# ReFlections

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## IN THIS ISSUE



## FROM THE EDITORS

We welcome you to a new year and a new edition of *ReFlections*, RGA's global medical newsletter. As always, it has been a pleasure to see many of you at recent industry conferences and client events.

This edition starts off with a comprehensive review and update in the form of a case review on kidney transplant recipient morbidity and mortality. The article by Dr. Georgiana Pascutiu, Medical Director, RGA, and a nephrologist, highlights some of the relatively recent favorable changes in long-term outcomes for these individuals.

Hezhong (Mark) Ma, Vice President and Actuary, RGA, teams up with Dr. Kamran Khan, an infectious disease specialist in Toronto, Canada and a consultant to RGA, to present a comprehensive analysis and review of predictive factors to strengthen insurer assessment of seasonal influenza mortality variation. These variations can be quite significant and can impact insurers' anticipated mortality experience. This article is interesting both from medical and actuarial perspectives, so please be sure to share it with your companies' actuaries.

Focusing on health and living benefits insurance, Dr. Daniel Zimmerman, Vice President and Medical Director, RGA, provides a Brief Report on sepsis. There is growing awareness of this syndrome, both medically and in the general public, and it is now considered a medical emergency on par with stroke and heart attack. Insurance costs can be high and insurers need to understand the epidemiology of this critical, life-threatening condition.

This edition's article about The Longer Life Foundation (LLF) launches our celebration of the 20th anniversary of LLF's founding. Our interview with one of our veteran multi-year grant recipients, Dr. Luigi Fontana, co-director of the Longevity Research Program at Washington University in St. Louis, focuses on his innovative and world-leading research in the field of caloric restriction and metabolism. His insights and discoveries may someday materially impact our industry.

We would like to thank everyone who participated in our readership survey which was conducted in the September edition of *ReFlections*. The results will help us serve you better and make *ReFlections* a more valuable resource for you.

Please enjoy this edition of *ReFlections*! We wish all of you, our readers, health and wellness in the New Year.

Thank you,

**Peter and Dan**

# RISK ASSESSMENT OF THE KIDNEY TRANSPLANT RECIPIENT


## Abstract

*End-stage kidney disease (ESKD), the most serious and dramatic manifestation of kidney disease, is today a worldwide public health issue, especially in developing countries. In developed countries, advances in the main treatment modalities – dialysis and transplant – have significantly improved life expectancies. Indeed, innovative transplant surgical techniques, improved immunological risk assessment of donors and recipients, and better and more sophisticated immunosuppressive drugs have made renal transplantation a more effective treatment for patients with ESKD than long-term dialysis.*

*For underwriters, correctly assessing the potential mortality and morbidity risk of applicants who are past renal transplant recipients involves understanding a broad range of issues related to kidney disease, current transplantation science, long term graft success, post-transplant survival predictors, and the common causes of death in kidney transplant recipients.*


## Introduction

Since the middle of the last decade, incidence rates for ESKD have stabilized for the world's more affluent countries, but have continued to increase for developing countries. Higher-income countries' renal health priorities, which are aimed at improving the detection of chronic kidney disease (CKD) in the hopes of delivering treatments to slow its progression, likely play a role in limiting the progression to Stage 5 CKD (ESKD).[2] In developing countries, however, diabetes, hypertension, and communicable diseases that can lead to acute kidney injury all play important roles in the rising rates.[2]

Part of the reason is continued treatment inequities, which need to be addressed. In addition, especially in tropical nations, environmental factors such as the higher rates of bacterial, viral, and parasitic infections found in these countries contribute to a glomerular disease prevalence 2.5 times higher than that of developed countries.

## CKD and ESKD – Basics

Chronic kidney disease (CKD) is diagnosed using three prognosticators: renal function (as indicated by estimated glomerular filtration rate [eGFR]), imaging results (whether ultrasound, CT, or MRI) showing kidney damage, and the proteinuria/creatinine (or albumin/creatinine) ratio.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), which provides evidence-based guidelines for all stages of CKD, currently recommends using serum creatinine concentration, expressed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, to calculate eGFR. Individuals with an eGFR of <60 ml/min/1.73m$^2$ for three months, according to this guideline, are classified as having CKD, irrespective

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of the presence or absence of kidney damage. ESKD, which is Stage 5 CKD, is defined as an eGFR of <15 ml/min/1.73m$^2$. Those at this eGFR level are candidates for permanent renal replacement therapy.

ESKD is considered to be caused primarily by diabetes, hypertension, glomerulonephritis (GN), and cystic diseases. Communicable diseases can also be causes. In the U.S., the most common ESKD etiologies are diabetes, hypertension, and GN. ESKD patients with GN as the primary cause are considered to have better prognoses than those whose ESKD is from other causes. However, these are the "primary" diagnoses for ESKD, assigned by the treating physician at the start of treatment. Quite commonly, the original etiology of the disease may be difficult to discern as renal patients are, unfortunately, frequently asymptomatic until they reach more advanced CKD stages.[4]

The convention of assigning only one primary cause to any ESKD case may be limited. This theory is supported by evidence that in many cases of ESKD attributed to hypertension, for example, preceding clinical features highly suggestive of renal parenchymal disease (moderate to severe proteinuria and hematuria) might have also been evident. In addition, ESKD ascribed to hypertension – usually a clinical diagnosis – could be wrong. The patient's disease could have actually been an unrecognized primary glomerular disease, ischemic nephropathy or analgesic nephropathy.

The practice of grouping all patients with ESKD due to GN as a single clinical entity has not been seriously challenged, although clinicians have long recognized the heterogeneous nature of GN in the non-ESKD setting.[9] A recent U.S. study illustrates the imprecision and heterogeneity of most of the categories used to describe causes of ESKD.[14] Using Medicare administrative claims data from the United States Renal Data System, which collects, analyzes and distributes information about CKD and ESKD in the U.S., patients with GN-caused ESKD were classified into the following six GN subtypes:

- focal segmental glomerulosclerosis (FSGS)
- IgA nephropathy (IgAN)
- membranous nephropathy
- membranoproliferative glomerulonephritis (MPGN)
- lupus nephritis (LN)
- vasculitis

## CASE STUDY, PART I

A 43-year-old male nonsmoker applicant with ESKD received a kidney in 2008 from a living donor. The Panel Reactive Antibody (PRA) score was low. The cause of the ESKD was an unknown primary kidney disease. He is maintaining well on the antirejection drugs tacrolimus and mycophenolate mofetil and no episodes of acute or chronic rejection have occurred. His laboratory evaluations are favorable (normal urinalysis and renal function tests) and he is currently taking an angiotensin-converting enzyme (ACE) inhibitor.

The attending physician report stated that in 2006 the applicant's primary physician had referred him to a renal clinic as he was complaining of nausea and severe fatigue. At the time, his renal function test results were markedly elevated. Extensive nephrological evaluation did not identify diabetes mellitus or autoimmune diseases such as lupus and vasculitis as underlying causes. Abdominal imaging had revealed small sclerotic kidneys, but no other renal or urinary tract abnormalities. Laboratory evaluation showed bland urinary sediment (i.e., no hematuria, casts, or proteinuria), an estimated glomerular filtration rate (eGFR) of 7 ml/min/1.73m2, and blood pressure of 180/110.

Further medical history questioning revealed that the applicant's mother had been diagnosed with hematuria in her 30s and died of breast cancer in her late 50s, and a maternal uncle had been diagnosed with ESKD in his 30s and was still alive, on dialysis. In addition, the applicant may have had a few episodes of gross hematuria in his 20s, which he attributed to intense training for a marathon.

The applicant has enjoyed good health until the present time.

Should underwriters be concerned that the applicant's primary renal disease is unknown (and is this unusual)?

Large differences in patient mortality, as measured by the adjusted mortality hazard ratio (aHR), were found among the six groups. After adjustment for demographics and comorbidity, patients with IgAN (also known as Berger's disease) had the fewest comorbidities and the lowest mortality. The next lowest were patients with membranous nephropathy (aHR 1.23), FSGS (aHR 1.37) and MPGN (aHR 1.38). The highest aHRs were in patients with LN (aHR 1.75) and diabetes (aHR 1.73), followed by vasculitis (aHR 1.51). Patients with IgAN were also found to have better survival rates than patients with autosomal dominant polycystic kidney disease (ADPKD), who are often considered to have among the best prognoses among patients with ESKD (aHR 1.22).[6]

Although this research partly illustrates the tendency for GN to become inactive and undifferentiated as kidney failure progresses to end stage (as may have occurred in our case study), it also raises questions, as there is no assurance that the diagnosis was based on biopsy. Also, an important prognostic factor is disease activity at onset of ESKD. This could be inferred by the presence or absence of immunosuppressive treatments given upon an ESKD diagnosis.

## Transplantation

Transplantation has been an accepted ESKD treatment for the last 60 years. CKD patients are generally educated soon after their diagnosis about the natural progression of their disease, the different types of dialysis available, and the renal transplantation option.

The best evidence from observational data show that transplantation confers a mortality benefit in addition to improved quality of life compared with maintenance dialysis.

Indications for transplantation for patients with ESKD include:

- severe metabolic acidosis
- hyperkalemia (elevated potassium levels)
- clinical manifestations such as pericarditis, encephalopathy, and intractable volume overload
- declining nutritional status
- a glomerular filtration rate of 5-9 ml/min/1.73m² in otherwise asymptomatic adults

Kidney donors can either be related or not to the recipient, and can be living or deceased as well. The degree of a transplant recipient's immune response

## CASE STUDY, PART II

Based on the limited information initially gathered, the applicant was first diagnosed with ESKD due to hypertension, which might have been caused by an undiagnosed glomerular disease. While the exact etiology of his ESKD is unclear, his family history suggested the possibility of hereditary nephritis (i.e., Alport Syndrome).

Hereditary nephritis leading to ESKD is X-linked in about 85% of cases and primarily affects males, is autosomal recessive in 10% to 15% of cases, and autosomal dominant in the remainder. Females tend to have much milder disease. Sensorineural deafness is a characteristic feature observed frequently (but not universally) in patients with Alport Syndrome, and there is no specific treatment.

In the case study, types of GN other than Alport Syndrome should be considered as the possible principal cause. Still, based on the known history, the applicant's current renal prognosis appears to be more favorable compared to ESKD attributed to diabetic nephropathy or lupus nephritis.

depends partly on the degree of genetic difference between an organ and its recipient. The human leukocyte antigen (HLA) system genes (or gene complex), which governs compatibility, are located on the short arm of the chromosome 6, and encode the major histocompatibility complex (MHC) proteins. These proteins are divided into class I (HLA A, B and C) and class II (HLA DR, DQ and DP) antigens and are responsible for regulating the human immune system. The role of these proteins is to present peptides to T-cells, enabling them to recognize and eliminate "foreign" cells. The most common form of acute rejection of grafts involve a recipient's T-cells (i.e. adaptive immune response) becoming activated against the donor's MHC antigens.

Long-term renal graft survival has been shown to be closely related to the number of HLA mismatches at the time of transplantation.[20] In our case study, the applicant had a low Panel Reactive Antibody (PRA) score and was fortunate to receive a kidney from a closely matched living donor.

### Immunosuppressants

The first successful immunosuppressant was the purine analogue azathioprine. Since then, many other agents have been approved. They are currently classified into two categories: antirejection induction agents (powerful antirejection medicine used at the time of transplant, e.g. basilixumab, rabbit antithymocyte globulin, and alemtuzuma); and maintenance immunotherapy agents (e.g. prednisone, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, and belatacept).

**Transplantation confers a mortality benefit in addition to improved quality of life compared with maintenance dialysis.**

Choosing the correct immunosuppressive therapy involves balancing the risk of graft injury against the risks of drug toxicity, infection, and malignancy.[7] Post-transplant immunosuppression therapy is normally a combination of agents, with the protocols developed following similar principles to antimicrobial and anti-neoplastic chemotherapy.

The intensity of the immunosuppression need is not constant. High levels are generally required right after the transplant, and can later be reduced to a maintenance level. Immunosuppression must, however, continue for the life of the recipient, for if it is stopped, rejection and then graft loss generally occurs. There is no optimal maintenance immunosuppressive protocol as yet, but the most common regimen used today in kidney transplantation is a CD25 monoclonal antibody such as basiliximab, followed by a combination of tacrolimus, mycophenolate mofetil, and steroids.[7]

Side effects of the immunosuppressors can also be an issue, as well as the higher risk of recipient infection and malignancy due to immunosuppression. Infection is the most common cause of their first-year mortality and morbidity. Recipients are at particularly high risk for non-Hodgkin lymphoma, Hodgkin lymphoma, Kaposi's sarcoma, and infectious cancers of the liver, stomach, oropharynx, anus, and vulva.[5]

### Assessment and Management of Renal Transplant Recipients

A kidney recipient's primary underlying renal pathology influences the survival of both the recipient and the transplanted organ with respect to disease recurrence and associated comorbidities.[5]

Transplantation candidates undergo extensive immunologic evaluation,[8] which helps to avoid transplants that are at risk for antibody-mediated hyperacute rejection. The evaluation consists of four components:

- **ABO blood group determination**. Determines if the patient is a potential target of recipient-circulating preformed cytotoxic anti-ABO antibody.
- **Human leukocyte antigen (HLA) typing (also called tissue typing)**. This measures the degree of incompatibility between the donor and the recipient. Six HLA antigens are determined for each. (Living donors with a six-antigen match with the recipient allow for decreased intensity of post-transplant immunosuppression.)
- **Serum screening for antibodies to HLA phenotypes (PRA score)**. Sensitization to histocompatibility antigens is of great concern in transplant candidate populations with high levels of HLA antibodies, usually due to having previously received multiple blood transfusions, a prior organ transplant, or pregnancy. These patients will have a high PRA score (the more HLA antibodies, the higher the PRA score), making them more likely to experience immunological issues from a transplant. Transplantation might still be possible, however, if the individual successfully undergoes a desensitizing protocol prior to the surgery.
- **Crossmatching**. This in-vitro assay method determines whether a potential transplant recipient has pre-formed anti-HLA class I antibodies against the antigens of the kidney donor. A negative crossmatch must be obtained before a kidney is accepted for transplantation.

**A kidney recipient's primary underlying renal pathology influences the survival of both the recipient and the transplanted organ.**

Transplant patients are also followed up for rejection, immunosuppressant toxicity, and recurrence of kidney disease in the native kidney.

### Outcomes – Patient and Graft Survival

Patient and graft survival after kidney transplantation have improved over the past decade. Even so, graft failure is still one of the most common causes of ESKD, accounting for 25% of all patients awaiting renal transplants.[5]

Life expectancy after renal transplantation depends on patient age, the source of the graft, primary kidney disease, and the presence and degree of comorbidities. Other possible predictive factors include gender, race, and degree of immunosuppression. Data from 2015 provided by the Scientific Registry of Transplant Recipients (SRTR) shows 10-year overall graft survival for both living and deceased donors of approximately 55% to 60% compared with 35% to 40% a decade prior.[3] One long-term European study, for example, evaluated determinants of patient survival after renal transplantation among 86 recipients from living donors and 916 from deceased donors. After the first year, an increased risk of death was observed among renal transplant patients >40 years of age, men, patients who received kidneys from deceased donors, patients with diabetes or hypertension, and smokers.[3]

Early graft loss can be due to vascular thrombosis and rejection, but these occur less often nowadays due to improved surgical techniques and more sophisticated

immunosuppressive drugs. Later graft loss is usually due to a combination of factors, including pre-existing donor disease, recurrence of the recipient's kidney disease, and the recipient's immunologic response to the new organ. Chronic rejection, another major long-term cause of graft loss, is characterized by slow, progressive renal function deterioration that cannot be altered by common antirejection drugs.

### Recurrent Disease

Recurrent renal disease affects as many as 10% of kidney transplant recipients. It accounts for fewer than 3% of all graft losses,[5] and is also the third most frequent cause of graft loss at 10 years after transplantation in patients with underlying GN. Although IgAN, the most common type of GN, histologically recurs in up to 60% of kidney transplant patients, only about 5% will lose their graft as a result of its recurrence. Recurrent focal segmental GN and membranoproliferative glomerulonephritis, however, are associated with high risk of graft loss.

ESKD patients with Alport Syndrome receiving renal replacement therapy (RRT) usually have excellent graft survival rates. They also have superior patient survival rates while undergoing dialysis and superior patient and graft survival after transplantation from a deceased donor compared with patients receiving RRT because of other causes of kidney failure. This superior survival might be explained by the lack of additional organ system involvement in Alport Syndrome and the non-recurrent nature of the disease.[10] Although individuals with Alport Syndrome are thought to benefit from the non-recurrent character of their disease in their kidney grafts, about 2% to 5% of them will develop anti-glomerular basement membrane (GBM) disease early in the post-transplant period, resulting in rapid graft loss.

Diabetic nephropathy can also recur in renal grafts. Time to onset is similar to that seen in native kidneys. This condition is generally an uncommon cause of graft loss.

### Patient and Graft Survival by Source of Graft

The quality of the graft has a direct effect on important clinical outcomes such as acute rejection, delayed graft function, and patient and graft survival. Recipients from related living donors have a lower mortality than recipients from deceased donors, likely because of lower rates of rejection episodes thus less complex immunosuppressive drug regimens.

According to the Scientific Registry of Transplant Recipients, in 2015, the five-year survival for patients who received a deceased-donor kidney in 2010 was 86.8% and for living-donor recipients was 93.5%. Survival was lower in recipients age 65 years and older and in recipients with diabetes as cause of kidney failure.[5] Fifteen-year graft failure among adult living donor transplant recipients was 37.3% (1990-2005) and 52.8% for adult deceased donor transplant recipients.[11]

Expanded-criteria donor (ECD) kidney longevity is believed to be much shorter, with the kidney's half-life estimated at six to eight years, compared with 10 to 12 years for a non-ECD kidney from a deceased donor.[12] ECDs are less-than ideal donors – over age 60 or age 50 to 59 and have two of the following: hypertension; terminal serum creatinine >1.5 mg/dl; or death at any age from cerebrovascular accident.

### Patient and Graft Survival by Diagnosis

The presence of systemic disorders, particularly vascular disease, is associated with poorer long-term patient survival after renal transplantation. The survival of diabetic

patients after renal transplantation is lower than that reported for nondiabetic patients due to the prevalence of extrarenal vascular disease. Five-year graft and patient survival by diagnosis among living donor kidney recipients shows an 83% graft survival and 86.6% patient survival for diabetic subjects (Figures 1 and 2). As expected, for deceased donor kidney recipient diabetic subjects, graft survival was 72% and overall patient survival was 82.5% (Figures 3 and 4).

On the other hand, patients with diseases that primarily affect the kidneys, such as autosomal dominant polycystic kidney disease and GN, have better long-term survival rates post-transplant than those with systemic disorders such as hypertension and diabetes. The same data shows an 87% graft survival and 97% patient survival for living donor kidney recipients with history of glomerular disease, while for deceased donor recipients it was 79% and 92.5%, respectively.

Older patients who undergo renal transplantation have higher mortality rates than do younger ones. Among recipients of any age, increased survival is noted with decreased age of the deceased donor, as shown in Figure 4.[5]

Renal function parameters one year after transplantation are the most important predictors of graft survival. Patient survival at 10 and 20 years has improved and is 75.9% and 64.8%, respectively.[1] Ultra-long graft survival (20 years and up) is not uncommon in this day and age. Approximately 25% of kidney transplant patients achieve this rate.

Graft survival after kidney transplantation has improved over the past decade. Death with a functioning graft occurs in about 25% of transplant recipients (15-year data, 1990-2005).[11] During the first year after a renal transplant, infections are the leading cause of recipient death. Long-term mortality is more dependent upon other

**Figure 1: Graft Survival from Live Donor by Diagnosis**

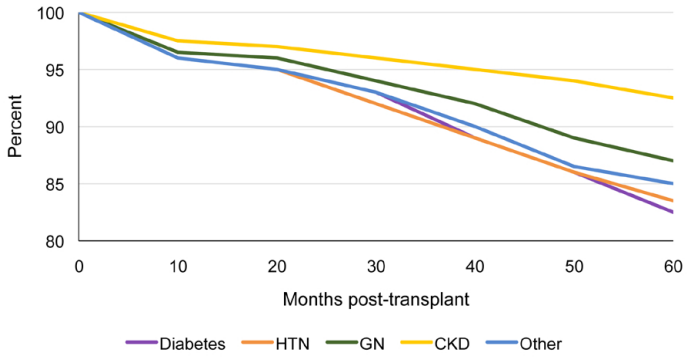


**Figure 2: Patient Survival from Live Donor by Diagnosis**

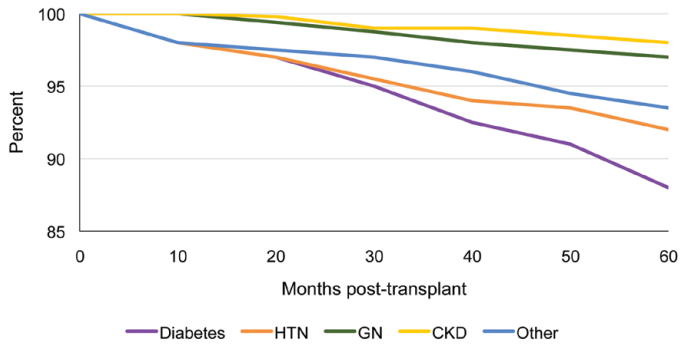


**Figure 3: Graft Survival from Deceased Donor by Diagnosis**

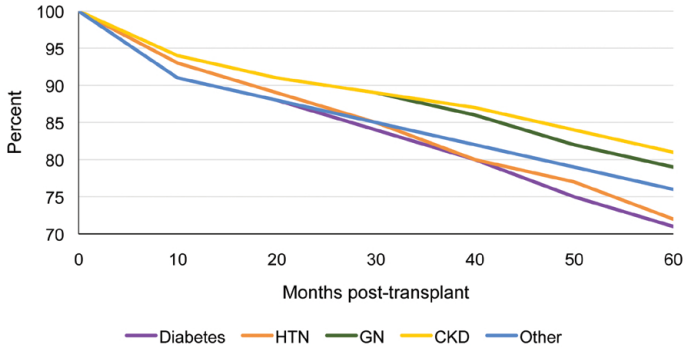


**Figure 4: Patient Survival from Deceased Donor by Diagnosis**

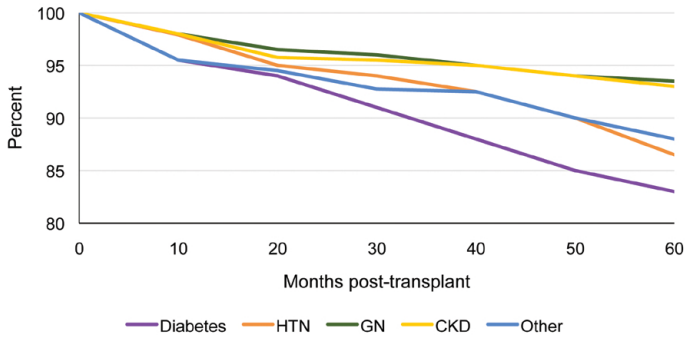


*Figure 1 - 4: Adapted from Hart A, et al. Am J Transplant. 2017*

## CASE STUDY, PART III

Our applicant is now nine years post-transplant. His graft is functioning well and he has no comorbidities except for history of hypertension, which is managed well with ACEI.

Favorable long-term graft survival predictors, such as young recipient age, living donor HLA matched/low PRA score, early kidney transplant, and optimal first year graft function, make his prognosis quite encouraging.

factors, such as coronary artery disease (30.4%), sepsis (27.1%), neoplasm (13%), and stroke (8%).[3, 5] The rate of malignancies appears to be directly related to the degree of immunosuppression.

Major morbidities for transplant patients include: hypertension (occurring in 75% to 85% of all recipients); hyperlipidemia (60%); cardiovascular disease (15.8% to 23% – a 10-fold increase over the general population); diabetes (16.9% to 19.9%); osteoporosis (60%); and malignant neoplasms (14%). Post-transplant lymphoma due to Epstein-Barr affects around 2% of recipients. Non-melanoma skin cancer is also particularly high, with human papilloma virus implicated. Diabetes is more likely to be present prior to transplantation, and new-onset diabetes related to post-transplant corticosteroid immunosuppressant drugs.[3, 5]

Graft and overall survival at 60 months, if hypertension is the primary cause of the ESKD, is 84% and 91.6%, respectively.

**The presence of systemic disorders, particularly vascular disease, is associated with poorer long-term patient survival after renal transplantation.**

### Summary and Underwriting Considerations

Insurers need to be aware of these improving outcome trends in renal transplant recipients and refine their underwriting guidelines in accordance with available data on the most important predictors of patient and graft survival.

However, even though long-term kidney graft function has improved, allowing patients with successful kidney transplants to experience enhanced quality and duration of life, insurance companies still need to be aware of the associated comorbidities when they design life, health, and other living benefits insurance products.

Further research in transplant immunology and immunosuppressant agents with the goal of inducing a state of tolerance towards the donor will allow more ultra-long graft survival and further improvements in the morbidity and mortality of kidney transplant recipients.

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# SEASONAL INFLUENZA AND MORTALITY


## Abstract

*This article follows up on two older articles by RGA associates: "Seasonality of Mortality," by Kyle Nobbe, published in the January 2017 edition of* ReFlections,[1] *and "Seasonal Flu and the Impact on Mortality," by Dr. Dave Rengachary.*[16] *These articles established that with the exception of cancer and non-natural deaths, almost all major causes of mortality are seasonal and more deaths are seen in winter. Also established was that influenza mortality exhibits significant variation from season to season, with a greater than tenfold difference in mortality between the least and most severe seasons. Finally, data from U.S. and Japan demonstrates a statistically significant positive correlation between excess deaths due to influenza and pneumonia and excess deaths due to all other medical causes.*

*Several theories attempt to rationalize why all-cause mortality is seasonal. The severity of influenza during a given season might offer insight into how severe overall mortality during that season might be. Additionally, although influenza and pneumonia deaths are only a small proportion of overall seasonal mortality, they could serve as valuable indicators of overall mortality during a given influenza season. Knowledge of an influenza season's potential severity, either in advance or at onset, might also help insurance companies improve their financial planning and explain their earning patterns. Also important to consider is that age is the most significant risk factor for influenza mortality: greater than 90% of influenza deaths in recent decades have occurred in people age 65 and older.*

*RGA is partnered with BlueDot, a Toronto-based company that studies how infectious diseases disperse worldwide through analysis of big data, and brings together predictive modeling and data visualization to deliver timely evidence to decision-makers. This article presents the RGA/BlueDot partnership's most recent, focused research on seasonal influenza mortality variation.*


## Introduction

Although influenza epidemics occur every year, the severity of these epidemics, as measured by physician visits, hospitalizations, and influenza-attributable mortality, varies from season to season. The ability to predict the severity of a particular influenza season improves as the season progresses. There is a continuous stream of influenza data collected globally, which when examined collectively, offers insights into how severe the upcoming influenza season might be.

Wading through the various data sources and understanding how all of these different metrics relate to influenza season severity is a complex task. RGA partnered with BlueDot to i) describe the process by which data about influenza are collected globally, highlighting the significance of these data with respect to influenza-attributable mortality, and ii) develop

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a statistical model, using 15 years of historical mortality data from the United States, to assess if and when selected indicators could predict excess influenza-attributable mortality.

An example of how influenza-attributable mortality varies across seasons is shown in Figure 1 (below). Here, data from the Centers for Disease Control and Prevention (CDC) WONDER databases from the 1999-2000 to the 2014-2015 seasons for the U.S. population age 65 and older was used to estimate excess deaths per month over that 15-year span. The baseline came from a Serfling periodic regression model, the standard CDC algorithm for calculating excess influenza-attributable mortality. This model controls for linear and quadratic trends as well as annual cyclical patterns.

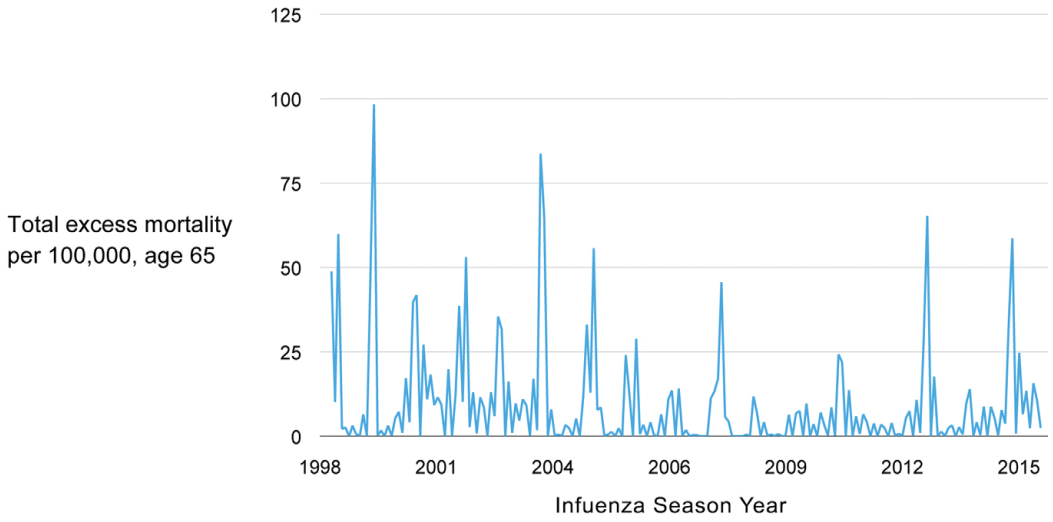
**As H1 influenza was most dominant in the childhoods of today's older adults – the most vulnerable population to influenza – the H3 strain is more dangerous to them.**

## Influenza Data Generation Process

In the northern hemisphere, influenza season normally starts in October and ends in April, while in the southern hemisphere, influenza season typically occurs between May and October. The different timing of influenza seasons in the northern and southern hemispheres means that data on influenza activity are generated throughout the year. These data are gathered by local, national, and international organizations, and their use has the potential to improve the ability to predict not only influenza and pneumonia mortality for a given season, but potentially overall mortality as well.

Before investigating how different indicators can help anticipate the severity of an influenza season, it is important to understand the various sources and types of data that are collected. A large volume of data are generated relating to both influenza activity and the characteristics of circulating influenza viruses. We sought to describe the complex processes by which influenza data are collected and to identify indicators that might be used prior to or during the early stages of influenza season to better predict influenza-associated mortality.

**Figure 1: Total observed excess mortality rates by month, age 65 and over, 1999-2000 to 2014-2015**



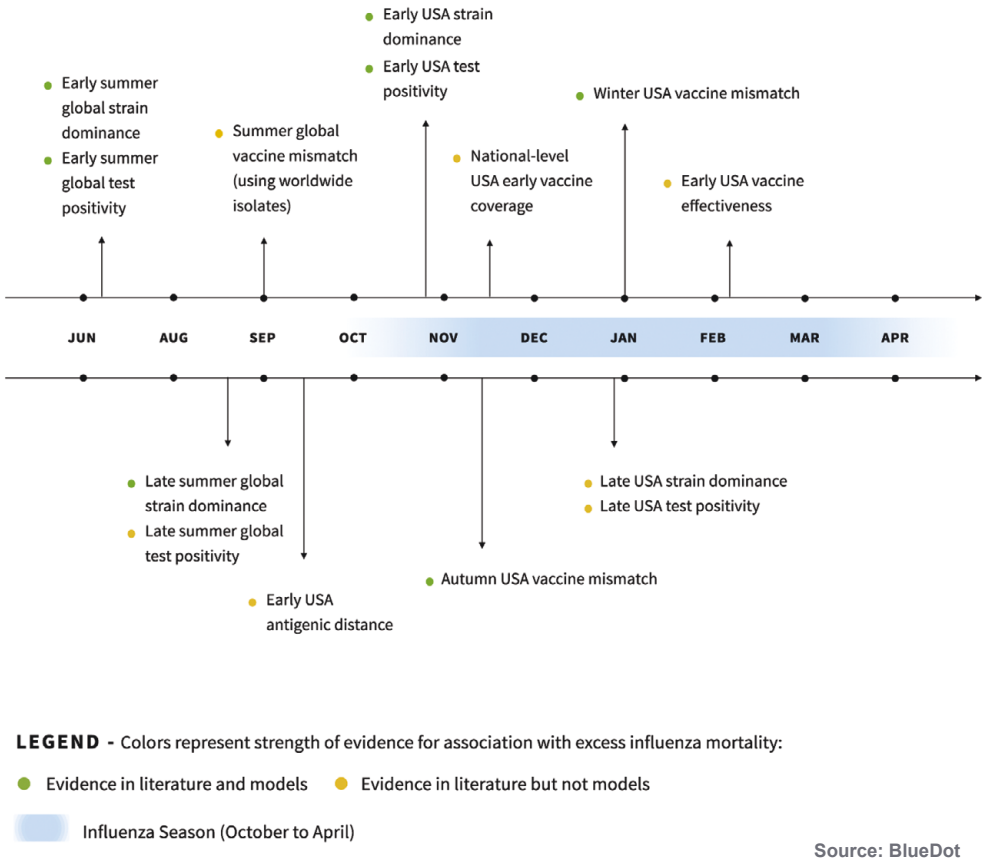

Source: BlueDot

Two important collectors and disseminators of influenza data are the World Health Organization (WHO) and the CDC. Each uses a variety of methodologies to monitor and collect data on the severity of influenza seasons. WHO's FluNet, a global tool for influenza virological surveillance, reports weekly, by country, the number of specimens processed that test positive for different influenza subtypes. The CDC's FluView provides similar information for the U.S. only, reported at the national and regional level.

In late September to early October, prior to the onset of the U.S. influenza season, the CDC's Morbidity and Mortality Weekly Report (MMWR) publishes a summary of influenza activity that occurred during the summer. The report includes the results of antigenic match assays performed in CDC laboratories, comparing the match between circulating viruses isolated in the U.S. and internationally to the viruses included in the seasonal influenza vaccine. The Worldwide Influenza Centre at the Francis Crick Institute in the U.K. also releases its summer report around September, although this report is more technical in nature and is not as easily interpretable as the MMWR report. Another source of antigenic match data comes from the Chinese National Influenza Center, which issues weekly reports of the proportion of influenza isolates matching the vaccine strain cumulatively since March. (The vaccine used in China is generally the same as the northern hemisphere vaccine used in the U.S.).

Starting in October and lasting throughout the U.S.'s influenza season, the CDC's FluView reports on the cumulative proportion of isolates that match the vaccine strain, by influenza type.

**Figure 2: Availability of Indicators**




Source: BlueDot

## Review of Indicators Associated with Influenza Mortality

These different data sources provide a number of potential indicators that may provide early warning signs as to the severity of an upcoming influenza season. BlueDot reviewed and synthesized the literature on different potential indicators and evaluated them on four criteria:

- What is currently known about the indicators' relationship with influenza-attributable mortality, based on the existing biomedical literature?
- Can the indicator(s) be measured in a timely fashion, ideally before or during the early stages of an influenza season?
- Is data about the indicator(s) easy to obtain?
- Can the indicator(s) predict population-level influenza-attributable mortality before the onset of, or during, influenza season?

To be used for early warning, the time at which each potential metric becomes available is important. Figure 2 (above) provides a summary timeline of predictive indicators and their association(s) with influenza mortality in subsequent months as determined from the literature review.

Based on the literature review and the criteria for indicator availability either prior to or early on in an influenza season, we identified three potential indicators to predict the severity of an influenza season: influenza test positivity, dominant influenza subtype, and vaccine match. Notably, most existing literature about the association of different indicators with excess influenza-attributable mortality is retrospective, as the indicators were measured at the end of the season. We examined if different conclusions about the effect of these indicators on influenza-attributable excess mortality would be reached if estimates of these indicators were obtained prior to or early on in the influenza season.

To do this, the predictive value of each season's severity indicators was measured at four time points during the season: June, September, November and January. At each time point, excess deaths due to influenza were summed from the month following the month when the indicator became available or October (whichever was later) until the following April, and the correlation between cumulative excess deaths and individual indicators selected was examined, controlling for age group and gender. The model was focused on the U.S., but many of the indicators are globally available and the approach could be reassessed for countries in both hemispheres. Each of the indicators and their association with influenza mortality, both in the literature and in our predictive model, is reviewed below.

**It is important to be aware that subtype dominance and vaccine match are related in their effects on influenza mortality.**

Some additional indicators that were identified in the literature review (vaccine effectiveness, vaccine uptake, and antigenic distance) were not included in the predictive models but are also described, as they have the potential to be used as early warning indicators in the future.

### Influenza Test Positivity and Dominant Subtype

Several influenza virus types, subtypes, lineages, and strains exist. The most common are influenza A subtype H1N1, which caused the 1918 Spanish flu pandemic, and subtype H3N2, which has begun to be seen more frequently in recent years. The influenza B type, which is classified into lineages and strains, is also frequently seen.

Influenza test-positivity refers to the proportion of influenza tests that are positive for any type of influenza virus, subtype or strain. Dominant subtype indicates the most prevalent subtype circulating during a season.

The association between dominant subtype and mortality severity is well documented in the scientific literature. In years when H3N2 was the dominant subtype, 2.7 times more deaths were recorded than in years when it was not.[2] Influenza B-dominant years typically cause less mortality than H3N2-dominant years, and H1N1-dominant years are generally associated with the least amount of mortality.[3] A possible reason for this observation may be due to how people develop immune responses to influenza viruses. People tend to develop a more effective immune response to the first influenza viruses they encounter in their lifetimes. As H1N1 influenza was most dominant in the childhoods of today's older adults – those most vulnerable to influenza – they tend to mount a less robust immune response to the H3N2 viruses, resulting in more severe disease.

In the model we developed, increased influenza test positivity globally in June, or in the U.S. in November, is associated with higher excess mortality for the rest of the influenza season. Indeed, for every one percentage point increase in the proportion of positive tests for influenza globally in June, excess mortality in the upcoming influenza season increased by 3% – a modest but statistically significant value. Meanwhile, for every one percentage point increase in the proportion of positive influenza tests in the U.S., for all tests cumulatively between the beginning of the influenza season to November, excess mortality in that season rose by 4%. This effect was not, however, observed in January. Higher test positivity could be reflective of either less population-level immunity to circulating strains or more transmissible circulating subtypes and strains, resulting in higher population influenza burden and mortality.

Figure 3, on page 15, compares the distribution of log excess mortality due to influenza by whether the influenza season is dominated by the H3 subtype or not. For this model, a subtype or strain was considered dominant if greater than 60% of influenza-positive

samples were positive for it. Each column indicates 5th, 25th, 75th and 95th percentiles, as well as median and average. H3 dominance was assessed in June and September, when only global data were available, and in November and January, when U.S.-specific information was also available.

At each observation point, for influenza seasons during which an H3 strain dominated, the mortality experience was significantly worse than otherwise. If an H3 strain was dominant globally in June, a 52% increase in excess mortality due to influenza would have been expected in the upcoming influenza season. If it was still dominant globally in September, it would have been associated with a 66% increase. In the U.S., as indicated above, data are only available after October. If an H3 strain was dominant in November, it would be associated with a 130% increase in excess mortality due to influenza. This effect was not observable in our model for January, possibly because much of the season's influenza mortality would generally have already occurred by then.

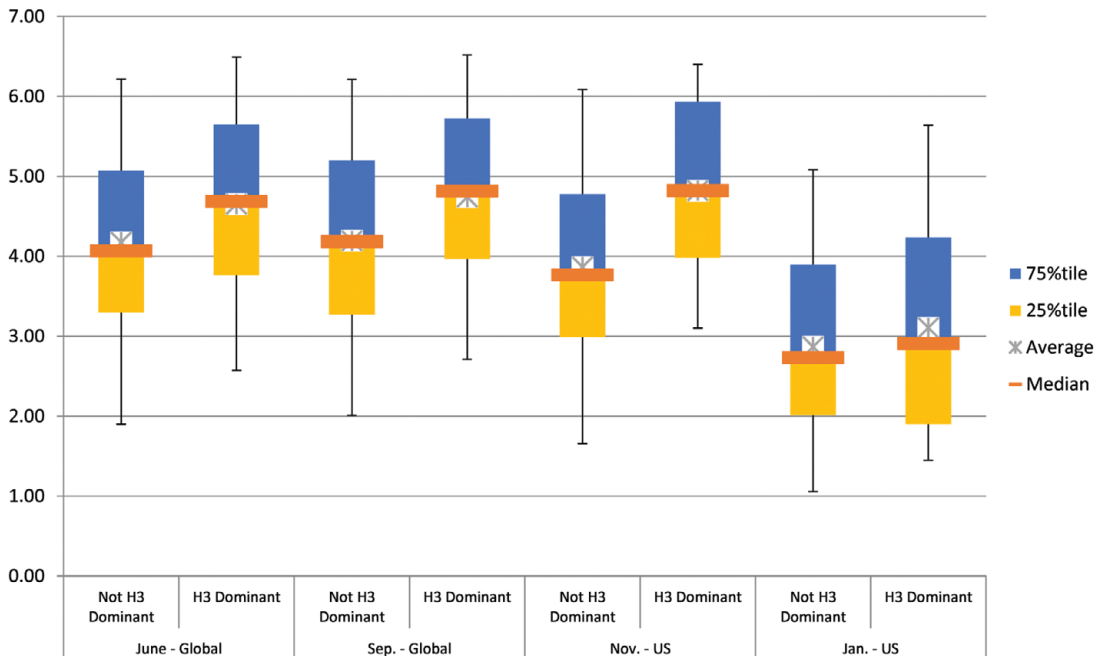
## Vaccine Match

Vaccines work by generating an immune response in the human body to the strains and subtypes incorporated into the vaccine. An influenza vaccine will typically contain three or four strains and subtypes: an H1 subtype, an H3 subtype, and one or two B strains. If the H1 type in the vaccine matches the type that is circulating, but the H3 type does not, the vaccine protects against the circulating H1 but not the H3.

Sometimes the immune response that develops from vaccination results in strong protection against influenza viruses circulating duration an influenza season, and at other times the protection is weaker. The strength of an immune response to a vaccine can be assessed in a laboratory using a test that determines how effectively antibodies generated by the immune system in response to the vaccine inhibit a sample of influenza virus. In our model, a vaccine is considered "matching" if greater than 90% of the isolates (virus samples cultured from sources) were an antigenic or genetic match for the strains and subtypes incorporated in the vaccine.

Because this is a laboratory test, the antigenic match may not always be a good predictor of observed vaccine effectiveness in humans. This may reflect the fact that other types of immunity (such as cellular immunity) can also be important in protecting against influenza infection. Overall, antigenic match is generally correlated with vaccine effectiveness[4, 5, 6] and is also correlated with other positive outcomes.[7] A matching H1 strain, for example, was found in a 2014 study to have lowered pneumonia and influenza hospitalizations

**Figure 3: Log Excess Mortality Rate by H3 Dominance and Models**




Source: BlueDot, RGA

among the elderly by 24% and a matching B strain lowered them by 5%.[8] A matching H3 strain lowers the number of excess pneumonia and influenza deaths by 22% in the elderly.[9]

For our model, the antigenic match over the summer reported by the CDC in September/ October was not found to be statistically significantly predictive of reduced rates of excess mortality. However, in subsequent months, matches for circulating H3 vaccine strains were associated with a downward trend in mortality. If greater than 90% of the H3 isolates by the end of November matched the vaccine strain, mortality decreased by 45% compared to years where it did not match.

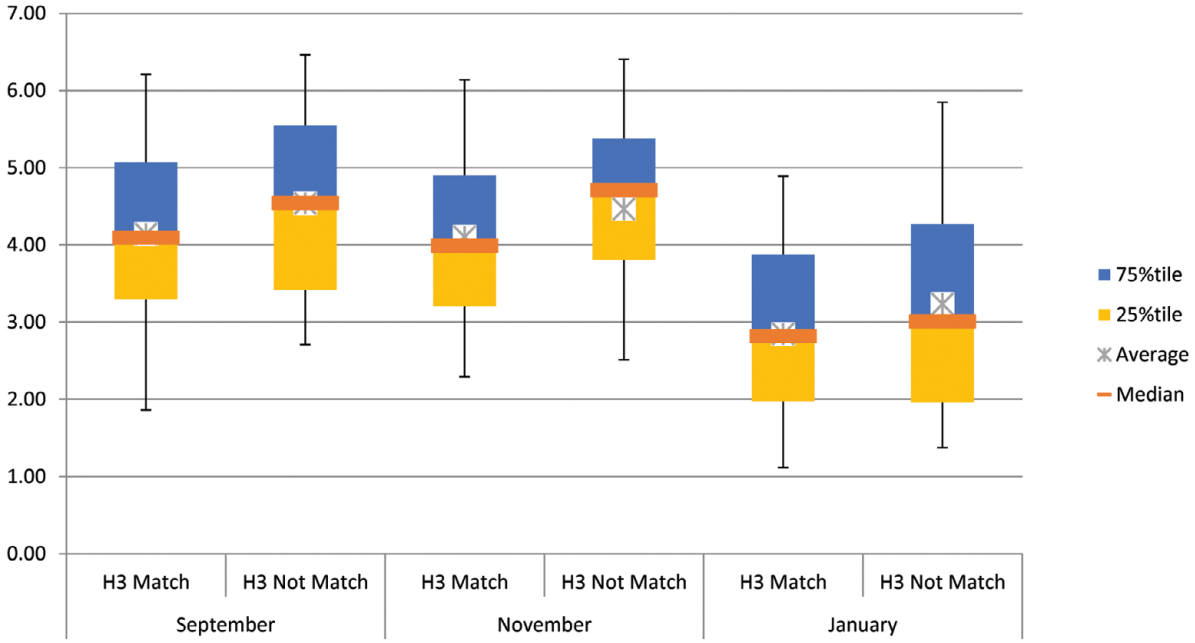
Figure 4 (below) is a chart of log excess mortality due to influenza by whether the vaccine matched the circulating H3 strain in September, November, and January. When there was no match, the data are more dispersed but indicates generally higher mortality than in influenza seasons where there was a match.

It is important to note that although the results are discussed for each of these indicators in isolation, each of the indicators considered in these models likely interact when considering their effects on influenza mortality. For instance, an H3-dominant season may result in more influenza transmission, and consequently, higher test positivity. Similarly, an H3 vaccine mismatch is unlikely to be as consequential in seasons that are dominated by H1N1 or B strains than in H3N2-dominant seasons.

## Vaccine Effectiveness

Influenza vaccine effectiveness measures the effect of a vaccine on decreasing test-positive influenza infection among the vaccinated population versus the unvaccinated population. This is a measure of how well a vaccine will protect a population against influenza. An effective vaccine is expected to decrease mortality by decreasing the overall number of cases and severity of infection in those who are infected.[10]

### Figure 4: Log Excess Mortality Rate by H3 Vaccine Match and Models




Source: BlueDot, RGA

Influenza vaccine effectiveness cannot be measured until influenza is circulating in the northern hemisphere, so early and interim measures of effectiveness against test-positive influenza are generally not available until January or February, and final estimates are not available until well after influenza season is over.

This may change in the future. Recently, research has been done in countries that routinely collect vaccine registry data to calculate vaccine effectiveness in real time. At the present time, since the data are not available until after the peak of the influenza season, it is not yet possible to use vaccine effectiveness as an "early warning" indicator.

**The correlation between excessive deaths due to influenza and pneumonia and all-cause deaths is not necessarily causal.**

### Vaccine Uptake

Vaccine uptake refers to the percent of a population vaccinated against a disease. For influenza, vaccine uptake is measured annually since the vaccine generally works for only one year. Higher vaccine uptake protects vaccine recipients and if effectiveness is high, it can also protect people who were not vaccinated or those for whom the vaccine failed by limiting influenza's spread through the community.

In the U.S., county-level vaccine uptake among adults 18-64 years old has been demonstrated to be associated with decreased odds of influenza among elderly residents, especially if the elderly adults were also vaccinated, if the antigen matches, or if the influenza season was more severe.[11] Increased vaccine uptake in children also reduces respiratory illness rates in the rest of the community.[12]

National-level U.S. influenza vaccine uptake rates, stratified by age, race and ethnicity, and high-risk comorbid conditions, are available in November from the CDC. Uptake rates at the state level, however, are not available until well after the end of the influenza season. Since the herd immunity effect associated with vaccination work only at a local level by reducing susceptible contacts, this indicator cannot currently be included in predictive models.

### Antigenic Distance between Current and Previous Circulating Strains

Antigenic distance measures how effectively exposure to one influenza strain can protect against another. It can be used to measure vaccine match or the difference between a current circulating influenza strain and a previous one. This is important, because if a person was exposed to an influenza strain in a previous season and the new one is antigenically close, that person will have some protection against the new virus.

Some evidence suggests that the antigenic distance between the current year's strain and previous years' strains is correlated with excess mortality.[13] Because these data are difficult to obtain and interpret, they were not analyzed in our predictive model, but this may be an important indicator to incorporate into future models.

### Implications for Insurers

While individual risk factors for influenza mortality have been well studied,[14] indicators explaining the seasonal variation in mortality at a population level have received less attention. They do exist, and importantly, may be measured early in the influenza season. Generally speaking, influenza-related mortality is pro-cyclical to all-cause death seasonality (meaning that if influenza-related mortality rises, a rise in all-cause death

seasonality will be seen). Thanks to different monitoring programs around influenza activities, indicators can be used for early warning or ongoing monitoring purposes. Although it is not currently possible to predict excess influenza-attributable mortality with accuracy, a high-level assessment of the general mortality experience may be possible prior to or early in an influenza season by examining early warning signs of severe influenza mortality.

Although the correlations between different indicators and influenza mortality may help predict influenza season severity, it is important to gain a better understanding of the underlying reasons for these relationships. Otherwise, we risk missing changing population trends. For example, as discussed above, people have been shown to develop a more robust immune response to the first influenza strains they encounter in their lifetimes. The current older generation, who are most vulnerable to seasonal influenza-associated mortality, encountered H1-dominated influenza seasons in their childhoods, making them more vulnerable to H3 infections. As populations age, and the older population transitions to individuals whose first exposure was to influenza of a different subtype (e.g., H3N2), this correlational relationship might also be expected to change. Additionally, there are other factors that may contribute to influenza severity but cannot currently be used as early-warning indicators. For instance, weather is believed to play a role in influenza season onset,[15] and so may potentially influence the impact of other indicators on the seasonal pattern of mortality.

Most studies of population-level indicators of risk have focused on the general population. The U.S. influenza mortality data used in our model are only available for the general population, which may have differences in age distribution, health status, and access to healthcare compared to the insured population. Because of this, population level indicators of risk may affect an insured population differently from the general population. Hence, it is also important to understand individual-level risk factors. Although they are unlikely to cause marked effects in season-to-season influenza mortality, they may explain differences between the general and insured populations.

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# SEPSIS: RECENT DEVELOPMENTS AND UPDATE


## Abstract

*On May 26, 2017 the World Health Organization (WHO) adopted a resolution that recognized sepsis as a global health priority, pledged to improve its prevention, diagnosis, and management, and made a number of recommendations to reduce its global burden.*[1]

*This brief update will present some of the recent developments in the diagnostic criteria, incidence, treatment, mortality outcomes, and sequelae of sepsis and draw conclusions about the relevance and impact these developments may have on insurance medicine and insurance products.*


## Introduction

Sepsis has recently been attracting significant attention from both medical and non-medical communities. The condition is now considered a medical emergency of equal importance with myocardial infarction (MI) and stroke. The early warning signs and symptoms of the latter two are well known to the public and have established emergency treatment protocols. With sepsis, the medical community is strengthening education for the general public about its risks, but work remains to be done. However, there is now a growing consensus among health care professionals that sepsis protocols are beneficial and can provide both life- and cost-saving outcomes.

Somewhat controversially, implementation of sepsis protocols is being mandated by some U.S. states in an attempt to decrease its mortality rate.

## Definitions

One of the great difficulties in assessing, diagnosing and treating sepsis has been its ever-changing medical definition. As sepsis' pathobiology becomes clearer and medical understanding evolves, so too does its definition. Sepsis does not have one etiology and one clinical manifestation: it is a syndrome with varying findings, and no gold-standard diagnostic test yet exists.

The many and diverse definitions sepsis has had over the years has made it difficult to track and observe its true epidemiology, thus complicating analysis and comparison of clinical studies on the condition.

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[2] was released – the first revision of sepsis definitions since 2001. It defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection," and septic shock as "a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality."

The Sepsis-3 clinical definitions are shown in Table 1.

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Daniel Zimmerman, M.D., is Vice President and Medical Director of RGA Reinsurance Company and a member of RGA's Global Support Team. He is responsible for case consultation, product development, internal and external education, client support, and representing RGA to key industry professional organizations. He has held leadership positions with the American Council of Life insurers (ACLI) and participated in program committees of the American Academy of insurance medicine (AAIM).

| Table 1: Clinical Definitions of Sepsis and Septic Shock (Sepsis-3) | |
|---|---|
| **Sepsis** | Suspected or documented infection + an acute increase of >2 SOFA* points |
| **Septic shock** | Sepsis and vasopressor requirement to maintain mean arterial pressure (MAP) >65 mm Hg + lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation |
| *SOFA = Sequential Organ Failure Assessment. This score weighs data on respiratory, coagulation, liver, cardiovascular, central nervous system, and renal function. It is a proxy for organ dysfunction. | |

It is hoped that these new definitions will enable better case definition, leading to earlier identification of sepsis, rapid and goal-directed clinical intervention, improved outcomes, and better standardization of epidemiologic and research data.

## Incidence Rates

Historically, most incidence studies of sepsis were done using insurance claims data, due to its greater availability. However, due to coding issues and the changing definitions of sepsis over time, the reliability and comparability of past studies is questioned. Additionally challenging is the fact that incidence rates and trends vary between Western and low- and middle-income countries,[3] making comparisons more difficult. Nonetheless, most studies would suggest that incidence rates have been increasing for at least 10 years. Speculation of cause include an aging population, increasing use of immunosuppressive therapies, and individuals in general having more comorbid conditions. A recent study, however, which compared clinical and claims data from 2009 through 2014, demonstrated no increased incidence based on clinical data. Claims data, however, suggested a 10% per year increase over that same period. The study's authors emphasized the importance of using clinical data to establish more accurate incidence trends.[4] If incidence rates are truly increasing, health insurers and medical reimbursement policies will clearly be impacted. In addition, since sepsis is one of the costliest medical conditions to treat, given the high likelihood of intensive care unit admissions and prolonged hospital stays, stop-loss portfolios may be increasingly affected as well.

**One of the great difficulties in assessing, diagnosing and treating sepsis has been its ever-changing medical definitions.**

## Treatment Protocols

The difficulty in developing treatment protocols for sepsis is the fact that it is not a disease but a syndrome and it presents heterogeneously in patients. In response to the Sepsis-3 guidelines, the *Surviving Sepsis Campaign* (SSC), a joint collaboration of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine,[5] recently updated its sepsis guidelines and treatment protocols. These guidelines, or "bundles," are standardized sets of interventions which, when implemented as a group, have more favorable impacts on outcomes. The bundles include recommendations for obtaining blood lactate levels and blood cultures, administering broad-spectrum antibiotics, and giving intravenous fluids, if indicated, all within three hours of presentation. Additional interventions should be completed within six hours of presentation.

There is also now a movement to legislate the treatment of sepsis. In 2013, the State of New York (U.S.) began mandating that hospitals follow protocols, such as those promoted by the SSC, for the early identification and treatment of sepsis. Data now indicates that completing a bundle in less than three hours can reduce in-hospital mortality. Nonetheless, these regulations remain controversial.[6]

## Mortality Outcomes

Most studies have demonstrated that sepsis' mortality rate has been decreasing. A report from Australia and New Zealand showed absolute mortality rates from sepsis had decreased from 35% to 18.4% (almost 50% relative risk reduction) from 2000 to 2012.[7] Mortality rates from sepsis have also decreased in the U.S., with one meta-analysis showing a decrease from 46.9% in the period 1991-1995 to 29% in the years 2006-2009.[8]

A more recent review of U.S. clinical data demonstrated a decrease in in-hospital mortality due to sepsis by 3.35% per year from 2009 to 2014. There was, however, no change in the rate of death or discharge to hospice. This study therefore challenges other reports supporting a decreasing mortality rate from sepsis.[4]

## Sequelae

According to a 2017 study, sepsis survivors have an exceptionally high 30-day unplanned hospital readmission rate (12.2%) compared with MI (1.2%), heart failure (6.7%), pneumonia (5.2%), and COPD (4.6%), and account overall for 14.5% of readmission costs. These data highlight the importance of discharge planning for survivors of sepsis.[9] Another study, from 2014, demonstrated a 17.9% 30-day readmission rate, but also found this increased to almost 50% within one year.[10]

**Even though mortality rates from sepsis might be decreasing, survivors can experience permanent impairments.**

The cognitive and functional recovery and status of sepsis survivors has also been studied. Among an elderly cohort (mean age 76.9 years), post-sepsis prevalence of moderate to severe cognitive impairment increased 10.6% with an odds ratio of 3.33. This group also experienced functional Activities of Daily Living impairment(s). Importantly, both cognitive and functional limitations persisted for up to eight years. Thus, even though mortality rates from sepsis might be decreasing, survivors can experience permanent impairments. These may impact their ability to live independently or increase other social and medical support needs. These outcomes are certainly relevant to long-term care insurance and potentially to other living benefits products.[11]

## Impact on Insurance and Conclusion

The growing importance of sepsis in the clinical world may have a significant impact on several lines of insurance. The high costs of treatment, both initially and due to high readmission rates, and prolonged hospital stays primarily affect health and stop-loss cover. In addition, due to significant sequelae including functional and cognitive impairment, long-term care and other living benefits are subsequently impacted.

Insurers would do well to establish a dialogue with all stakeholders in the health care systems of the markets they serve to strengthen early recognition and standardize treatment for sepsis. In doing so, we can create a win-win scenario for both patients and insurers. ReF

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Longer Life Foundation

An RGA/Washington University Partnership

# LLF Interview: Luigi Fontana, M.D., Ph.D.

*Professor of Geriatrics and Nutritional Science, Washington University in St. Louis School of Medicine*
*Professor of Medicine and Nutritional Sciences, University of Brescia, Italy*

*Luigi Fontana, M.D., Ph.D. is an internationally known human systems biologist and one of the world's leaaders in the fields of nutrition and the biology of human aging.*

*Dr. Fontana directs the Longer Life Foundation's Longevity Research Program, a Washington University in St. Louis program that focuses on the impact of nutrition, physical exercise and caloric restriction (CR) on human longevity. His specific areas of interest are the processes of aging and age-related diseases, including cardiovascular function, glucose metabolism, inflammation, neuroendocrine and immune function, and microbiome and cancer biology.*

*In a recent interview with Dr. Daniel Zimmerman, managing director of the Longer Life Foundation and co-editor of* ReFlections*, Dr. Fontana discussed several aspects of his constantly evolving research on calorie restriction – a regimen that reduces caloric intake without incurring malnutrition – and the potential for what he and his colleagues are discovering to impact the future of how we age.*

### *Q: What are the main factors you see as predictive of longevity and wellness?*

A: Over the years several factors have emerged – smoking, lack of exercise, and the most interesting one – sleep. Research published in the journal Nature in 2013 discussed the two-way relationship of sleep and Alzheimer's disease, which highlighted the fact that sleep disruption increases the deposition of beta amyloids and tau protein in the brain. There are a number of interventions that could be implemented that have been found over the past few years. I believe, though, that the only thing that can consistently and drastically increase life span is CR without malnutrition.

### *Q: How did you first get interested in researching caloric restriction?*

A: When I was in medical school, one of my professors talked about CR. I was interested in researching how to prevent disease, and CR clearly was a path to that end.

### *Q: How and why does CR result in increased lifespans?*

A: CR results in increased lifespans by lowering the levels of several growth factors and hormones that drive cellular proliferation, which ultimately reduces the risk of damage to the body. For example, if insulin, testosterone, and inflammatory drivers are reduced, the organism benefits through increased genomic stability, and cells are made younger and less dysfunctional. Cellular senescence is also decreased.

### *Q: Life expectancy and maximum life span are different. What do you think is the maximum human lifespan?*

A: Everyone has a genetic predisposition for disease/aging, but if a person does everything right, they might be able to live longer than what their genes might determine. Right now, the maximum confirmed life span is 122 – the age at which Jeanne Calment, the oldest known and verified person, passed away. That being said, she was not doing CR or exercising. If someone with her genes did, I think they might live to 150.

### *Q: How might an average person benefit from CR?*

A: Around 10-15 years ago, there were two main accepted dogmas about CR: one, the more CR the better; and two, macronutrients are not important. These are no longer the case. The picture today is more complex. It is clear that there is a specific degree and mode of CR that is right for every person. For example, with mice, when (that is, the time of day) they ate their calories made a difference in how CR affected their bodies. It will be interesting to see what happens when we move from mice to humans.

We don't yet have a clear understanding of which CR interventions work on which pathways. My research has always focused on understanding which pathways are important, and how different interventions impact these pathways. Each CR option affects different pathways. Once we know what is affected by what, we can prescribe something depending on the specific factors.

### *Q: Do you think a personalized CR-based approach might be possible as a way to treat conditions such as obesity or diabetes?*

A: Some research I did recently with Bettina Mittendorfer, Ph.D. (also an LLF investigator) found that people can lose weight and body fat without any metabolic benefits. Our study focused on the metabolic effect of high protein CR on insulin sensitivity for women. Participants all lost 10% of their body weight and lost fat as well, but surprisingly experienced no increase in their insulin sensitivity. However, other types of diets did improve their insulin sensitivity. Losing weight, we found, will not provide a metabolic benefit unless the diet is done right.

### *Q: What do you think is the potential of CR in the future?*

A: Currently, people have high accumulations of molecular damage in their bodies. I believe CR has huge potential – not just to slow cellular aging and damage, but also to help diabetes, obesity, cardiovascular disease and cancers. CR provides a framework for us to investigate the biology of aging from a range of novel perspectives.

For additional information about Dr. Fontana's research and other LLF-funded investigations, please visit www.longerlife.org.

# ReCite

*Interesting and relevant articles to the field of insurance medicine recently appearing in the literature...*

**The Cumulative Burden of Surviving Childhood Cancer: An Initial Report from the St. Jude Lifetime Cohort Study (SJLIFE)**
Bhakta N, et al. The Lancet. 2017 Dec 9; 390(10112): 2569-82.
http://dx.doi.org/10.1016/S0140-6736(17)31610-0

This study followed 5,522 ten-year survivors of childhood cancer and assessed the cumulative burden of chronic health conditions (CHCs) in comparison with community controls. The results demonstrated that survivors have twice the burden of disease (by an excess of seven more CHCs) at age 45 compared to the general population. The burden, however, is quite variable and depends on the type of cancer, the type of treatment received, age at diagnosis, and treatment era.

**Editor's Note:** *Given ongoing success in the treatment of childhood cancers, insurers are seeing increasing numbers of adult survivors applying for many types of insurance products. This paper serves as a good reference for medical directors and actuaries to help establish long-term risk assessment guidelines for these individuals. Keep in mind, however, that more recent treatments may be more "precise" and less toxic, and might lead to fewer long-term adverse consequences.*

**The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review**
Nugent SM, et al. Ann Intern Med. 2017 Sep 5;167(5):319-31.
https://www.ncbi.nlm.nih.gov/pubmed/28806817

The authors of this systematic review note that little comprehensive and critically appraised information exists about the benefits and harms of using cannabis preparations to treat chronic pain. Their analysis showed that cannabis may alleviate neuropathic pain in some patients, but there is insufficient evidence for other types of pain. Harms include increased risk for motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment. They also report that there is moderate evidence that light-to-moderate cannabis smoking does not adversely affect lung function over 20 years.

**Editor's Note:** *With ever-increasing legalization of medical cannabis in various jurisdictions, insurers are encountering it more frequently during underwriting. The risk assessment of individuals using this form of treatment includes reviewing the underlying disorder for which the cannabis is being prescribed along with an assessment of the potential benefits and harms from the treatment itself. However, this information is often difficult to ascertain or verify.*

**Long-Term Morbidity and Mortality in Patients Without Early Complications after Stroke or Transient Ischemic Attack**
Edwards J, et al. CMAJ. 2017 July 24;189(29):E954-61.
https://www.ncbi.nlm.nih.gov/pubmed/28739847

Much is already known regarding the risk of subsequent cardiovascular events after stroke. However, the authors note that most long-term studies included those with adverse outcomes in the early high-risk period. This study specifically looked at those individuals with a history of stroke or transient ischemic attack (TIA) who did not have any adverse complications in the first 90 days after discharge. In

this group, researchers found that the hazard for death, stroke, heart attack or admission to continuing care was more than double at 1-, 3-, and 5-years post initial event compared to matched controls.

**Editor's Note:** *While quick recovery from stroke or TIA without early complications is seen as favorable, it should be kept in mind that even in these individuals long-term mortality and morbidity risk persists.*

**Separate and Combined Associations of Obesity and Metabolic Health with Coronary Heart Disease: A Pan-European Case-Cohort Analysis**
Lassale C, et al. European Heart Journal. 2017 Aug 14.
https://doi.org/10.1093/eurheartj/ehx448

The existence of a "metabolically healthy obese" phenotype is debated. To assess this concept, researchers conducted an analysis of the 520,000-person European Prospective Investigation into Cancer and Nutrition study cohort. Incident fatal and non-fatal coronary events were tracked over a median of 12.2 years in healthy and unhealthy normal weight, overweight, and obese individuals. Those at "unhealthy normal weight" were defined as meeting the definition of metabolic syndrome. Relative to the healthy normal weight group, the hazard ratio for the primary outcome for the healthy overweight and healthy obese groups was 1.26 and 1.28, respectively. The groups deemed unhealthy, regardless of weight, had HRs greater than 2.0.

**Editor's Note:** *The authors challenge the concept of "metabolically healthy obesity" and support general population strategies to address obesity. Assessing morbidity and mortality risk associated with build is a complex issue for insurers. This study provides additional insights.*

**No Calm After the Storm: A Systematic Review of Human Health Following Flood and Storm Disasters**
Saulnier D, et al. Prehosp Disaster Med. 2017 Oct;32(5):568-79.
https://www.ncbi.nlm.nih.gov/pubmed/28606191

This review sought to describe the health problems which develop following flood and storm disasters. In addition to death, these events can lead to increased morbidity and health care costs due to transmission of infectious diseases, injuries, exacerbation of existing conditions, malnutrition, and decreased access to preventative and curative treatment. While limited outbreaks of infectious diseases can result, the group did not find evidence to support the occurrence of sustained epidemics after flood and storm disasters.

**Editor's Note:** *Recent large storms causing significant human suffering should prompt life and living benefits insurers to reassess the risks associated with the potentially changing global climate.*

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