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# COST-EFFECTIVENESS ANALYSIS OF REACQUIRING AND USING ADENOVIRUS TYPES 4 AND 7 VACCINES IN NAVAL RECRUITS

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*Abstract.* Adenovirus vaccines have controlled acute respiratory disease (ARD) in military recruits since 1971. Vaccine production, however, ceased and new facilities are required. We assessed whether reacquiring and using vaccines in naval recruits is cost-effective. Three policy options were evaluated: no vaccination, seasonal vaccination, and year-round vaccination. Morbidity (outpatient and inpatient), illness costs (medical and lost training), and vaccine program costs (start-up, acquisition, and distribution) were modeled using a decision-analytic method. Results were based on a cohort of 49,079 annual trainees, a winter vaccine-preventable ARD rate of 2.6 cases per 100 person-weeks, a summer incidence rate at 10% of the winter rate, a hospitalization rate of 7.6%, and a production facility costing US$12 million. Compared to no vaccination, seasonal vaccination prevented 4,015 cases and saved $2.8 million per year. Year-round vaccination prevented 4,555 cases and saved $2.6 million. Reacquiring and using adenovirus vaccines seasonally or year-round saves money and averts suffering.

## INTRODUCTION

Adenovirus was first isolated from military personnel with acute respiratory disease (ARD) in 1954.[1] Adenoviruses, particularly types 4 and 7, have been causally associated with large ARD outbreaks, which typically occur in military recruit (initial entry) settings during winter months.[2] Acute respiratory disease is a febrile illness with symptoms such as sore throat, cough and/or rhinorrhea. Symptoms typically last 3–10 days.[3] Acute respiratory disease may develop into pneumonia but deaths have rarely been reported.[4] There is no specific therapy for adenovirus-associated ARD.

Before routine administration of adenovirus vaccine, 60–80% of ARD in recruit training camps was caused by adenoviruses.[2,3,5,6] In a small, recent adenovirus-ARD outbreak associated with unvaccinated trainees, weekly hospitalization rates for the most strongly affected military unit reached 11.6%.[7] Since 1971, live oral vaccines for adenovirus types 4 and 7 have controlled adenovirus-related ARD.[3,8,9] The vaccines were first used during the colder months only. In 1984, year-round vaccination was implemented to control outbreaks occurring when the vaccines were not in use. Outbreaks associated with vaccination lapses have been documented.[3,7,9,10] In 1996, the sole manufacturer ceased production. There are no vaccines remaining, and no plans exist to resume production since a new manufacturer has not been identified.

Vaccination is the only reliable control measure for adenovirus-related ARD.[11] Environmental controls, such as germicidal sprays and ultraviolet light sterilization, have failed.[12,13] Hand washing has had only anecdotal success. Cohorting, maintaining recruits in separate training groups with minimal interaction, has been partially successful; however, it may only delay adenovirus-ARD until later stages of training.[14,15]

In 1973 Collis and others studied the costs and benefits of vaccination against adenovirus-related ARD and reported that the benefits outweighed the costs.[16] With the loss of vaccines imminent, Howell and others recently analyzed the cost-effectiveness of adenovirus vaccinations in army recruits.[17] They compared the policy options of year-round, seasonal, and no vaccination. The seasonal and year-round vaccination options were cost saving over no vaccination. Howell and others projected increased vaccine prices in their model, but they did not address the substantial start-up costs (estimated at over $12 million) needed to resume production. They also used ARD incidence data from the 1960s and 1970s, as current respiratory disease incidence rates in the absence of the vaccines were not available.

In this study, we examined the cost-effectiveness of the adenovirus vaccines, types 4 and 7, in a navy-recruit basic-training population, used current United States Navy respiratory disease incidence rates, and included vaccine production facility start-up costs. Adenovirus-associated ARD may be more prevalent in civilian populations than has been previously considered.[3,18,19] Adenovirus infections can cause significant morbidity and mortality in immunosuppressed people and other populations, such as those living in close contact.[20,21] Assessing the cost-effectiveness of the adenovirus vaccines in a military recruit training population may serve as a useful model for similar civilian populations, such as the Job Training Corps.

## MATERIALS AND METHODS

**Model characteristics.** A computerized (DATA 3.0, TreeAge Software, Inc., Williamstown, MA), decision-analytic probability model was used to estimate the cost-effectiveness of three vaccination policy options: no vaccination, seasonally targeted vaccination during colder months (November through March), and year-round vaccination. Outcomes associated with each policy option included number of ARD cases prevented, direct and indirect medical costs of ARD, lost military training costs, and associated vaccination program costs. Outcomes were modeled for the actual cohort of male and female navy recruits who entered basic training in fiscal year (FY) 1997 at Recruit Training Command (RTC), Great Lakes, Illinois. Recruit Training Command is now the only U.S. Navy recruit training center. All

TABLE 1
Reference case acute respiratory disease (ARD) incidence parameters

| Variable | Reference case value | Source |
|---|---|---|
| Vaccine-preventable ARD* (November–March) | 2.6 cases/100 person-weeks | RTC clinic records* |
| Vaccine-preventable ARD† (April–October) | 0.26 cases/100 person-weeks | NAMRU-4† |
| ARD hospitalizations‡ | 7.6% | NAMRU-4† |

* ARD rate that is preventable with adenovirus vaccination based on respiratory infection incidence data extracted from the Recruit Training Command (RTC) Primary Care Clinic records, Great Lakes, IL.
† Extrapolation from data collected by the Naval Medical Research Unit No. 4 (NAMRU-4), Great Lakes, IL.[22]
‡ Percentage of recruits with ARD expected to be hospitalized.

trainees were assumed to have received the vaccines at the start of their eight-week training period.

Reference case costs and probability parameters were based on Naval surveillance data for adenovirus vaccine-preventable respiratory disease; accounting and financial reports; expert opinion of military preventive medicine physicians; and manufacturers' quotations for new facility construction, production, and purchase of adenovirus vaccines types 4 and 7. Disease prevented and total costs associated with each policy option were compared to each other (incremental cost-effectiveness) and to the no vaccination option (average cost-effectiveness). Reference case incidence rates and costs were varied in sensitivity analyses to examine how changes in these variables would affect the results. This analysis was done from the navy's perspective and examined costs on an annual time frame. The program start-up costs were annuitized over 25 years—the expected life of the new vaccines.

**Probability estimates.** In FY 1997, 49,079 male and female recruits entered basic training at RTC. Attrition was modeled to reflect actual seasonal- and gender-specific differences and was considered uniform over the eight-week training period. Current incidence data were extracted from medical records at the RTC primary care clinic. Some incidence data were obtained from old surveillance studies done by the former Naval Medical Research Unit No. 4 (NAMRU-4) at Great Lakes (Table 1).[22] In army treatment facilities, ARD is generally defined as consisting of one or more symptoms of an acute respiratory infection and an oral temperature of 100.5° F or greater. Army basic trainees with ARD are usually hospitalized, which could mean admission to a minimal care facility. At the RTC primary care clinic, respiratory illness in recruits was usually classified as an ''upper respiratory infection,'' or URI. Upper respiratory infection was not precisely defined, and providers determined the dispositions of patients to include hospitalization. From January to March 1995 when adenovirus vaccines were unavailable due to a logistical error (they had also been unavailable for the previous two months), the associated URI incidence rate was 6.5 cases per 100 person-weeks. During the same months in 1994 when adenovirus vaccines were in use, the associated URI incidence rate was 3.9 cases per 100 person-weeks. Both these rates are understandably high when compared with the U.S. Army's ARD epidemic threshold of 1.5 cases per 100 person-weeks.[17] The difference in the URI rates, obtained by subtracting 3.9 from 6.5, is 2.6 cases per 100 person-weeks. This difference is significant (OR = 1.66, 1.57–1.72) and was attributed to immunization for adenovirus types 4 and 7. We therefore chose the rate of 2.6 cases per 100 person-weeks as the vaccine-preventable ARD incidence rate for navy recruits. The vaccine-preventable ARD incidence rate used in the recently published cost-effectiveness evaluation of adenovirus vaccines in army recruits was also 2.6 cases per 100 person-weeks.[17] In this study, adenovirus-vaccine preventable respiratory illness is based upon the above calculations and is referred to as ARD.

Surveillance data collected by NAMRU-4 from 1949–66 (before widespread use of any adenovirus vaccines) showed that summer ARD incidence averaged 10% of the winter rate (Table 1).[22] The expert opinion of preventive medicine physicians at RTC was that most recruits with ambulatory ARD who were not hospitalized were treated with bedrest in their quarters for 2.5 days. In addition, 5% of these outpatient cases required one follow-up visit. The NAMRU-4 study also showed that an average 7.6% of ARD cases were hospitalized.[22] The expert opinion of RTC physicians was that hospitalization for ARD was usually four days with two associated outpatient visits. Consistent with large controlled studies, the adenovirus vaccines were considered to be over 95% effective in preventing adenovirus-associated ARD.[23]

**Costs estimates.** Costs associated with illness include missed training (both direct and indirect) and medical (both direct and indirect) costs (Table 2). Training costs ($148.48 per day) represent the cost of running the basic training camp plus the salary paid to the recruit while sick and unable to train.[24] Total outpatient clinic costs at the RTC recruit primary care clinic for FY 1997, including direct, supplementary, ancillary, and patient workload expenses, were divided by total visits to give $60.52 per visit. In-patient hospitalization costs were captured by the general internal medicine service at Naval Hospital Great Lakes and were obtained from the Naval Medical Information Management Center, Bethesda, Maryland. Total inpatient costs for FY 1997, including direct, supplementary, ancillary, and patient workload expenses, were divided by the total number of in-

TABLE 2
Costs associated with acute respiratory disease (ARD)

| Variable | Reference case cost | Source |
|---|---|---|
| Training costs | $148.48/day | GAO* |
| Outpatient medical costs | $60.52/visit | NMIMC† |
| Inpatient medical costs | $1334.41/day | NMIMC† |

* General Accounting Office (GAO) report, 1996.[24] Data are adjusted to fiscal year 1997 dollars using the Consumer Price Index.
† Naval Medical Information Management Center (NMIMC), Bethesda, Maryland.

TABLE 3
Production start-up costs for the adenovirus vaccines*

| Cost | Amount |
|---|---|
| Facility construction | $10,345,163 |
| Profit | $1,034,516 |
| Clinical support | $900,000 |
| Total costs | $12,279,679 |
| Annual cost per recruit: | |
| Year-round vaccine option | $8.66 |
| Seasonal vaccine option | $15.13 |

* Sources are described in the text.

patient days to give an occupied bed-day cost of $1,334 per day.

Costs attributed to a recruit with ARD who is treated as an outpatient only were one clinic visit, with 5% requiring one follow-up visit, and 2.5 days lost training. Total medical and lost training costs for ARD cases treated as outpatients were averaged, giving a cost of $434 per case. Costs associated with illness requiring inpatient care were four days of hospitalization and four days of lost training costs plus two associated outpatient clinic visits. Total medical and lost training costs for ARD cases treated as inpatients were averaged to give a cost of $6,052 per case. The average total medical and lost training costs for all ARD cases (inpatient and outpatient) were calculated by weighting the medical and lost training costs by the likelihood of the case being ambulatory versus hospitalized and were determined to be $860 per case.

The facilities used to produce the adenovirus vaccines no longer exist and must be rebuilt. Construction estimates are from the sole offer received by the U.S. Department of Defense (DOD) in 1997 (Table 3). The last manufacturing facility produced vaccines for 25 years, and it was assumed that its replacement would have a similar productive life.

Start-up costs to resume vaccine production include: construction costs for the new facility that include an estimated $1,000,000 for the purchase of technology and manufacturing rights, manufacturer's profit, and no-cost clinical support provided by the U.S. Department of Defense to the potential manufacturer to conduct studies required by the U.S. Food and Drug Administration for re-licensure. The total start-up costs were annuitized over 25 years at a 5% discount rate with a $1,000,000 scrap value, resulting in an annual start-up cost of $850,321. These costs were assumed to be equally shared by the army and navy, the principal users of the vaccines.[9] Dividing the navy's share by the number of navy recruits receiving vaccines each year, the annual start-up costs were $15.13 per recruit for the seasonal option and $8.66 per recruit for the year-round option.

Total program costs include the following: vaccine production start-up, vaccine tablets, the Department of Defense Supply Center Philadelphia's distribution surcharge (55% of the manufacturer's 1997 price), and a nominal administration cost (Table 4). This administration cost represents vaccination during initial medical processing at RTC, compliance at 100%, and no adverse events associated with vaccination. The total cost of vaccination per recruit is $26.46 for the year-round option and $32.93 for the seasonal option. All costs are expressed in FY 1997 dollars, and a discount rate of 5% is used to calculate future costs.

TABLE 4
Adenovirus vaccine program costs per recruit

| Variable | Cost | Source |
|---|---|---|
| Production start-up: | | Table 3 |
| Year-round | $8.66 | |
| Seasonal | $15.13 | |
| Vaccine tablets (4 and 7) | $11.45 | 1997 Bid* |
| Distributor's surcharge | $6.30 | DSCP† |
| Vaccine administration | $0.05 | RTC‡ |
| Total | | |
| Year-round | $26.46 | |
| Seasonal | $32.93 | |

* Total cost per recruit for both adenovirus vaccines (types 4 and 7) tablets. These costs were taken from the last bid submitted to the Department of Defense for vaccine production.
† Defense Supply Center Philadelphia (DSCP), 55% surcharge for fiscal year 1997.
‡ U.S. Navy Recruit Training Command (RTC), Great Lakes, IL.

Basic training for men and women was consolidated at Great Lakes in 1994. Approximately 15–20% of recruits in any training cohort were women. Navy policy, since 1994, has been to vaccinate all recruits because men and women are similarly exposed, except that sleeping quarters are segregated. All women are tested for pregnancy at arrival at RTC. Consequently, reproductive health concerns were considered extremely minimal. All recruits received the adenovirus vaccines in the first few days of training. Therefore, the costs of vaccination were modeled for all recruits in this analysis. Potential savings from preventing adenovirus ARD in recruits who left the navy after vaccination were not modeled.

## RESULTS

The cases of ARD expected and prevented under the three vaccination policy options are presented in Table 5. Expected costs, savings, and average and incremental cost-effectiveness (C/E) ratios under the three policy options are shown in Table 6. The average C/E ratio represents cost per case of ARD prevented with the seasonal or year-round options compared to the no-vaccination option. The incremental C/E ratio represents cost per case of ARD prevented over the next most effective option. A negative C/E ratio indicates a cost-saving strategy. Vaccination by any strategy is cost-saving. Implementation of a year-round program would cost $263 per case of ARD prevented over seasonal vaccination.

**Sensitivity analysis.** To evaluate the stability of the conclusions with changes in essential variables, sensitivity analyses were conducted on three major factors: incidence of ARD, costs of illness, and program costs. Threshold values

TABLE 5
Expected morbidity under the three vaccination options

| Policy options | ARD cases expected* | Average ARD cases prevented† | Incremental ARD cases prevented‡ |
|---|---|---|---|
| No vaccination | 11,470 | – | – |
| Seasonal vaccination | 7,455 | 4,015 | – |
| Year-round vaccination | 6,915 | 4,555 | 540 |

* Annual expected Acute Respiratory Disease (ARD) cases based on the 1997 cohort of 49,079 trainees.
† Average ARD prevented represents number of cases prevented by the seasonal or year round options, compared to the no vaccination option.
‡ Incremental ARD prevented represents number of cases prevented over the next most effective strategy.

TABLE 6
Expected costs and savings under the three vaccination policies

| Policy options | Total costs | Average C/E ratio* (cost/case prevented) | Incremental C/E ratio† (cost/case prevented) |
|---|---|---|---|
| No vaccination | $9,860,000 | – | – |
| Seasonal vaccination | $7,099,000 | −$688 | −$688 |
| Year-round vaccination | $7,241,000 | −$575 | $263 |

* Average cost-effectiveness (C/E) ratio represents cost per case prevented with the seasonal or year-round options, compared to the no-vaccination option. A negative ratio indicates a cost-saving strategy.
† Incremental cost-effectiveness (C/E) ratio represents cost per case prevented over the next most effective strategy. A negative ratio indicates a cost-saving strategy.

(TV) represent the points at which changes in these variables cause vaccination to no longer be cost saving. Results of sensitivity analyses are shown in Figures 1–3. The TV are the points at which the plotted lines intersect the x-axes.

For ARD incidence, vaccine-preventable ARD was systematically lowered from the reference case of 2.6 cases per 100 person weeks (Figure 1). Vaccination was cost saving even when vaccine-preventable ARD fell to 20% of the reference case. If the seasonal vaccination option fails to prevent more than 0.53 cases per 100 person-weeks (the TV), vaccination is no longer cost saving. If the year-round option fails to prevent more than 0.94 cases per 100 person-weeks (the TV), then year-round vaccination is no longer cost saving.

For costs of illness, the weighted average cost of illness, determined to be $860 in the reference case, was systematically decreased (Figure 2). As shown, vaccination produced a cost savings even when costs of illness were one-fifth of the reference case. The TV, where the costs of illness averted by vaccination become so low that vaccination ceases to be cost-saving, were $172 or 20% of the reference case costs for the seasonal option and $285 or 33% for the year-round option.

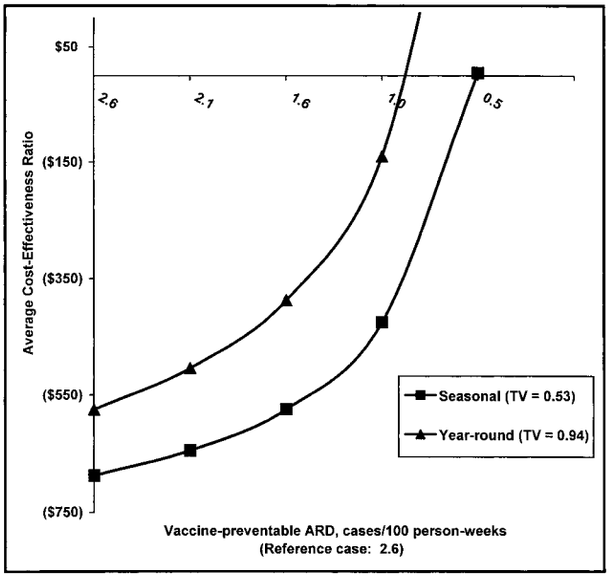


FIGURE 1. Variations in the average cost-effectiveness ratio with changes in vaccine-preventable acute respiratory disease (ARD). Vaccine-preventable ARD is lowered from the reference case of 2.6 cases per 100 person-weeks to 0.5. The threshold values (TV), the rates of vaccine-preventable ARD at which vaccination ceases to be cost-saving, occur where the plotted lines intersect the x-axis. Vaccine-preventable ARD can fall to 0.53 cases per 100 person-weeks (20% of the reference case) for the seasonal and 0.94 cases per 100 person-weeks (36% of the reference case) for the year-round policy options and vaccination will still be cost-saving.

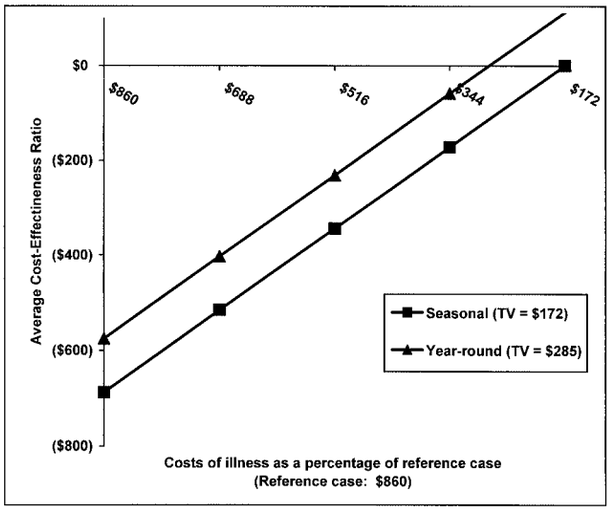


FIGURE 2. Variations in the average cost-effectiveness ratio with changes in the costs of illness. The costs of illness (medical and lost training) are systematically lowered from the average weighted cost for the reference case, $860, in 20% increments. The x-axis represents the resulting costs as the cost of illness is decreased in percentage steps. The threshold values (TV), where the average costs of illness for all recruits with vaccine-preventable ARD become so low that vaccination ceases to be cost saving, are $172 (20% of the reference case) for the seasonal policy and $285 (33% of the reference case) for the year-round options.

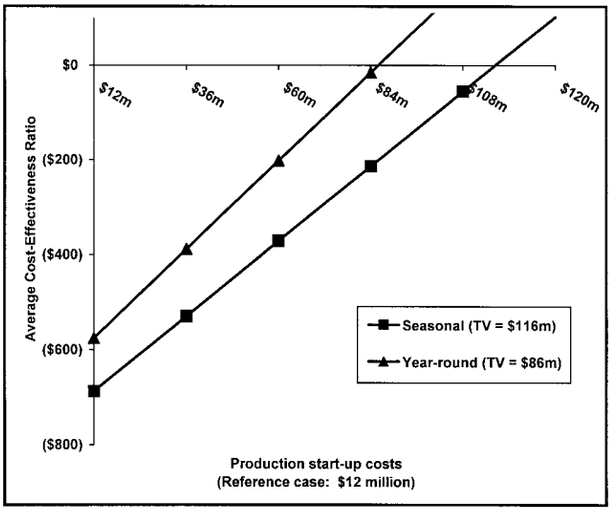


FIGURE 3. Variations in the average cost-effectiveness ratio with changes in the production start-up costs. The vaccine production start-up costs are increased from the reference case of $12 million. The threshold values (TV), where the production start-up costs become so expensive that vaccination ceases to be cost-saving, are $116 million for the seasonal policy and $86 million for the year-round policy options.

For program costs, the start-up costs were systematically increased from the reference case of $12 million (Figure 3). As depicted, the cost-saving ability of using adenovirus vaccines persists to more than nine times the start-up costs in the reference case. The TV, where the program start-up costs are so high that vaccination ceases to be cost saving, are $116 million for the seasonal and $86 million for the year-round policy options.

## DISCUSSION

Vaccination of U.S. Navy recruits, either on a seasonal or year-round basis, produced a cost savings over no vaccination. In this analysis we used recent incidence data, accounted for both ambulatory and hospitalized medical costs, and incorporated the substantial program start-up costs involved with resuming production. In some cases, our assumptions were based upon the expert opinion of healthcare providers at RTC. However, these providers were experienced in managing recruit illnesses and were in strong agreement regarding their opinion of dispositions of basic trainees with respiratory disease. Moreover, sensitivity analyses demonstrated that our conclusions were robust even under worst-case assumptions.

The vaccine-preventable ARD rate of 2.6 cases per 100 person-weeks used in this analysis is identical to that used in the recent army recruit study.[17] Both rates were arrived at independently using different methods and populations. In 1997, the U.S. Navy did not do patient-level billing or classify costs by diagnosis-related groups (DRGs). In this analysis, outpatient medical costs were based on the average per visit cost at the recruit primary care clinic since ARD-specific costs per clinic visit were not available. It is not known how closely the average clinic visit represents a visit for ARD. Similarly, inpatient costs were not available for hospitalization secondary to ARD caused by adenovirus and only total inpatient data for the general medicine service were available. It is not known how closely the occupied bed-day costs for hospitalized ARD caused by adenovirus are represented by the average occupied bed-day costs.

In the reference case, the life of the new vaccines is estimated at 25 years. It is not known when the new vaccines would be available even if a new manufacturer were identified today. This potential delay is not modeled. Costs associated with an outbreak, which would include costs of investigation and costs of treating co-morbid illnesses, are not modeled, but would increase the cost-savings of vaccination. The effect of adenovirus-related ARD outbreaks on military readiness cannot be modeled. Military readiness is the preparedness of service men and women to be able to perform their mission at all times. Significant disruptions in basic training, such as a large and persistent ARD outbreak, would interfere with the flow of recruit graduates to other training programs and to the naval fleets, which both rely on a stream of new, trained sailors. Outbreaks could be severe enough to close down a training camp. During times of military mobilization, outbreaks would profoundly interrupt readiness.

The current U.S. military medical community has not experienced frequent and sustained outbreaks of ARD. It is probable that significant ARD outbreaks in military basic training camps will produce patient loads that exceed the resource capacity of the military medical system. This situation could necessitate increasing the medical provider support at basic training centers and contracting with non-military medical treatment facilities during outbreaks. These actions could significantly increase the medical care costs for basic trainees and place an unexpected workload on proximate non-military healthcare organizations.

The military recruit setting affords many advantages for studying the cost-effectiveness of vaccination against adenovirus. For example, both illness- and program-associated costs are identifiable and available. However, this cost-effectiveness analysis should be applicable to other settings. Adenovirus-related diseases are common in nursing homes and day care settings, among immunocompromised people, and in individuals living in close contact.[18–21,25] Increased availability of diagnostic tests for adenoviruses may reveal greater morbidity from these agents than previously considered.[26,27]

One factor that has been associated with the delay in finding a new manufacturer is a market that is perceived to be limited to the U.S. military. A high rate of adenovirus infections has recently been reported in Finnish military conscripts.[28] Additionally, in 1994, Kajon and Wadell reported that little was known about the clinical impact of adenovirus type 7 associated respiratory disease in South America.[29] New molecular diagnostic techniques, coupled with an awareness of the potential for adenovirus-associated diseases in the military, other populations living in close contact, the immunocompromised, and infants and young children may identify new markets for the traditional adenovirus vaccines or for a new polyvalent vaccine. Potential users of adenovirus vaccines should find this analysis useful in evaluating their options.

Reacquiring and using adenovirus vaccines seasonally or year-round will save money for the navy and avert suffering. The year-round option would be preferable because more ARD cases would be prevented, and it would be easier to administer since the program would not have to be stopped and restarted each year. Additionally, the incremental cost of vaccinating year-round versus only seasonally is minimal.

This is the second cost-effectiveness analysis of adenovirus vaccines, types 4 and 7. This study complements a recent army study by providing strong support for reacquiring and using the adenovirus vaccines.[17] Vaccine reacquisition should be expedited since delay will only serve to increase costs, prolong suffering, and hinder readiness.

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