agreement with a partnering physician, a pharmacist could initiate antimicrobial therapy based on RIDT results within minutes of patient presentation and refer other patients to a provider if warranted. Pharmacists trained and certified to perform RIDTs and provide follow-up care can manage the pharmacotherapy for straightforward, uncomplicated patients, allowing diagnosticians to manage more complex patients.

According to the Infectious Diseases Society of America (IDSA), during influenza season the diagnosis of influenza should be considered regardless of vaccination status in a variety of scenarios, including fever and acute onset of respiratory signs and symptoms in adults and children; fever and no other signs or symptoms in infants and young children; and new or worsening respiratory symptoms, including exacerbation of congestive heart failure or altered mental status, with or without fever in elderly patients [36].

Symptoms of influenza start 1–4 days after the virus enters the body. Adults can transmit the virus 1 day before symptoms develop and up to 7 days after becoming sick [37]. Children can transmit the virus for longer than 7 days. Influenza is primarily transmitted by respiratory droplets from coughing, sneezing, or talking. It may also be transmitted by fomites [37].

Influenza is one of many acute respiratory infections (ARIs), a disease group that includes respiratory syncytial virus (RSV) and pneumonia [38]. ARIs are extremely common, and influenza is the most serious viral ARI. It is difficult to distinguish symptoms of influenza from other viral ARIs [39]. Differentiating influenza virus from the highly contagious RSV, which also causes epidemics and can severely affect the same age groups as well as those with weakened immune systems, is especially important [40, 41]. Clinical characteristics are rarely distinctive enough, and laboratory tests to detect RSV in respiratory secretions of the patient are necessary [41].

Clinicians should contact their local or state health department for information about current influenza activity. National information is available online from the CDC's Flu Activity & Surveillance page at http://www.cdc.gov/flu/weekly/fluactivitysurv.htm [20].

2.4 Influenza-Associated Morbidity and Mortality

Although morbidity and mortality associated with influenza have declined among most age groups since 1980, hospitalizations have increased for those aged ≥65 years [14]. This increase has been attributed to the aging of the US population and the increased prevalence of chronic medical conditions [42]. During the 1990/1991 through to 1998/1999 influenza seasons, 90 % of influenza–pneumonia deaths occurred in individuals aged ≥65 years [43]. The number of annual influenza-associated deaths with

Table 3 US total economic burden[a] of influenza in 2003 by age group and health outcome

	Portion of total burden	Share of direct medical costs[b]
Age group		
≥65 years	64 % (US$55.7 billion)	40 % (US$4.2 billion)
50–64 years	21 % (US$18.3 billion)	27 % (US$2.8 billion)
18–49 years	10 % (US$8.7 billion)	18 % (US$1.9 billion)
<18 years	5 % (US$4.3 billion)	15 % (US$1.7 billion)
Health outcome		
Deaths	83 % (US$72.2 billion)	18 % (US$1.9 billion)
Outpatient care	8 % (US$6.8 billion)	30 % (US$3.1 billion)
Hospitalizations	7 % (US$6.0 billion)	52 % (US$5.4 billion)
No medical attention	2 % (US$2.0 billion)	<1 % (<US$0.1 billion)

[a] Total economic burden = direct medical costs, lost earnings from illness, and the value of statistical life (VSL) method of valuation [medical + lost earnings + lost life]

[b] To treat the disease and its complications; total US$10.4 billion annually

Data from Molinari et al. [2]

underlying respiratory and circulatory causes[1] from 1976 to 2007 was 16,612 during the 1976/1977 influenza season and 15,573 during 2006/2007. The range was 3,349 during the 1986/1987 season to 48,614 during 2003/2004 [44]. For these underlying causes, the average annual rate of influenza-associated death was 9.0 deaths per 100,000 persons (range 1.4–16.7) [44].

3 Impact of Seasonal Influenza in the USA/Economic Burden

Seasonal influenza can sweep through schools, nursing homes, workplaces, and towns, resulting in high levels of worker absenteeism and productivity losses [7]. Clinics and hospitals can be overwhelmed when large numbers of sick people present for treatment during peak illness periods [7]. The economic impact on society results primarily from lost work time and reduced productivity for patients and caregivers (indirect costs) and increased use of medical resources (e.g., healthcare professionals' time, prescribed medications, laboratory investigations, hospitalizations) required to treat patients (direct costs) [3]. Typically, indirect costs account for a greater proportion (>80 %) of the total societal cost of seasonal influenza epidemics [3].

According to the most current published data on this topic, in 2003 the total economic burden of influenza epidemics in the USA across all age groups was US$87.1 billion (95 % CI 47.2–149.5; Table 3) [2]. Indirect costs were about US$76.7 billion (88 %) [2]. The annual burden per capita ranged from US$92 (considering only lost earnings) to US$299 (including lost lives) [2].

The US healthcare system bears a significant portion of the economic burden. From 2004 to 2008, influenza was identified as the fastest-growing disease state in terms of healthcare spending by employers [10]. Based on 2003 population demographics and prices, direct costs of medical treatment for influenza amounted to US$10.4 billion annually, or 12 % of the total economic burden [2].

It has been estimated that influenza results in 0.6–2.5 lost workdays per patient [4], which means, based on an estimated 24.7 million cases in 2003 [2], that 14.8 million to 61.7 million workdays may be lost to influenza per year. The high morbidity and mortality associated with influenza result in substantial productivity losses [10], amounting to about US$16.3 billion annually in 2003 (US$6.2 billion due to morbidity only) [2]. Many adults find that their work performance is still impaired after returning to work: self assessments have estimated a maximum effectiveness of 46 % [3]. Caregivers miss work while tending to sick children and elderly parents. Interestingly, 89 % of consumers believe that OTC medicines are an important part of their overall family healthcare [45].

4 Prevention of Seasonal Influenza

Influenza vaccination is the primary tool to prevent influenza [36]. Because influenza viruses mutate constantly, the vaccine has to be modified every year based on a prediction of which strains will be most predominant [5]. In the USA, annual vaccination against seasonal influenza is recommended for individuals aged ≥6 months [46]. In older people and those with chronic illnesses, vaccination may

[1] Per the CDC, if only one category is used to summarize the mortality effects of influenza, the respiratory and circulatory data likely provide the most accurate estimates.

not necessarily prevent influenza, but it can reduce the symptoms and risk of complications if these individuals do get sick [25]. Older people are also advised to receive the pneumococcal vaccine because pneumonia is a major complication of influenza [5].

4.1 Current Vaccines

There were 13 influenza vaccines available for the 2013/2014 influenza season: nine trivalent and four quadrivalent [47]. Each year's trivalent[2] intramuscular vaccine contains 15 μg of viral antigens from each of two A strains and one B strain [48] and is specifically formulated to protect against the three influenza strains that research suggests will be the most common during the upcoming season [49, 50]. An intradermal formulation (Fluzone® Intradermal; Sanofi Pasteur) first became available in the 2011/2012 influenza season for use in adults aged 18–64 years [49]. This vaccine contains 9 μg of viral antigens from each strain; however, intradermal administration elicits a stronger immune response [48].

Fluzone® and Fluzone® High-Dose contain the same inactivated strains; however, the high-dose formulation contains 60 μg of viral antigens from each strain and is designed specifically for people ≥65 years old [51]. An ongoing study designed to determine the effectiveness of Fluzone® High-Dose compared with Fluzone® is expected to be completed in 2014/2015. Other trivalent intramuscular vaccines include Fluvirin® (Novartis) for individuals ≥4 years old, Fluarix® (GlaxoSmithKline) for those ≥3 years old, FluLaval® (ID Biomedical Corporation of Quebec) for those ≥18 years old, and Afluria® (CSL Biotherapies) for those ≥9 years old [46].

All but one of the nine current vaccines are inactivated. FluMist® (MedImmune) is the only live, attenuated influenza vaccine (LAIV) and is administered intranasally to healthy, non-pregnant individuals aged 2–49 years [15, 48]. A new quadrivalent formulation of FluMist® for the same age group is available for the 2013/2014 influenza season and has replaced the trivalent formulation [47, 50]. Quadrivalent influenza vaccines contain the same three antigens as trivalent vaccines, along with an antigen from a second influenza B vaccine virus strain [46]. Other quadrivalent vaccines (all inactivated) available for the 2013/2014 season are Fluarix® Quadrivalent (GlaxoSmithKline), Fluzone® Quadrivalent (Sanofi Pasteur), and FluLaval® Quadrivalent (ID Biomedical Corporation of Quebec) [47, 52, 53].

Flucelvax® (inactivated trivalent; Novartis) and Flublok® (recombinant trivalent; Protein Sciences) are two new influenza vaccines that are manufactured using cell culture technology [54]. Cell-based influenza vaccines are made by growing viruses in animal or insect cells, instead of the traditional egg-based process. A major advantage of cell culture technology is the potential for faster start-up of the vaccine manufacturing process in the event of a pandemic [55]. This formulation is also advantageous for use in individuals with an egg allergy [55].

4.2 Vaccine Efficacy

As of February 2013, overall vaccine effectiveness for the 2012/2013 season was estimated to be 56 % (95 % CI 47–63) [45]. This efficacy rate was considered "moderate efficacy for most people" [17]. Against influenza Type A (H3N2) the efficacy rate was 47 %—only 9 % in individuals aged ≥65 years—and against Type B it was 67 % [56]. Subtype H3N2 was the main virus spreading, and there were not enough H1N1 viruses to estimate the efficacy rate against that subtype [17]. The CDC's National Center for Immunization and Respiratory Diseases concluded that more effective vaccines and vaccination strategies are needed [56].

There are fewer data on vaccine efficacy in elderly and high-risk patients. A 2006 Cochrane review of five randomized trials including >5,000 patients demonstrated a rate of vaccine effectiveness of 58 % against influenza and 43 % against ILI in these populations [57, 58]. A 2010 Cochrane review of 50 study reports (40 of which included >70,000 subjects) found that vaccination had a modest effect on workdays lost and reduction in influenza symptoms but had almost no effect on rates of hospital admissions or complications. There is no evidence that vaccination affects complications (e.g., pneumonia) or virus transmission [59].

One study found that vaccinated individuals ≥65 years old had a 27 % reduction in the risk of hospitalization for pneumonia or influenza and a 48 % reduction in the risk of death [5]. These reductions occurred despite the fact that the individuals also tended to have more serious medical conditions that should have increased their risk of hospitalization or death.

The protection afforded by vaccination is greatly reduced or absent in some seasons [60]. This conclusion was based on efficacy data derived from an analysis of 31 studies [17 randomized controlled trials (RCTs) and 14 observational studies] that met strict criteria for design and conduct. Efficacy of trivalent vaccines in adults 18–64 years old was shown in 8 of 12 seasons (pooled rate

[2] Nomenclature alterations for the 2013/2014 season: the term *trivalent influenza vaccine,* previously used for inactivated influenza vaccine, is being replaced with inactivated influenza vaccine (IIV). IIVs as a class will include egg-based and cell culture-based trivalent inactivated influenza vaccine (IIV3) and egg-based quadrivalent inactivated influenza vaccine (IIV4). To refer specifically to cell culture-based vaccine, the prefix "cc" (e.g., ccIIV3) will be used [47].

of 59 %) in ten RCTs. Evidence for protection in individuals 2–17 years old was inconsistent and was lacking in those ≥65 years old. Efficacy of LAIVs in children 6 months to 7 years old was shown in 9 of 12 seasons (pooled rate of 83 %) in ten RCTs. Evidence for protection in individuals ≥60 years old was inconsistent and was lacking in those aged 8–59 years [60].

4.3 Vaccination Rates

In March 2010, RAND conducted a survey of >4,000 US adults and found that only 39 % underwent influenza vaccination during the 2009/2010 season. Among adults specifically recommended for vaccination, rates were only slightly higher—45 % overall. Reasons for these low seasonal influenza vaccination rates include public resistance to vaccination and missed opportunities, i.e., visits to a healthcare provider during flu season when vaccinations could have been delivered but were not [61]. Additionally, racial and ethnic disparities exist. Early season data for the 2013–2014 season show a 7.8 % increase in coverage among Hispanics, making the vaccination rate similar to that for non-Hispanic whites. However, disparities in vaccination remain among non-Hispanic blacks [62].

Influenza vaccination rates for healthcare workers have remained low for more than three decades, adversely affecting patient safety [63]. The IDSA suggests that the USA should require all healthcare workers to undergo annual influenza vaccination to lower the costs of providing care and the rates of patient morbidity and mortality [6].

4.4 Cost Effectiveness and Cost Savings of Vaccination

Multiple studies in the USA, Canada, UK, and France have found vaccination to be cost effective and often cost saving in the elderly and in healthy adults, but other studies offer an opposing viewpoint regarding vaccination in healthy adults [64]. A critical factor in determining cost effectiveness and cost savings is vaccine efficacy, which fluctuates from year to year. Many other variables integral to studying this topic (e.g., influenza rate, number and timing of physician visits, geographic area) make a true cost–benefit analysis difficult. To determine the cost effectiveness of influenza vaccination, antiviral therapy, or no intervention in healthy working adults, one study of WHO surveillance data from 1993 to 2002 employed a Markov model and a number of intensive analyses in an attempt to address these issues [65]. Results showed that for every influenza season, except 1997/1998, annual vaccination was the most cost-effective strategy, and in four of ten seasons, it was also the least expensive strategy. In half the years, vaccination was less expensive than no intervention, which was always the least effective strategy. The authors stated: "After 20 years of data collection and public-health policy analysis, experts agree that vaccination benefits healthy adults, but there is still no consensus on whether the benefit justifies the cost". Therefore, the answer may be that vaccination cannot be considered cost effective under all circumstances [65].

Supportive of this position is a review of seven cost-effectiveness analyses (three RCTs and four simulation models) conducted in the USA among healthy adults 18–49 years old and published from 1990 to 2010 [66]. Results suggested that vaccinating the healthy, working-age population against influenza is generally not cost saving "but may be economically attractive under certain conditions, such as higher illness rates, lower costs of vaccination, and higher wage rates" [66].

4.5 Antiviral Chemoprophylaxis

Prescription antiviral medications can be used to prevent influenza (approximately 70–90 % effective) [67]. These medications are useful adjuncts to vaccination, but widespread or routine use of antiviral therapy for chemoprophylaxis is not recommended because it may promote antiviral resistance [67]. Additionally, antiviral therapy must be administered for the duration of potential exposure and continued for 7 days following exposure, and adverse events (AEs) associated with long-term use are uncertain [68]. Use of preventive antiviral therapy is recommended for people at high risk for influenza complications who have been exposed, those with severe immunodeficiencies, and those who are residents of an institution during an influenza outbreak in the institution [67]. See Sect. 4.4 for information on cost efficacy.

5 Treatment of Seasonal Influenza

5.1 Antiviral Drugs

Two US Food and Drug Administration (FDA)-approved antiviral medications for influenza were recommended for use in the USA during the 2012/2013 influenza season: oseltamivir (Tamiflu®; Gilead Sciences and F. Hoffmann-La Roche) and zanamivir (Relenza®; GlaxoSmithKline) [67]. Both are neuraminidase inhibitors (NIs) active against the influenza A and B viruses and are typically administered for 5 days [68]. Oseltamivir is available in pill or liquid form and is indicated for patients ≥2 weeks old. Zanamivir is an inhaled powder indicated for patients ≥7 years old [15, 67]. Zanamivir is licensed only for use in patients without underlying pulmonary or cardiac disease

[69]. Antiviral therapy can help decrease symptom severity, shorten disease duration by 1 or 2 days, reduce the risk of complications and death, and shorten hospitalization time [15, 67]. The benefit is greatest when treatment is started as soon as possible after illness onset [68]. Treatment should be started within 48 h of the occurrence of symptoms and is most effective when begun within 6 h [57]. However, if a patient with confirmed or suspected influenza requires hospitalization or has progressive, severe, or complicated illness, then treatment is recommended even if >48 h have passed since illness onset [68].

5.2 Clinical Efficacy and Cost Effectiveness of Antiviral Drugs

Controversy exists regarding the clinical efficacy and cost effectiveness of NIs [70]. Michiels et al. [70] examined nine systematic reviews and found >50 % efficacy of each NI for seasonal prophylaxis in healthy adults and individuals at risk for complications, as well as for post-exposure prophylaxis in healthy adults. Treatment benefit was <1 day in alleviation of symptoms. The authors concluded that "diagnostic uncertainty, risk for virus strain resistance, side effects, and financial cost outweighs the small benefits" of prophylaxis or treatment of ILI in healthy adults. Prophylaxis of at-risk and elderly groups may be considered in individual cases, but there is no evidence supporting NI treatment in these groups. A systematic review of 22 studies found that use of NIs appeared to be consistently more cost effective in at-risk and elderly populations [71]. Like Michiels et al., these authors noted marked variations across studies in approaches, settings, populations, and assumptions, which led to important differences in the cost-effectiveness estimates [71]. Of note, a 2014 Cochrane review of 46 RCTs testing the effects of NIs for prophylaxis, post-exposure prophylaxis, and treatment of influenza found treatment benefit of only half a day; no evidence that either medication reduces the risk of complications, hospitalization, or death, even in patients at high risk; and minimal effect on prevention [72].

5.3 Inappropriate Antibacterial Use

Unnecessary antibacterial use for influenza continues, contributing to the ongoing public health problem of antibacterial drug resistance [10]. In fact, millions of antibacterials are prescribed by physicians for viral infections each year [73]. A nationwide US survey of ambulatory care visits from 1997 to 2001 showed that 38 % of >6.5 million visits (primary practice, outpatient, and emergency room) by individuals aged 5–49 years with a sole diagnosis of influenza were associated with an antibacterial prescription [74].

A study that assessed the frequency of inappropriate prescribing of oral antibacterials among 270,057 influenza patients found that 58,477 (22 %) had received antibacterial prescriptions. Of these, 46,316 antibacterial users had neither a secondary infection during the ensuing 15-day period nor a relevant co-morbidity, suggesting that approximately 79 % of antibacterial use was inappropriate [10]. Furthermore, the mean cost of an antibacterial prescription was US$40.09. Extrapolated to the entire US population, inappropriate prescribing of antibacterials for patients with influenza costs more than US$200 million annually [10].

5.4 Over-the-Counter (OTC) Medicines

Use of OTC medicines can minimize the discomfort associated with influenza symptoms, although these drugs do not treat the infecting virus [5]. OTC medicines are determined by the FDA to be safe and effective in addressing label-specified symptoms via a process that includes review of active ingredients within a therapeutic class and subsequent development of an OTC Drug Monograph. The monograph defines the safety and effectiveness of all OTC active ingredients [75].

Of note, 93 % of US adults prefer to treat minor ailments with OTC medicines before seeking professional care [45]. According to an analysis by the Consumer Healthcare Products Association (CHPA), OTC medicines provide US$102 billion in annual savings [45]:

- US$77 billion in clinical cost savings (avoided doctor's office visits and diagnostic testing); and
- US$25 billion in drug cost savings (lower priced OTCs versus higher priced prescription medicines).[3]

Nearly one-third of that amount results from consumers self-treating cough/cold and influenza symptoms [45] (see Sect. 6.1 for additional study details).

6 Use of OTC Medicines in the USA

Approximately 35 % of US adults use OTC medicines on a regular basis, and there is a trend for increasing use as more medications move from prescription to OTC status [11]. In

[3] CHPA references: "Overall industry sales and volume data as well as frequency of purchase data for OTC medicines were sourced from Symphony IRI, a leading aggregator of consumer health products industry sales data. List prices for Rx [prescription] products were obtained from the 2010 version of the Red Book: Pharmacy's Fundamental Reference. Ratios of generic-to-branded Rx sales were estimated based on the 2011–2012 Healthcare Distribution Management Association *Factbook* and Booz & Company analysis. Broader literature searches contributed the remaining information" [13].

a 2001 survey commissioned by the National Council on Patient Information and Education, 598 of 1,011 adults (59 %) surveyed indicated that they had taken OTC medicine in the past 6 months [76]. Among these, 52 % reported that they had taken it to treat cough, cold, influenza, or sore throat. A survey by the Center for Medicine in the Public Interest of 1,007 adults showed that 66 % relied on OTC cough medicines to relieve cough symptoms [77], which are common with influenza.

More than four of five US adults (82 %) who have experienced various illnesses that can be treated or relieved by non-prescription medicines self-medicate for these conditions. The main reasons for self-medicating are familiarity with how to treat the illness because of past experience (90 %); desire to save time, travel effort, and money (89 %); and belief that the illness is not serious enough to require consulting a doctor (78 %) [78]. There are many additional benefits to use of OTC medicines (Table 4).

According to Euromonitor International, US consumers spent US$23 billion on OTC medicines in 2010 [13]. Consumers frequently consult pharmacists about OTC medicines: according to the American Pharmacists Association's 2008 Annual OTC Product Survey, pharmacists give approximately 31 OTC medicine recommendations per week, and an average of 83 % of individuals purchase the OTC medicine that their pharmacist recommends [76].

Notably, certain high-risk individuals (described previously) would benefit from a physician visit and diagnosis rather than self management of influenza-like symptoms. An 80-year-old patient with asthma, for example, is especially vulnerable to complications and hospitalization, and taking OTC medicines may only delay needed care. Pharmacists can identify such high-risk patients and facilitate referral to a physician or other prescriber. For patients determined to be at lower risk, pharmacists can conduct assessments and expeditiously recommend either self management or referral. This would represent a highly efficient means to access care.

Table 4 Characteristics and benefits of over-the-counter medicines

Characteristics [76]
- Have benefits that outweigh risks
- Have low potential for misuse and abuse
- Can be used for self-diagnosed conditions
- Do not require consultation with a healthcare provider

Benefits to patient [76]
- Offer direct, rapid access (prescription not needed) [11]
- Offer convenience and wide availability: drugstores (pharmacies), grocery stores, mass merchandisers, etc.
- Offer choice: wide variety of treatment options
- Offer self treatment of common conditions
- Can be kept on hand (e.g., home first-aid kit, travel kit)

Benefits to society
- Decrease use of healthcare system (fewer physician visits, lower system costs) [11]
- Allow healthcare system to focus limited resources on [76]:
  - Diagnosis and treatment of serious diseases that require physician involvement
  - New research
  - Innovative services
- Provide significantly expanded access to treatment [13]
- Contribute to increased economic productivity because of less time absent from work [13]
- Reduce "treatment gap" (number of people with a condition who need treatment but do not get it because of cost, inconvenience, difficulty getting an appointment with their physician, etc.) [76]

6.1 Socioeconomic Cost Savings with Use of OTC Medicines

The CHPA created a hypothetical model in which OTC medicines were unavailable for seven of the most common categories of acute and chronic, self-treatable conditions: allergy, analgesics, antifungals, cough/cold/flu, lower and upper gastrointestinal, and medicated skin [13]. Among the data sources was a survey of 3,200 consumers to estimate their likely behavior in this scenario. Overall results showed that:

- Approximately 75 % of today's OTC medicine consumers ($N = 180$ million) would seek medical treatment if OTC medicines were not available in the seven categories studied, triggering significant costs to the US healthcare system.
- The availability of OTC medicines is estimated to provide US$102 billion in annual savings to the US healthcare system:

  ~50 % (US$52.7 billion) of total OTC value is captured by employer-based insurance,
  ~25 % (US$27.5 billion) by Government programs (Medicare and Medicaid)
  ~25 % (US$21.7 billion) by the self-insured and uninsured populations.

- Drug cost savings are about US$25 billion as a result of using lower-priced OTC medicines rather than higher-priced prescription medicines.
- The magnitude of savings is particularly high in the cough/cold/flu category because of the frequency and prevalence of these conditions.

7 The Self-Care Movement

OTC medicines play an increasingly vital role in the US healthcare system [75]. The use of OTC medicines is one

aspect of a growing movement toward medical self care and has become a tool to help individuals gain control over their health [11]. People already treat and manage many of their ailments without consulting a physician or pharmacist [79]. In a CHPA 2001 survey, 59 % of Americans polled said that they were more likely to treat their own health conditions than they were a year ago [67]. Furthermore, 73 % would rather treat themselves at home than see a doctor, and six out of ten said that they would like to do more of this treatment in the future [80]. Interest in self care has grown as technological advances have created an information explosion involving wide-open access and infinite resources. Also, the number of OTC medicines has surged, patients increasingly want choices, and new and innovative ways of managing ailments (e.g., self-monitoring equipment, self-diagnosis tools) have evolved [81].

The free market in which non-prescription medicine manufacturers, who are highly competitive, set prices based on supply and demand benefits consumers [12]. Furthermore, self medication is being promoted worldwide as a tool for reducing the healthcare burden on the public budget [79]. OTC products, such as cough/cold remedies, analgesics, and decongestants, are commonly used to treat influenza [81]. The World Medical Association (WMA) defines responsible self medication as is the use of a registered or monographed medicine legally available without a physician's prescription, either on an individual's own initiative or following advice of a healthcare professional. The WMA further notes that use of prescription medicines without a prior medical prescription is not responsible self medication [82]. Benefits of responsible self medication include the ability to [83]:

- Help prevent and treat symptoms and ailments that do not require a doctor;
- Reduce the pressure on medical services when healthcare personnel are insufficient;
- Increase the availability of health care in rural or remote areas;
- Enable patients to control their own chronic conditions;
- Potentially increase wellness and productivity;
- Allow economic gain for employers; and
- Initiate cost savings to healthcare budgets.

In 2013, the World Self-Medication Industry (WSMI) reviewed 24 independent, published consumer surveys (conducted from 1987 through 2006) with specific emphasis on consumers' practices and attitudes regarding self care and self medication [84]. The WSMI found that approximately 92 % of respondents are satisfied with non-prescription medicines, many believe that they can be as effective as prescription medicines, OTC drugs are needed to treat common health problems, and they are used appropriately, carefully, and safely by most consumers [84]. Potential risks include [11, 81]:

- Incorrect self diagnosis, delaying diagnosis and treatment of serious illnesses by a healthcare professional;
- Lack of awareness that interactions can occur with prescription medicines;
- The perception that OTC drugs are less dangerous than prescription drugs, which may result in overconsumption or inappropriate use;
- Faulty self-monitoring for AEs related to the medication;
- Vulnerability, leading to reduced capacity for self management; and
- Absence of a risk:benefit analysis of the OTC drug.

In May 2012, the FDA began consideration of a model in which some drugs for chronic conditions, such as asthma and allergies, would be sold under "conditions of safe use", a proposed category that would describe prescription drugs sold as OTC medicines. The model would require development of new technology (e.g., patient kiosks, remote diagnostic tools, online questionnaires) to help diagnose and assess patients' needs. It would expand the role of pharmacists and reduce that of physicians [85]. Additionally, the model may improve accessibility of primary healthcare physicians for patients with more severe illnesses if those with less severe conditions could be managed by pharmacists.

8 Conclusion

As concerns about the efficacy of the influenza vaccine remain and healthcare costs continue to rise, OTC medicines may play an increasingly important role in mitigating the socioeconomic burden of this pervasive seasonal illness. For individuals with mild to moderate influenza symptoms, OTC medicines allow early, cost-efficient self treatment and patient control. They also offer convenience, wide availability, and a range of treatment choices. Socioeconomically, OTC medicines can reduce use of the healthcare system and contribute to increased economic productivity by reducing time absent from work.

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