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Is Appendicitis a Viral Disease?

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Abbreviations: NHDS-National Hospital Discharge Survey,

Running Head: Appendicitis and Viral Illness

Abstract

Introduction: What causes appendicitis is not known; however, studies have suggested a relationship between viral diseases and appendicitis. Building on evidence of cyclic patterns of appendicitis with apparent outbreaks consistent with an infectious etiology, we undertook an epidemiologic study of possible relationships between population rates of appendicitis and several infectious diseases.

Methods: ICD-9-CM discharge diagnosis codes of the National Hospital Discharge Survey (NHDS) were queried from 1970-2005 to identify admissions for appendicitis, influenza, rotavirus and enteric infections. Cointegration analysis of time series data was used to determine if the disease incidence trends for these various disease entities varied over time together.

Results: Rates of influenza and nonperforating appendicitis declined progressively from the late 1970s to1995 and rose thereafter, but influenza rates exhibited more distinct seasonal variation than appendicitis rates. Rotavirus infection showed no association with the incidence of nonperforating appendicitis. Perforating appendicitis showed a dissimilar trend to both nonperforating appendicitis and viral infection. Hospital admissions for enteric infections have substantially increased over the years but are not related to appendicitis cases.

Conclusion: Neither influenza nor rotavirus are likely proximate causes of appendicitis given the lack of a seasonal relationship between these disease entities. However, because of significant cointegration between the annual incidence rates of influenza and nonperforated appendicitis, it is possible that these diseases share common etiologic determinates, pathogenetic mechanisms, or environmental factors that similarly affect their incidence.

Introduction

Appendectomy is the most common emergency general surgical procedure with more than 250,000 cases performed annually in the United States (1). Despite its ubiquitous nature, why appendicitis occurs remains unknown. Several theories exist attempting to explain this disease's cause. At the heart of most appendicitis theories is luminal obstruction. The appendix becomes obstructed either by a fecolith or enlarged lymphoid tissues resulting in high luminal pressures that compromise mucosal integrity leading to infection. Infections are thought to cause appendicitis (2) by stimulating lymphoid hyperplasia which obstructs the appendix. Many viral disorders are associated with lymph node enlargement, which, in turn, can obstruct the appendiceal lumen. Viral infections could cause mucosal ulcerations that could result in subsequent bacterial infection of the appendix (3;4). Appendicitis has been associated with a viral prodrome compatible with a viral illness preceding the first symptoms of appendicitis. Early epidemiologic investigations found that appendicitis was more frequent during months when respiratory infections were present (5).

Several epidemiologic patterns suggest a link between appendicitis and infections. Appendicitis outbreaks have been described. In one small Texas town, a significant cluster of cases was described over a very short period of time suggesting an infectious etiology (6). Larger scale investigations from Sweden revealed that the disease has a propensity to cluster in time and location (7). A 35-year epidemiologic investigation from our group uncovered apparent appendicitis outbreaks in the U.S. (8).

To develop further evidence possibly linking specific infectious etiologies with appendicitis, we analyzed a national sample of hospital discharge data for associations between

rates of appendicitis and certain candidate infectious diseases including influenza, rotavirus and other intestinal infections.

Methods

The annual National Hospital Discharge Survey (NHDS) databases for the years 1970-2005 were acquired from the Centers for Disease Control (CDC) ((http://www.cdc.gov/nchs/about/major/hdasd/nhds.htm) and the Inter-University Consortium for Political and Social Research web sites (http://www.icpsr.umich.edu/index-medium.html). The NHDS is the principal database used by the U.S. Government for monitoring hospital utilization. Each year approximately 300,000-hospital discharges are selected for the NHDS from the 35,000,000 total discharges nationally. The NHDS uses a complex, multistage design to ensure that the database is representative of the U.S. hospitalized population. Using U.S. Census information, the CDC provides statistical weighting factors for each patient entry in the NHDS database so that incidence and prevalence estimates of hospitalized disease can be made for the entire U.S. population. These weighting factors were used to determine the national prevalence of appendicitis. The estimated U.S. population for each year of the study was obtained from the U.S. Census Bureau as accessed through the CDC web site (http://wonder.cdc.gov/population.html). Disease incidence per geographic region was determined in regions as defined by in the NHDS.

The NHDS converted from ICDA-8 encoding to ICD-9 in 1979. Before 1979, codes for the various forms of appendicitis diagnoses were the same in the ICDA-8 system as in the ICD-9. The same was true for enteric infections. For cases in the database occurring from 1970 through 1978 procedures were identified as: drainage of appendiceal abscess (410),

appendectomy (411), appendicostomy (412), closure of appendiceal fistula (413) and other appendectomy (419). Hospital admissions for influenza were identified by diagnostic codes ranging from 470 to 474. Abdominal pain was encoded with 785.5.

Beginning in 1979, the ICD-9 coding system was implemented. Appendicitis was defined as a patient having any of the following 7 NHDS discharge diagnostic codes: 540.9 (Acute appendicitis), 541.0 (Appendicitis-Unqualified), 542.0 (Other appendicitis), 543.0 (Other diseases of the appendix), 543.0 (Unspecified disease of the appendix). Perforated appendicitis (540.0) or Appendiceal abscess (540.1) were aggregated into a single category called "perforated appendicitis". Nonperforated appendicitis was defined as having any appendicitis diagnostic code except for 540.0 or 540.1. Procedures codes used were: Appendectomy (47.0), laparoscopic appendectomy (47.01), other appendectomy (47.09), incidental appendectomy (47.1), laparoscopic incidental appendectomy (47.11), other incidental appendectomy (47.19), drainage of an appendiceal abscess (47.2), "other" appendiceal operation (47.9), appendicostomy (47.91), closure of an appendiceal fistula (47.92), and other appendiceal operation (47.99). Incidental appendectomies were identified if there were any of the following 3 procedure codes: 47.1, 47.11 or 47.19. Nonincidental appendectomies were defined as having any appendectomy procedure codes excluding those for incidental procedures. A negative appendectomy was defined as having any procedure code: 47.0, 47.01 or 47.09 without any diagnostic coding for appendicitis.

A diagnosis of any type of intestinal infectious disease was established if the diagnostic codes ranged from 008.00 to 008.89. Of these, a subset of intestinal viral diseases (ICD-9 008.6X) was assessed in greater detail. Only rotavirus (008.61) had sufficient numbers of admissions to be analyzed. A specific Rotavirus ICD-9-CM diagnostic code was introduced in 1993. There were too few cases to assess on a monthly basis. For that reason, rotavirus

admissions were aggregated into 3-month quarters. All other data were analyzed by monthly or annual aggregations of the disease incidences.

Disease incidence estimates can be affected by coding changes. When a major change in disease classification occurs, disease entities may be grouped differently, they may have new names or definitions that cause diseases to be classified in other sections of the coding schema than before, or the definitions for a disease may change resulting in its classification into new areas. When this occurs, plotting of the disease incidence over time will have discontinuities at the years in which the coding change was implemented. If the discontinuity is obvious and the trends on either side of the break are reasonably linear, then correction factors can be determined. Correction factors are calculated by dividing the disease incidence ratio for the years before the new code introduction by that for the years after the new codes were used. The resultant ratio is known as the *comparability ratio*. The ICD system is assessed for this phenomenon with each major update and comparability ratios published. Of the disease entities we studied, only intestinal infections had a significant discontinuity when ICDA-8 was converted to ICD-9 in 1979. We applied a correction factor of 5.49 to the pre-1978 data for intestinal infections, removing the observed 1978-1979/ ICD8 to ICD9 coding change-induced disease incidence discontinuity (9-11).

Similarity in the long-term trending or wandering behavior of two disease rates was tested using the technique of cointegration analysis (12) which has been widely used in econometric time series analysis. See the Appendix for a discussion of cointegration testing. The analysis was based on an autoregressive modeling of the disease rate time series. In this setting two disease rates were considered to be cointegrated (varying together over time) if each rate was unit-root nonstationary and the processes showed significant indication that they were

"tethered together[1]" over time as measured by cointegration analysis. We tested the null hypothesis that the time series had a unit root and, therefore, was nonstationary using the Augmented Dickey-Fuller test (13;14). Rejecting the null hypothesis ($P \leq 0.05$) supports stationarity; whereas, failing to reject the null hypothesis ($P > 0.05$) supports unit root nonstationarity. Based on the evidence of a unit root, the next step was to test for a cointegrating relationship between nonperforated appendicitis and influenza, both nationally and regionally, We considered panel cointegration tests designed to increase the power of detecting cointegration when cross-section data (i.e. regional data in our case) are available. Panel cointegration tests proposed by Pedroni (15;16) and by Maddala and Wu (17) were also applied. All time series computations in this paper were done using the econometrics software package EVIEWS 6 © (1997 – 2007, Quantitative Micro Software, LLC, Irvine, California).

[1] When we say that the co-integrated series are "tethered together" we are implying that, although the individual series themselves have random walk characteristics, a linear combination of them, a*appendicitis + b*influenza, behaves like a stationary time series. That is, the two non-stationary time series never wander too far apart.

Results

Both nonperforating appendicitis and influenza were declining in overall incidence until 1995. After that, both diseases' overall incidence has been increasing (Figure 1). This "U"-shaped curve was not observed for perforating appendicitis which has exhibited a slowly rising incidence over the years. Influenza exhibited a sharp increase in incidence in the winter months with the disease rarely observed during the remaining months of the year (Figure 2). Appendicitis occurs throughout the year with a slight tendency to occur more frequently in the summer months. Intestinal infections also are observed throughout the year but have a propensity to occur in the winter months. Influenza admissions occur mostly between December and February and rarely occur at other times of the year.

Although the strong winter presence of influenza was not observed with appendicitis, the overall annual incidence for these diseases appears to wander in time together (Figure 3). The results of unit root tests for the national and regional data are shown in Tables 1 and 2 where it can be seen that the national data on nonperforated appendicitis and influenza as well as the regional data on both disease rates show evidence of a unit root since the null hypothesis of a unit rate is not rejected in any of the cases. Because of the small sample size of our overall analysis (i.e. 35 data points, one representing each years disease incidence), we also examined the consistency of the appendicitis-influenza disease incidence relationship in the 4 major U.S. regions. In Figure 4 we show normalized overlays of the incidence rates for nonperforated appendicitis and influenza for the four regions. From Table 1 it can be seen that the Augmented Dickey Fuller test shows evidence of a unit root for both disease incidence rates in each region. Table 2 shows that both the trace and maximum-eigenvalue tests indicate cointegration between nonperforated appendicitis and influenza both nationally and regionally. Panel cointegration tests

proposed by Pedroni (15;16) and by Maddala and Wu (17) were also applied, and the results (not reported here) were consistent with those previously obtained in the region by region analysis using the Johansen tests. That is, the panel results, like these Johansen test results, were supportive of cointegration in all the major regions of the United States.

Figure 5 shows the relationship between appendicitis and intestinal rotavirus infection. ICD-specific codes for rotavirus were only available after 1993. Because of the relatively low rotavirus incidence, data were aggregated into quarters rather than months. Rotavirus infection peaked in the winter months, but there was no obvious correlation between rotavirus infection and appendicitis, and the Dickey-Fuller tests showed no evidence of cointegration (data not shown).

Unlike the secular trends in nonperforated appendectomy rates, intestinal infections have been steadily increasing in incidence (Figure 6). These infections have peak incidence in about March of any given year (Figure 2). The overall and peak admission rates in each year began increasing in 1989. As with influenza, the annual peak incidence for hospital admissions attributable to rotavirus infections occurs in March. Whereas influenza admissions are unusual in the non-winter months, intestinal infection admission rates are observed throughout the year. Of interest is the tendency for the within-year variation to dramatically increase in approximately 1989. Investigation showed that this was not due to a coding change, and we believe that the source of the increased variation should be further investigated

Discussion

What causes appendicitis remains a mystery. Our previous analysis of appendicitis time trends demonstrated that the increasing appendicitis rates observed after 1995 paralleled the rise, and could possibly be related to, increased utilization of CT scanning and laparoscopic surgery (8). However, the year-to-year variation in the nonperforating appendicitis incidence and apparent disease outbreaks suggested that appendicitis is caused by an infectious agent (8). The current study was performed to further investigate this possibility. We did find that there were epidemiologic similarities between the rates of nonperforating appendicitis and influenza. The annual incidence rates for both diseases progressively fell in parallel over the two and one half decades from 1970 until 1995 and thereafter both began to rise in parallel. Moreover, time series analysis demonstrated statistically significant cointegration of the wanderings of the annual incidence rates of the two diseases. Appendicitis shared no common pattern with intestinal infections or with documented rotavirus infections. These findings suggest that nonperforating appendicitis may be caused by an infectious agent or other process related to influenza virus infection; however, since influenza has a winter peak that is not observed with nonperforating appendicitis, it an unlikely to be a proximate cause. These findings also suggest that our previously observed parallel rise in the nonperforating appendicitis after 1995 and in use of laparoscopic appendectomy and/or CT scanning was coincidental and not causative.

Further evidence for the likelihood that appendicitis is caused by an infectious disease is the observation that the disease occurs in clusters. Several well defined disease outbreaks have been identified (6;18-20) in addition to our previously described pattern of disease outbreaks (8). Seasonal changes in appendicitis have also been described (21), however, we found that although

there was a tendency for appendicitis to be more common in the summer months, the seasonal variation was modest, consistent with previous reports (22).

The incidence of perforated appendicitis did not correlate with nonperforating appendicitis or with the other infectious diseases we evaluated, suggesting that perforated appendicitis has causative factors that are more complex than the simple delay in treating acute appendicitis. This has important clinical ramifications since appendectomy is generally performed as an emergency operation for fear of causing a perforation if treatment is delayed. Our epidemiologic findings suggest that patients who have perforated appendicitis have a different disease entity than those with nonperforating disease

Intestinal infections have been increasing with time. In 1989 there was a marked upsurge in their annual peak incidence. These findings appear to contradict a theory explaining changes in the incidence of appendicitis called the hygiene hypothesis. The rising appendicitis rate observed in the early 20th century paralleled an improvement in living conditions with fewer intestinal infections (23;24). This observation led to the "hygiene hypothesis" wherein it was posited that better hygiene caused less exposure to infectious agents reducing the immune system's ability to prevent appendicitis (25). Up to 1995 our findings were consistent with this hypothesis since increasing numbers of persons with intestinal infection could result in enhanced immunity to other gastrointestinal infections such as appendicitis. That both intestinal infections and nonperforating appendicitis appear to have increased in incidence for the past decade mitigates against the hygiene hypothesis.

Our observation that intestinal infections are on the rise is interesting. One could hypothesize that increased use of potent antibiotics has changed the intestinal flora or that increased use of potent inhibitors of gastric acid secretion has reduced the pH barrier to intestinal

infection. The intestinal infections resulting in hospitalization might be due to resistant strains of bacteria or from increased susceptibility to unidentified organisms that have become more pathogenic.

Viral illness has been implicated by some researchers as the cause for appendicitis. Viral infection of the appendix could cause mucosal ulceration followed by secondary bacterial infection of the appendix. Alternatively, viral disease could result in lymphoid hyperplasia of the appendix with resultant obstruction and mucosal injury followed by bacterial infection. Several viral agents have been hypothesized to cause appendicitis. Coxsackie has been associated with cecal inflammation and periappendiceal lymphoid hyperplasia (26;27). Animal studies have shown that Coxsackie infection can result in an appendicitis-like syndrome (28;29). Lymph nodes and serum obtained from appendicitis patients have shown evidence for simultaneous adenovirus infection (30-32). Measles virus and cytomegalovirus (CMV) have also been associated with appendicitis (33-35) . Bacterial infection with pathogens such as *Yersinia enterocolitica* has been implicated in appendicitis pathogenesis (36). One viral illness that we could investigate was rotavirus since the NHDS database had sufficient numbers of these cases allowing for a comparison between rotavirus and appendicitis admissions. We found no correlation for these disease entities suggesting that rotavirus is not a cause of appendicitis.

Most theories regarding the underlying causes of appendicitis rely on the notion that the appendix becomes obstructed. This line of thinking dates back to Reginald Fitz's first description of appendicitis wherein he had observed fecoliths on autopsies and assumed that they contributed to the pathogenesis of this disease (37). Animal studies have shown that artificially elevating appendiceal luminal pressure can result in appendicitis (38). Although an attractive hypothesis, experimental evidence suggests that the role of fecoliths as a cause for appendicitis is limited

(39). Intraoperative intraluminal pressure measurements revealed that pressures were normal in acute appendicitis and only became elevated in late stage disease suggesting that obstruction occurs as inflammation progresses (40). Although fecoliths can be seen in appendicitis specimens, they only occur rarely (41). Factors more complex than simple obstruction must contribute to appendicitis pathogenesis.

In conclusion, although influenza and nonperforating appendicitis have dissimilar seasonal peak incidences, parallel year-to-year peak incidence trends suggest a viral etiology for appendicitis. No association was found between the intestinal infections, rotavirus, and appendicitis. Further work more precisely identifying infectious agents in cases of appendicitis is necessary to identify potential causative agents.

Table 1. Augmented Dickey-Fuller test statistic, ADF_τ, with the lag order of the Dickey-Fuller test equation and p-values (one-sided) taken from MacKinnon (42). P-values > 0.05 suggest that the time series are nonstationary due to a unit root.

		ADF_τ	Order*	p-value
National	Appendicitis	-1.9050	0	.3263
	Influenza	-1.6286	2	.4571
Northeast	Appendicitis	-1.5173	0	.5133
	Influenza	-2.1284	1	.2353
Midwest	Appendicitis	-1.5384	1	.5024
	Influenza	-1.5289	1	.5071
South	Appendicitis	-2.2195	2	.2035
	Influenza	-1.0792	1	.7126
West	Appendicitis	-1.6510	2	.4460
	Influenza	-1.7845	2	.3813

* The lag order of the Dickey-Fuller test was determined by successive deletion of lags until the last augmenting term is statistically significant at the 5% level. The choice of the order of the augmenting terms is important for insuring that the test statistics have the correct size and are as powerful as possible for detecting the alternative hypothesis of stationarity.

Table 2. Johansen Multiple Equation Tests for Cointegration. P-values (one-sided) found in the parenthesis test the null hypothesis of no cointegrating relationship between influenza and nonperforating appendicitis incidence versus the alternative hypothesis of cointegration between the series. Therefore, p-values <0.05 indicate cointegration, i.e. that the disease incidences are "tethered together" over time. These reported p-values were obtained from MacKinnon, Huag, and Michelis (43).

	Trace Test	Maximum Eigenvalue Test	Order*
National	44.4338	38.2385	0
	(0.0000)	(0.0000)	
Northeast	41.5064	38.8133	0
	(0.0000)	(0.0000)	
Midwest	21.2618	15.5759	1
	(0.0358)	(0.0566)	
South	32.5830	27.2217	0
	(0.0006)	(0.0006)	
West	28.7620	22.2073	0
	(0.0026)	(0.0044)	

* The order of the lagged differences in the Johansen Error Correction Model (ECM) multivariate test equation was determined by first choosing the optimal lag length for a levels vector autoregression (VAR) on the data and then reducing that optimal lag length by one to accommodate the differencing imposed by the Johansen ECM equation. The optimal lag length of the levels VAR was chosen by minimizing the Schwartz Bayesian goodness-of-fit criteria. The lag length is again important for assuring that the test statistics have the correct size and are as powerful as possible for potentially detecting the relevance of alternative hypotheses. Given the sample size of our data, we choose the Schwartz criterion because it tends to choose more parsimonious models.

Figure 1. Monthly hospital admission rates for perforated and nonperforated appendicitis and influenza from 1970 to 2005. Data are presented as the number of hospital admissions per month per 10,000 U.S. population. The left axis represents the scale for influenza rates and the right scale for appendicitis. Influenza occurs almost exclusively in the winter months; whereas, appendicitis is present throughout the year.

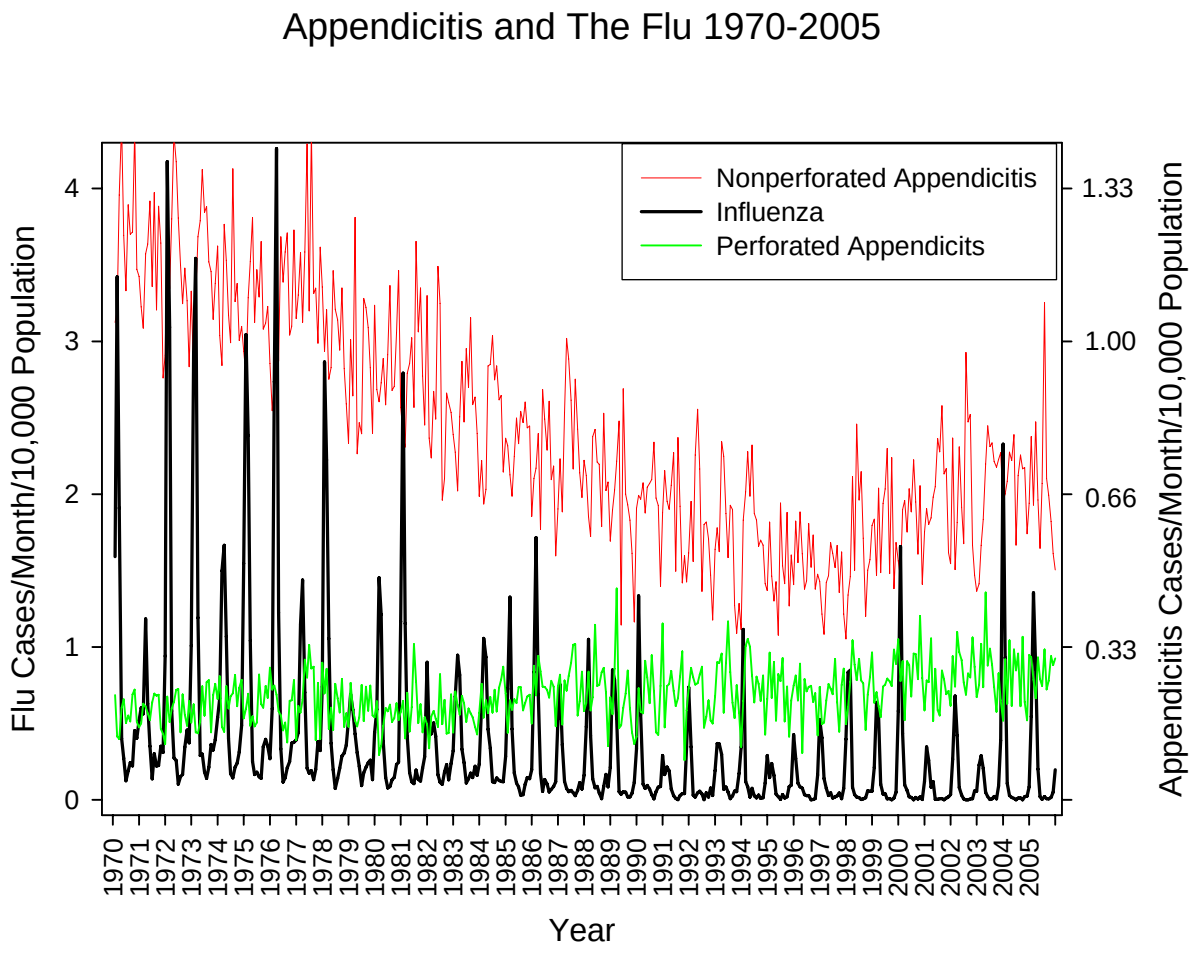


Figure 2. Histograms of the monthly incidence rates of nonperforating and perforating appendicitis, intestinal infections and influenza. There is a weak tendency for appendicitis to be more common in the summer months, Intestinal infections are more common in the winter, and influenza is clearly a winter disease. Data are presented as the average for any given month in all the years between 1970 and 2005. Error bars are too small to be seen because of the very large sample sizes.

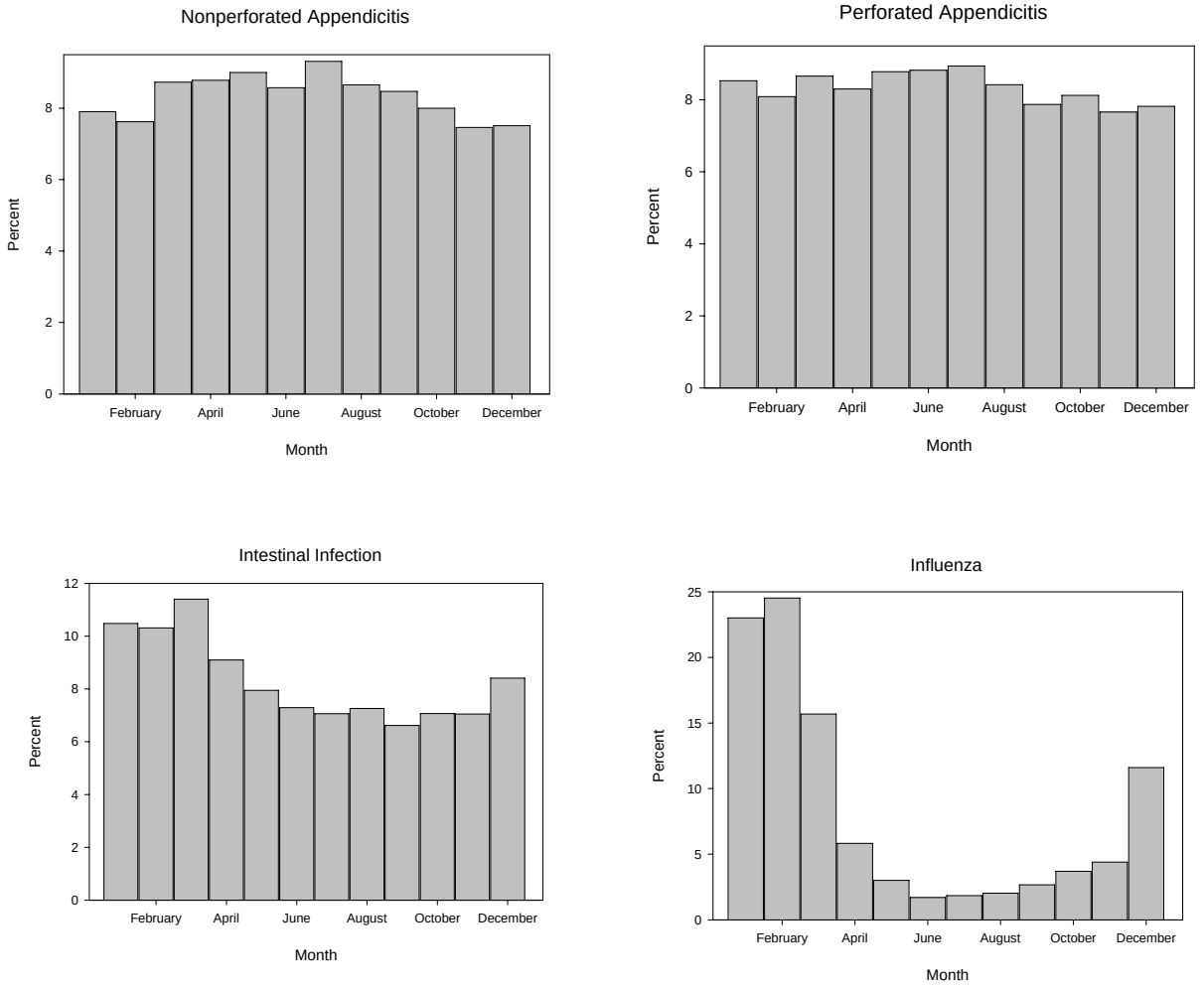
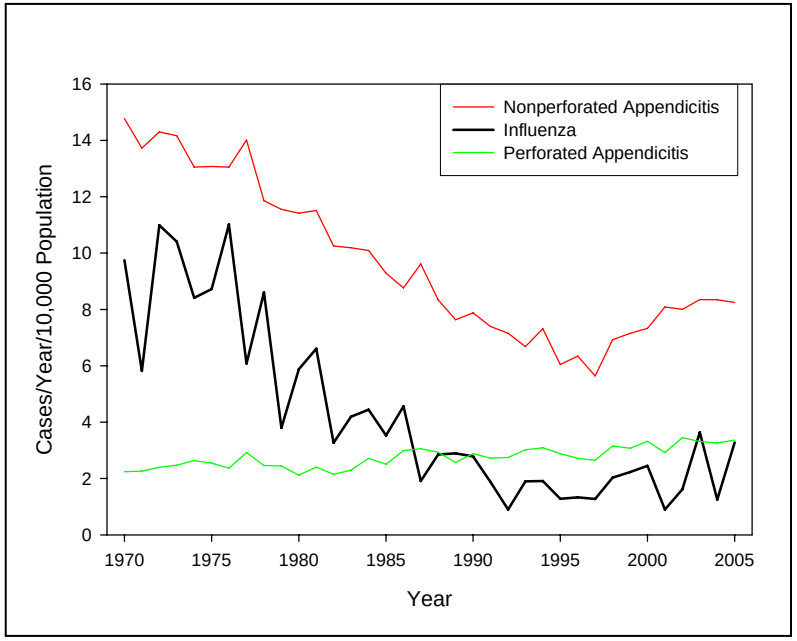


Figure 3. Cointegration analysis of appendicitis and influenza rates. Panel A shows that both the nonperforated and influenza rates are nonstationary over time. Panel B shows the residual rate (annual non-perforated Appendicitis rate minus 0.788 times the annual Influenza rate) as determined by applying ordinary least squares to the co-integrating equation app = a + b*flu +residual. This provides the consistent estimates of a = 6.27 and b = 0.788.

A



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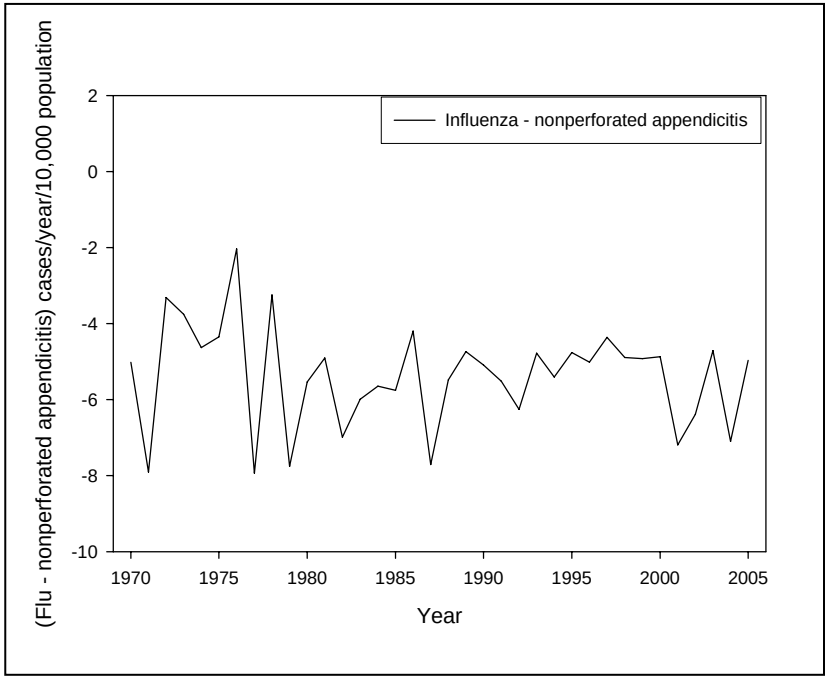


Figure 4. Nonperforating appendicitis and influenza in the 4 major regions of the United States. To facilitate comparison of the rate at which these disease change over time, the data were normalized to a mean of zero and standard deviation of one.

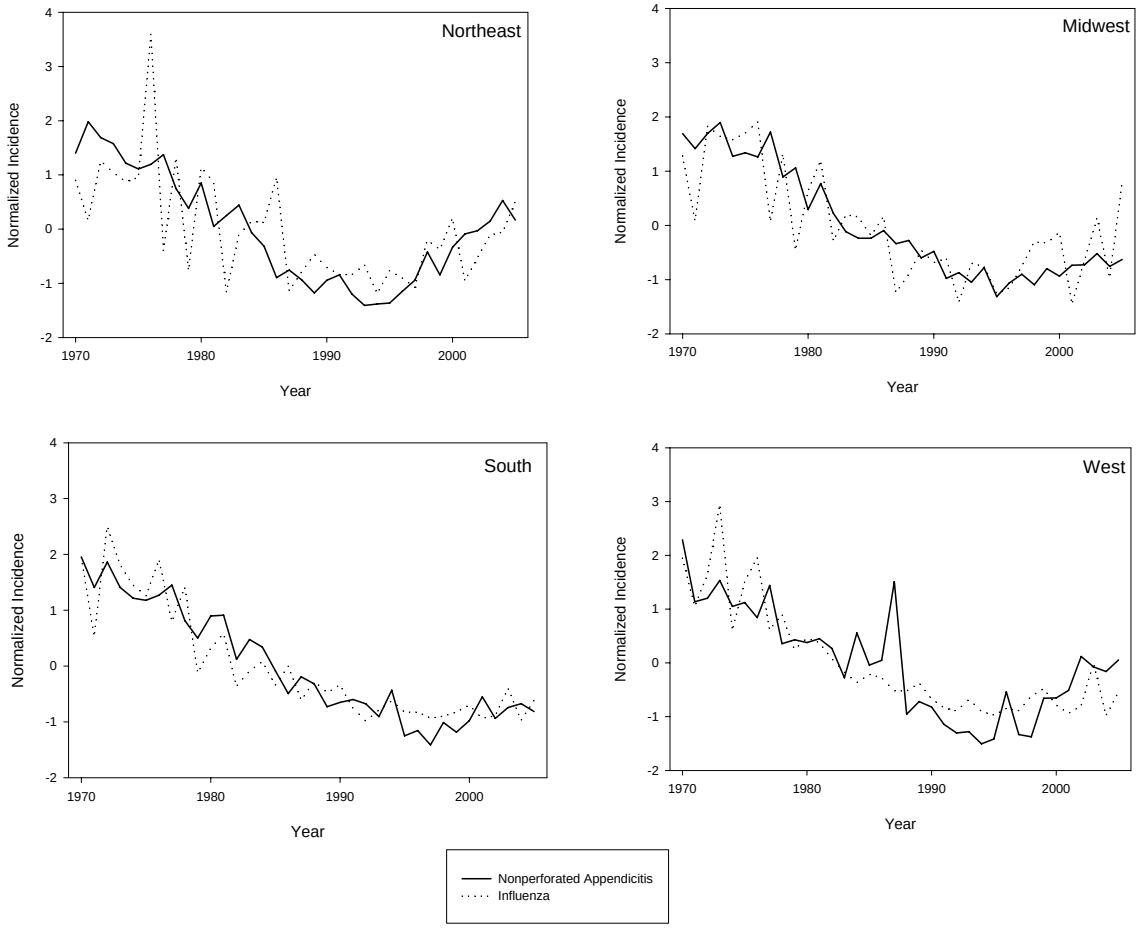


Figure 5. Quarterly rates of appendicitis and rotavirus Infection. Data are reported in terms of the number of hospital admissions per 3-month quarter per 10,000 U.S. population. No correlation was observed between rotavirus infections and appendicitis rates.

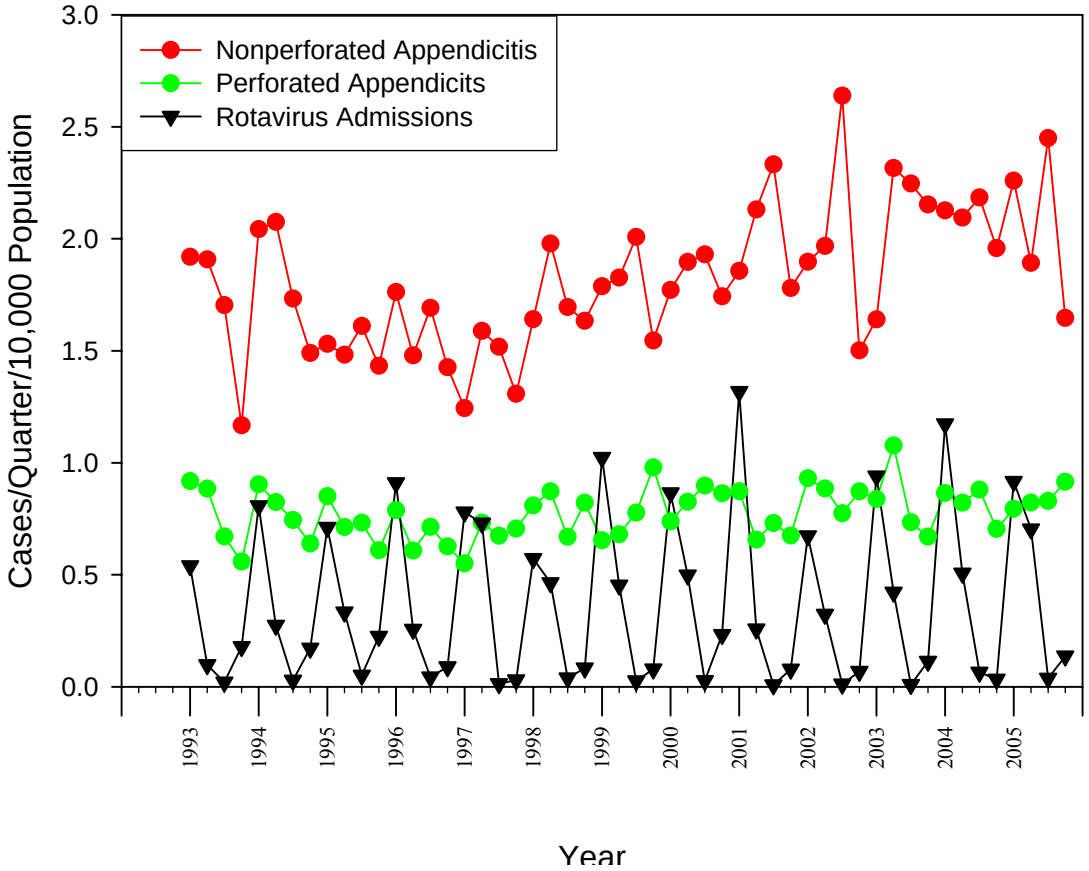
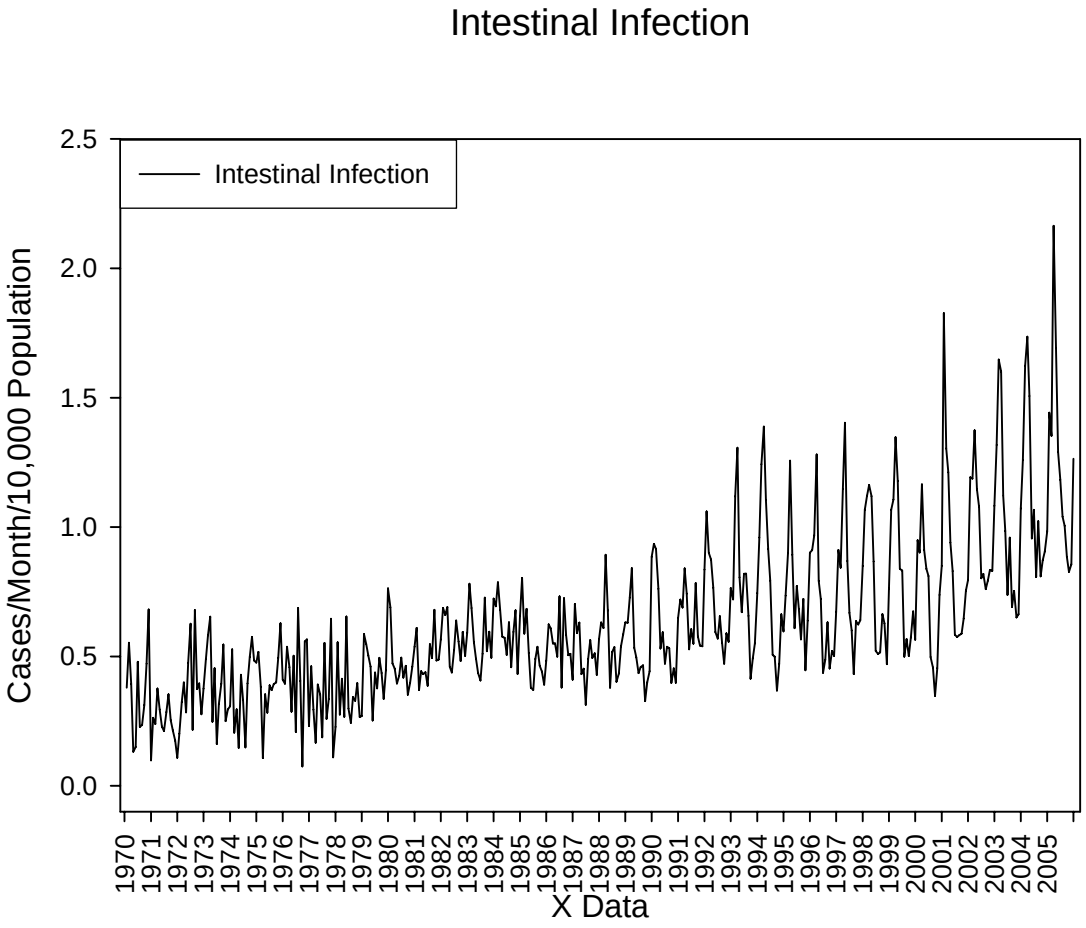


Figure 6. Montly rates of intestinal infections. Intestinal infections have been increasing in frequency over the years with substantial increases in peak incidence occurring after 1989.



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APPENDIX

A popular model for describing the behavior of time series data is the autoregressive model of order one [AR(1)] given by

$$X_t - \mu = \varphi(X_{t-1} - \mu) + w_t \qquad (1)$$

which states that the value of some phenomenon X at time t is related to the value for the same phenomenon at the time point preceding it, X_{t-1} plus a white noise w_t. The coefficient φ determines the strength of this relationship. For example, when $|\varphi| < 1$ the process is said to be stationary in that realizations (i.e. samples) from such a time series are in equilibrium about a constant mean level μ Thus, AR(1) time series realizations for which $|\varphi| < 1$ will tend to move back and forth across a mean level (and are called fast turning) . However, when $\varphi = 1$ the process is nonstationary and realizations tend to wander without an attraction for a mean level (and are called slow turning). See Appendix Figure 1. The time series model in (1) is sometimes rewritten as $X_t - \mu - \varphi(X_{t-1} - \mu) = w_t$. By replacing $X_{t-j} - \mu$ by r^j on the left-hand side of this equation (where r is a real number) and setting the resulting polynomial equal to zero, we obtain the so-called characteristic equation $1 - \varphi r = 0$. The root of this simple first-order polynomial equation is $r = 1/\varphi$. Before proceeding to discussion of the more general AR(p) model, we note that the AR(1) model is stationary if $|r| > 1$. Note also that the process is nonstationary if $r = 1$, i.e. if the characteristic equation has a "unit root".

An extension of the AR(1) model that is a widely used model for time series data such as the disease rate data in this paper is the autoregressive model of order p [AR(p)] which for the process X_t has the form:

$$X_t - \mu = \varphi_1(X_{t-1} - \mu) + \cdots + \varphi_p(X_{t-p} - \mu) + w_t \qquad (2)$$

where X_t specifies the variable of interest evaluated at time *t*, μ is the mean of X_t, and again w_t is white noise. Medical scientists are familiar with the concept of statistical regression analysis where an outcome variable is predicted by a set of explanatory variables. For time series analysis, the regression is performed on a series of data points that precedes the "outcome variable", i.e. X_t is predicted by the data points X_{t-1} to X_{t-p} that occur before X_t in the series, a set of multiplying coefficients $\varphi_1, \ldots, \varphi_p$, and a noise component w_t. See (44) for a discussion of autoregressive processes. We use autoregressive models to describe the behavior of nonperforated appendicitis and influenza incidence rates. Thus, (2) expresses $X_t - \mu$ as a linear combination of observations at the previous *p* time periods plus a noise component w_t which is assumed to be uncorrelated (zero mean white noise). In the following we will assume without loss of generality that $\mu = 0$. As in the case of the AR(1), by rewriting (2) as $X_t - \mu - \varphi_1(X_{t-1} - \mu) - \cdots - \varphi_p(X_{t-p} - \mu) = w_t$, and replacing $X_{t-j} - \mu$ by r^j on the left-hand side of this equation (where *r* is a complex number) and setting the resulting polynomial equal to zero, we obtain the characteristic equation which is defined as:

$$1 - \varphi_1 r - \varphi_2 r^2 - \cdots - \varphi_p r^p = 0 \quad . \qquad (3)$$

From mathematical theory of equations it is known that the roots of this polynomial equation are either real or appear as complex conjugate pairs. In either case, an important result is the fact that the AR(p) process given in (2) is stationary if and only if the roots of the equation in (3) are such that $|r| > 1$ where $|\cdot|$ denotes the absolute value or modulus of the complex number *r*. If (3)

has one or more roots *r* such that *r* = 1, then the model in (2) is said to be a "unit root" process. Time series realizations from such processes are characterized by random trending behavior such as that visible in Appendix Figure 1 and Manuscript Figure 4 for the nonperforated appendicitis and influenza disease rates. The autoregressive process in (2) can be rewritten as

$$\Delta X_t = \alpha + \tau X_{t-1} + \beta_2 \Delta X_{t-1} + \cdots + \beta_p \Delta X_{t-p+1} + w_t \qquad (4)$$

where Δ is the difference operator specified by $\Delta X_{t-j} = X_{t-j} - X_{t-j-1}$ and the β_j's are determined from the φ_j's. Trends are removed form the data by the process of differencing. The model in (4) is said to have $\ell = p$ -1 augmenting terms (i.e. the number of data points prior to the data point at time *t* incorporated in the autoregression process). The model in (4) can be used to test for a unit root using the Augmented Dickey Fuller test (13;14;45). Specifically, if $\tau = 0$, the model in (4) has a unit root, and thus, we test the null hypothesis $H_0 : \tau = 0$ versus the alternative hypothesis $H_1 : \tau < 0$ (which implies that X_t is stationary). The lag order ℓ in (4) is selected to be sufficiently large to insure that the errors w_t are uncorrelated. In Table 1 the lag order was selected by successive deletion of lags until the last augmenting term is statistically significant at the 5% level. The Augmented Dickey-Fuller t test statistic given in Table 1 is based on the ordinary least squares estimate of τ, say $\hat{\tau}$, and its standard error $se(\hat{\tau})$, resulting in $ADF_\tau = \hat{\tau} / se(\hat{\tau})$. See Dickey and Fuller (13). It is well known that the sampling distribution of the Dickey-Fuller *t*-statistic, ADF_τ, does not follow the usual *t*-distribution or, even asymptotically, the normal distribution. Instead its sampling distribution is heavily skewed to

the left and is not symmetric around zero. Therefore, *p*-values for the *ADF* test have been calculated and are derived from the tables from MacKinnon (42).

The annual incidence rates in Figures 4 for nonperforated appendicitis and influenza from 1970-2005 both have a slow-turning, random wandering appearance typical of unit root processes. The interesting feature is that they seem to be "moving together" so it is of interest to test whether there is a significant relationship between the two incidence rates. When investigating the statistical relationship between two time series, X_t and Y_t, such as the nonperforated appendicitis and influenza incidence rates, one might consider the regression equation

$$Y_t = \beta_0 + \beta_1 X_t + \varepsilon_t \quad . \qquad (5)$$

However, Granger and Newbold (1974) and Phillips (1986) have shown that when X_t and Y_t have unit roots and are independent, the traditional regression, (5), will have a high probability of concluding a statistically significant relationship when, in fact, there is none. Engle and Granger (46) coined the word cointegration to describe the situation in which the unit root (i.e. nonstationary, slow turning) processes X_t and Y_t are sufficiently "tethered together" that the residuals of the regression (5) are stationary (i.e. do not have a unit root). The cointegration concept has been used extensively in the econometrics literature to analyze topics in international trade, e.g. purchase-power parity, in finance, e.g. the term structure of interest rates, and in macroeconomics, e.g. the analysis of the money supply and the price level, among many other applications.

A number of cointegration tests have been developed for assessing the relationship

between X_t and Y_t in this setting that are based on a replacing the oversimplified regression model in (5) with an "Error Correction Form"

$$\Delta Y_t = \alpha_0 + \alpha_1 \Delta Y_{t-1} + \cdots + \alpha_p \Delta Y_{t-p} + \gamma_1 \Delta X_{t-1} + \cdots + \gamma_p X_{t-p} + \delta_1 \varepsilon_{t-1} + u_t \quad (5)$$

$$\Delta X_t = \theta_0 + \theta_1 \Delta X_{t-1} + \cdots + \theta_P \Delta X_{t-p} + \psi_1 \Delta Y_{t-1} + \cdots + \psi_p \Delta Y_{t-p} + \delta_2 \varepsilon_{t-1} + \nu_t \quad (6)$$

where $\varepsilon_{t-1} = Y_{t-1} - \beta_0 - \beta_1 X_{t-1}$ is the previous period's "disequilibrium error" in the cointegrating relationship $Y_t = \beta_0 + \beta_1 X_t + \varepsilon_t$ between the unit root processes Y_t and X_t. The fact that a cointegrating relationship between two unit processes implies this error correction form is due to a proof called the "Granger Representation" theorem provided by Granger (47) and expanded on in Engle and Granger (46). Thus, when two unit root series are cointegrated they can be represented by a two-equation system as in (5) whereby the changes in each of the variables can be expressed linearly as a function of the lagged changes in the variable itself, the lagged changes in the companion unit root process, and last period's disequilibrium error in the cointegrating relationship. Engle and Granger (46) developed single-equation tests of cointegration but more recently developed tests based on (6) proposed by Johansen (48-50) and Johansen and Juselius (51) have been shown to be more powerful and thus been applied and reported in Table 2. In this paper we use the trace test and maximum eigenvalue test. For more details on these tests see Johansen (48-50) and Johansen and Juselius (51).

These tests are reported in Table 2 where in each case a p-value less than 0.05 indicates a cointegrating relationship at the 5% level. In the implementation here the lag length *p* in (6) is chosen using the system-wide Schwartz Bayesian criterion. For further discussion see the note

below table 2 in the main text. Tests of cointegration in the econometrics literature tests often proceed in a panel data setting because of the desire to increase the power of cointegration tests by assuming, under the null hypothesis, that none of the cross sections (in our case the regions) exhibit cointegrating relationships while for the alternative hypothesis it is assumed that cointegration among the variables exists simultaneously across all of the cross sections**.** Of course, these null and alternative hypotheses are starkly different in their character but if at least some of the cross sections have cointegrating relationships, the panel cointegration test will have more power than individual cointegration tests applied cross-section by cross-section, especially in the case where the time series dimension of the panel is not large (as is the case here.) We used the panel cointegration tests of Pedroni (15;16) and Maddala and Wu (17) on the regional influenza/nonperforated appendicitis data and found the results to be comparable to those presented in Table 2 in the main text.

Appendix Figure 1. Realizations of the time series $X_t=\varphi X_{t-1} + w_t$ for differing levels of φ. The top and bottom panels differ because they were generated with different random noise components, *w*. A realization of the time series is the equivalent of a "sample" in that it represents a sampling of a process under study. When $|\varphi|<1$, the realization tends to scatter around the series mean value (zero in this case), crossing the mean frequently (i.e. a fast turning process) and is a stationary series. When φ = 1 (i.e. a unit root) the series is nonstationary, and crosses its mean value infrequently and is referred to as a slow turning process.