*• Dedicated to all the vaccine injured, but especially the children •*

# Vaccine Safety Report 3

## An analysis of 2016 Adverse Events Data & Databases

Canada's two Adverse Events Surveillance Systems—***Canada Vigilance (CV) database and the Canadian Adverse Events Surveillance System (CAEFISS)***—are intended to monitor post-market vaccine safety by evaluating information received in voluntarily submitted adverse event reports and to make public their findings.

1) **AEFI Reports**: Adverse Events Following Immunization reports
   An AEFI is defined as "any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease."
2) **SAE Reports:** Serious Adverse Events within all the AEFI reports.
   An SAE is defined as one that results in
   - Death or a
   - Life Threatening event (say, cardiac arrest or anaphylactic shock)
   - Hospitalization, or Extended Hospitalization if already hospitalized or
   - Disability (say, paralysis or blindness) or
   - Congenital deformity (relates to pregnant mother vaccination resulting in damage to the fetus)
3) **Safety Signals**
   Safety signals relate to the use of a vaccine in the general population after the vaccine has received license approval based on trials by the manufacturer of the vaccine. Their **pre-market** testing determines the list of adverse events in the product literature (which is why one should always read these monographs).
   Safety signals are defined as follows:
   - An increase in the severity or volume of known pre-market adverse events as documented in the product literature, or
   - A post-market "incidence of interest" not documented in the product literature.

   None of the recent reports (2014–2016) from either surveillance system have reported a safety signal.

## *Contents*



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VACCINE CHOICE CANADA
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## Introduction

For readers new to the *VCC Vaccine Safety Reports*, we suggest you read the previous two reports published in **November 2016** and **March 2016** available on our website for broader understanding of the issues discussed below.

We had intended to publish this Safety Report on 2016 data in 2017, as all data from the two AEFI surveillance databases is normally published for a given year by the fall of the following year. However an **unexplained hiatus** in publishing the data occurred for both databases. The way report data were compiled when they were tardily published had also changed.

### CAEFISS

CAEFISS 2016 Q4 (Oct–Dec) data was not published until mid-March 2018. The data cannot be effectively summarized and compared to other CAEFISS reports since the **Q4 2016 CAEFISS report** contained a lot of data from previous years. As explained in the report,

*"It is important to note that technical issues have affected data submission from three jurisdictions and must be considered when interpreting these results. Technical issues prevented one jurisdiction from providing some data from 2012-2015; these issues were resolved in 2016.* ***Also, one jurisdiction provided a batch of serious reports in Q4 2016 with dates of vaccination dating back to 2013.*** *Together, these resulted in an apparent increase in the number of AEFI reports received in Q4 2016 when compared to previous quarters."* [Emphasis ours]

Because the number of the Q4 SAE reports is not attributed by year, how many are actual 2016 reports is unknown. CAEFISS appears to have no intention of sorting the SAE data for the years 2013-2016 for effective comparisons of actual annual data. As they say in the report,

"*In this report, the 2016 quarterly data as well as the four year averages are shown. However,* ***because these data reflect the date the reports were received and not the date the vaccine was given, the ability to compare and interpret patterns is limited."***

This problem is worsened by the 2016 **Q1 Report** noting **2,174 AEFI** reports from another jurisdiction for vaccines administered from 2001 to 2015. However these reports were <u>not included</u> in the 2016 Q1 data (unlike the Q4 data), so comparisons were still possible to previous quarters. But we do not know if this old data will ever be sorted into the annual data for the 15 years it was from. The Q1 Report only notes the proportion of serious reports was 4%, representing 90 SAEs and the median age was 9 at time of vaccination.

Therefore, it is clear that the data in the CAEFISS reports does not necessarily reflect what happened in any given time period. This is why the reports now state that ***the ability to compare and interpret patterns is limited***.

Unfortunately, the whole point of this surveillance system is to be able to do exactly that, compare AEFI data and report changes in patterns that could signal needed safety changes to immunization programs. Each report states this purpose as follows:

*"The primary purpose of vaccine post market surveillance is to detect safety concerns. These concerns include a possible increase in the severity or frequency of expected AEFIs, or occurrence of one or more unexpected events... This allows immunization providers and public health immunization program providers to take public health action..."*

So not only has the **quantity** of publicly reported data been reduced as report numbers have declined year after year, the **quality** of that AEFI data is now compromised as well.

### CV Canada Vigilance

The 2016 *CV Safety Summaries* contained references to high numbers of AEFI reports that recorded **vaccine failure/drug ineffective**. These terms (used interchangeably) mean the person vaccinated subsequently acquired the disease they were vaccinated against.

In order to discover which vaccines had notable failure rates, searches of the CV on-line database were required. However, unlike other adverse event terms, one cannot search for the terms ***vaccine failure*** or ***drug ineffective,*** even though these terms were recorded in the adverse events section of the reports themselves. In order to find these adverse event records, by necessity, all AEFI reports had to be exported and manually tallied to determine the incidence of failure for each vaccine type investigated. Ages were also tallied.

When any report recorded an incident of succumbing to the disease being vaccinated against, even if the terms *vaccine failure* or *drug ineffective* were not recorded, it was also tallied as a vaccine failure.

### Our Concern

Is the decline in quality and quantity of AEFI reported data a reflection of the desire to quell public hesitancy to submit to vaccination programs? If so, coupled with the decline in the overall health of Canadians, these data declines have had the opposite effect on the discerning public. Trust is lost in the surveillance systems and in the medical/public health community declarations that they are truly concerned with the health of the public.

# Part 1 CAEFISS

## The Canadian Adverse Events Following Immunization Surveillance System

### Adverse Events Following Immunization 2016 AEFI Reports

Up until two years ago, the CAEFISS Q4 reports contained cumulative data. Now the total number of AEFI reports each quarter and annual data must be calculated from the published quarterly reports. All CAEFISS reports are found on-line under the heading *Immunizations & Vaccines* **here**.

For 2016, CAEFISS reported a total of 2,685 AEFI reports received. Of these 2,450 or 91% were non-serious reports and 235 or 9% were serious reports (SAEs).

As discussed in the Introduction, the **Q4 report from CAEFISS** contained a dump from one jurisdiction for 4 combined years. As a result the 103 Serious Reports for Q4 are double the previous 3-year average of 54 SAE. With the caveat that the data is compromised by the Q4 unquantified data dump, we present the following information from the four 2016 reports and draw what comparisons seem appropriate using the data as it was published in CAEFISS reports to date.

### Decline in Number of CAEFISS Reports

The number of CAEFISS Reports for the last 11 years is shown the chart below. The steady decline in the number of reports since 2006 is evident. The Canadian population has increased by almost 8% from 2006. Vaccines have been added to routine schedules for children and adults as well. Yet the reporting numbers continue to decline. The decline rate from 2006 is 39%.

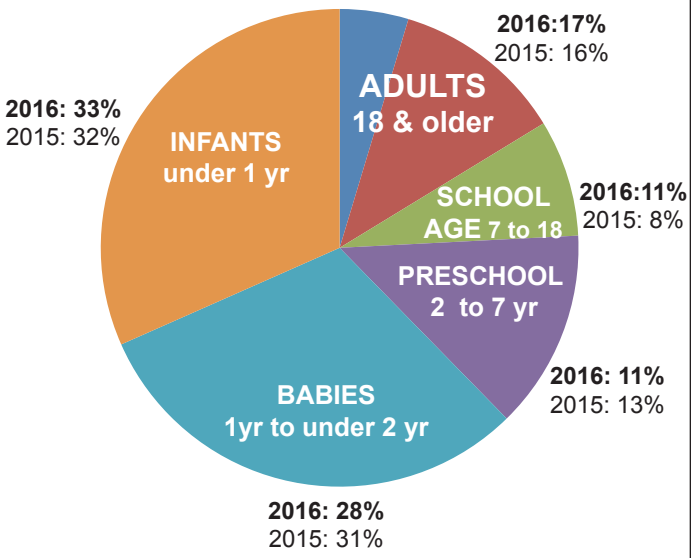
### Serious Adverse Events by Age 2016 vs. 2015

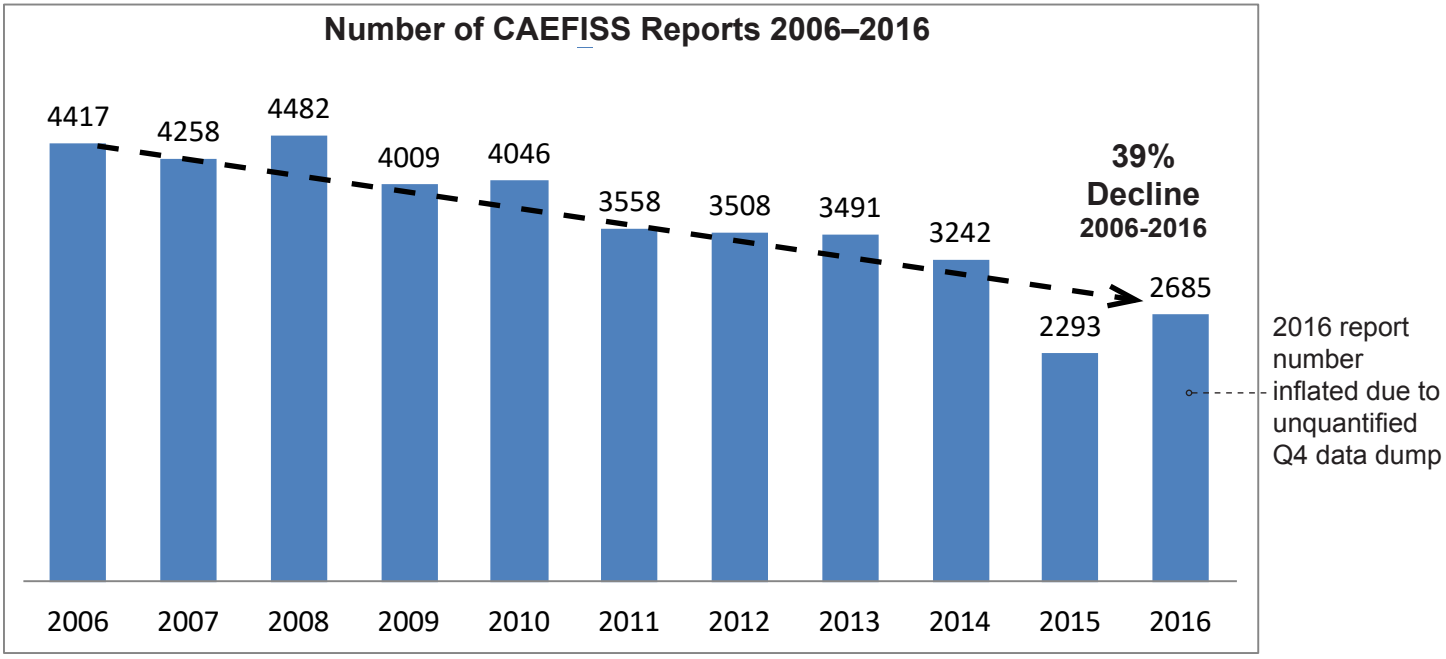
Children always experience the bulk of serious adverse events since they are so heavily vaccinated when they are vulnerable infants and babies. Safety Report 2 covered the 2015 AEFI data from CAEFISS. The chart below from that report has been updated to include the total SAEs for 2016 in comparison to 2015.

There is little change in the Age Chart other than a slight 3% increase for school age children and slight 3% decrease for babies. 3% would represent 7 cases.

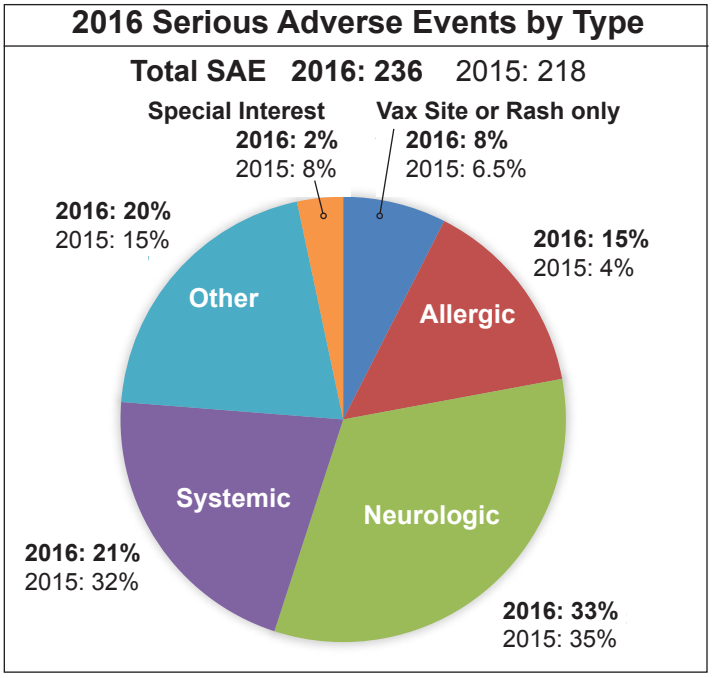
**2016 vs. 2015 Serious Adverse Events by Age**

**2016 Total SAE = 236 Children 83% Adults 17%**
2015 Total SAE = 218 Children 84% Adults 16%



There is more change in the type of adverse events that occurred. This is especially evident in allergic reactions with an 11% increase. Since mid-2015 all anaphylactic shock events have been reclassified as serious allergic reactions since they are life-threatening. Previously only if the event led to hospitalization or death was it classified as serious.




Systemic events involving more than one body system, usually with fever, saw an 11% decrease.

Other events increased 5% and include arthritis, arthralgia, gastro-intestinal reaction, para/anesthesia, intussusception, hypotonic-hyporesponsive episode, thrombocytopenia, parotitis, persistent crying, SIDS/SUDS, and undefined events.

Events of Special Interest (reported in Q1 only) now appear to be included in Other events category.

## Suspect Vaccines

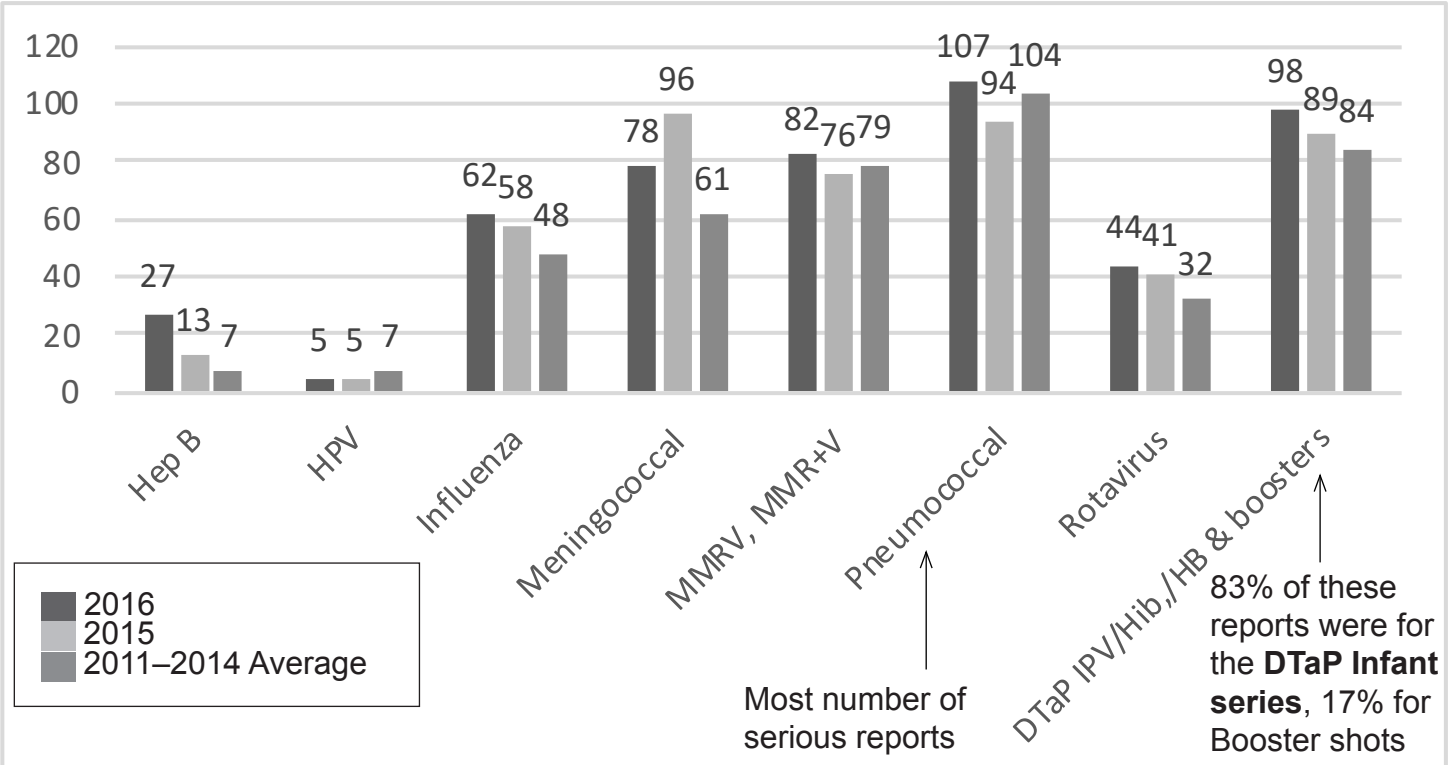
The Suspect Vaccine chart below includes only Serious reports that resulted in hospitalization, disability, congenital deformity, a life-threatening event or death.

CAEFISS does not report ages with this data. However, all of the vaccines in the chart are used in the child vaccine schedule. Hepatitis B, HPV, Tdap boosters and the 4-conjugate Meningococcal vaccine are mostly used for older children. All of the rest are used for infants/toddlers. Influenza and pneumococcal vaccines are also used in the adult population (see page 5).

CAEFISS data is weighted with AEFI reports for children by the IMPACT reporting system located in many pediatric hospitals in Canada.

However this does not explain why no provinces/territories have reported shingles vaccine AEFIs to CAEFISS. As you will see in the CV report, many AEFIs and serious advert events, including deaths, have occurred in seniors who have used this vaccine.

## CAEFISS SAE Reports by Suspect Vaccine: 2016, 2015 & 2011-2014 Average



## AEFI Reporting Rates

CAEFISS quarterly reports do not routinely contain information on reporting rates of adverse events in Canada. Their summary reports do contain this information, either by population counts or by vaccine doses distributed. The *CAEFISS 2013-2015 Summary Report* has apparently been ***delayed***. Last winter an email inquiry informed us, it would be published in April 2018. However it has not yet appeared on-line.

In the first ***VCC Vaccine Safety Report (March, 2016),*** we reported that we had found a "small clue" as to actual, recent reporting rates of adverse events by number of vaccine doses distributed. For the years 2011/12 that rate was 15.2 AEFIs per 100,000 doses. To reflect the ACTUAL number of AEFIs occurring in the Canadian population we developed this chart.

| per 100,000 doses of vaccines distributed | AEFI | SAE |
|---|---|---|
| Number of Reported Events | 15.2 | .85 |
| Number of Actual Events @ 10% reporting rate | 152 | 8.5 |
| Number of Actual Events @ 1% reporting rate | 1520 | 85 |

It reflects the estimated 1% to 10% reporting rates of the passive CAEFISS AEFI reporting system. At these rates actual adverse events are 10 to 100 times more frequent than reported.

In *Vaccine Safety Report 2* we published the chart (on the left below) from the ***2006 CAEFISS Summary Report***. It shows the number of AEFI reports and reporting rates by doses of vaccines distributed. As you see by 2003 & 2004 both the number and the reporting rate had fallen significantly. We have placed our chart from page 3 next to the older chart and also inserted the reporting rate for 2011/12. This only confirms our concerns that AEFI reporting continues to decrease.

In *Vaccine Safety Report 2* (on page 10), we also published a CAEFISS chart from their **2014 Summary Report.** It was based on reporting rates per 100,000 population (rather than per doses distributed). The reporting rates for all age groups combined were given as follows:

| AEFI (SAE) reporting rates per 100,000 population | | | |
|---|---|---|---|
| **2005** | **2006** | **2007** | **2008** |
| 14.8(0.7) | 13.5(0.6) | 12.9(0.7) | 13.4(0.6) |
| **2009** | **2010** | **2011** | **2012** |
| 12.1(0.7) | 11.9(0.7) | 10.3(0.6) | 10.1(0.6) |

We see the reporting rate for Serious Events has remained stable at 0.6 to 0.7/100,000 population. However the overall reporting rate has declined each year, from almost 15/100,000 in 2005 to 10/100,000 population in 2012.

Until the next Summary Report is published we will not have more recent data. Perhaps CAEFISS has decided to cover 2016 as well as 2013–2015 and that is why the report is late in being published?

We did note on page 22 in the ***2016 Annual Report on Vaccine Safety in Ontario***, a statement that the "**national AEFI reporting rate was 8.4 per 100,000 population in 2016**."—down from 10 in 2012.

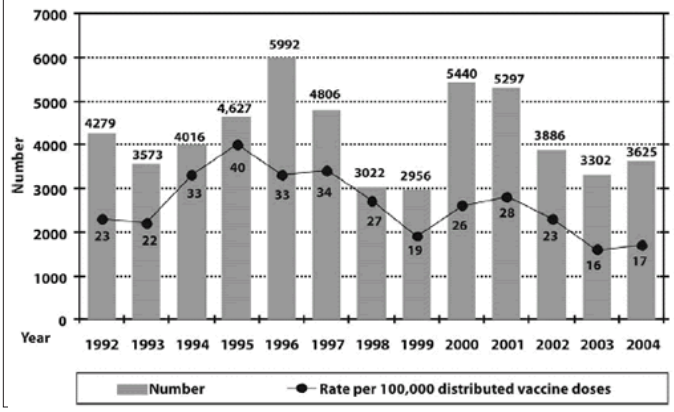
The Ontario report also has an interesting discussion on their provincial reporting rates. After reporting that the rate had dropped from 5.1/100,000 population in 2015 to 4.5/100,000 in 2016, they say:

*"This overall decrease in the provincial reporting rate was somewhat unexpected given that Ontario implemented two new publicly funded immunization programs (Zos for adults aged 65 to 70 years and HPV for boys in grade seven) later in 2016. An increase in reporting rate is typically expected with the implementation of new programs…"*

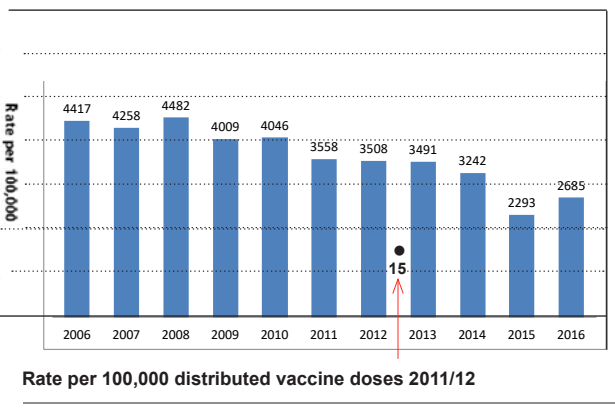
They do suggest they may not see the changes until 2017. However, Ontario has a perennial problem with low AEFI reporting rates. We shall see what happens.

**Number of CAEFISS AEFI Reports**

**1992–2004**




**2006–2016** (No reporting rates except 2011/12)



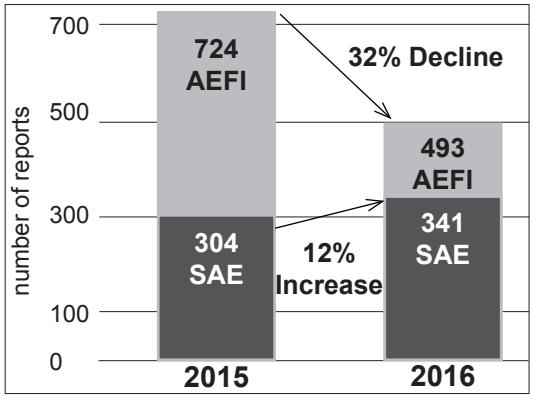
# Part 2 Canada Vigilance Database

## Adverse Events Following Immunization 2016 AEFI Reports

The Canada Vigilance *Vaccine Safety Quarterly Summaries* are difficult to find on the internet. They are found in the index to MedEffect Canada's publication **Health Products InfoWatch**. The issues must be scrolled through to find the CV reports. The 4 reports for 2016 are linked directly here: **Q1**, **Q2**, **Q3** and **Q4**.

As usual there is minimal data in the Canada Vigilance quarterly *Vaccine Safety Summaries*. In 2016 a total of 493 adverse event reports were received. 341 or 69% were Serious Adverse Event (SAE) reports. As this is the database that manufacturers are required to report all serious reactions to, it is not unusual to have a high per cent of Serious reports. In 2015 there were many more AEFI Reports—724 total reports—of which 304 or 42% were Serious.

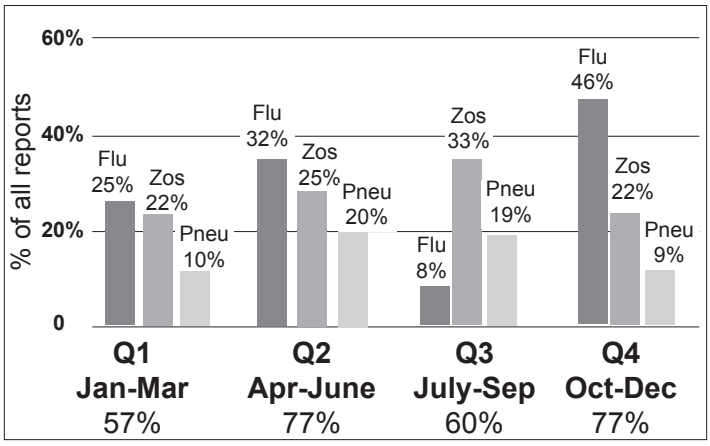
**2016 & 2015 Comparison: All Reports vs SAE**




No explanation is given for the 32% drop in total reports, nor for the 12% increase in Serious Reports. As we have stated previously, the population is increasing, the number of vaccines administered is increasing, yet adverse event report numbers are down.

The vaccines with the largest percent of reports are noted in each of the four Quarterly Reports.

**2016 Vaccines: Most Frequent AEFI Reports**




The three vaccines with the most reports are still Influenza, Zostavax (shingles vaccine) and the Pneumococcal vaccines. No mention is made of other vaccines that would account for anywhere from 20%–40% of all reports.

## More Shots Means More Reactions

### 13 Million Annual Influenza Vaccines

Keep in mind when looking at the frequency of specific vaccine AEFI reports that one must consider the size of the population receiving the vaccines and the number of doses administered.

The annual Influenza vaccines is recommended for almost everyone in Canada every year and is therefore by far the largest vaccine market by volume. According to the **2016/2017 Influenza Vaccine Coverage Report**, 36% of all adults and 24% of all children received influenza vaccines (a 'flu' shot). With a 2017 population of almost 37 million, comprised of 7 million children and 30 million adults, this means approximately 13 million influenza vaccines were administered in the 2016/2017 'flu' season in Canada. The more vaccines administered, the more AEFI reports.

### 4.2 Million Annual Pneumococcal Vaccines

The Pneumococcal vaccines have the next largest market since babies, the elderly and those with chronic medical conditions receive these vaccines as part of publicly-funded routine schedules. The 13-valent conjugate vaccine is administered to babies under 1 year old usually in 3 doses. According to StatsCanada, in 2015/16 388,000 babies were born and the latest data on coverage rate was 88%. This means over **1 million** pneumococcal vaccines were administered to Canadian babies. There were 6 million adults over 65 years of age for which one dose of 23-valent vaccine is recommended. With a **coverage rate** of 37%. This means **2.2 million** vaccines administered. It is difficult to find information on the number of chronically ill adults. A **2016 PHAC report** states that 1 in 5 adults lives with at least 1 of 4 chronic conditions—cancer, diabetes, cardiovascular or respiratory disease. Even using this limited definition, this means 6 million adults live with chronic conditions. With a **coverage rate** of 17.3%, another **1 million** pneumococcal vaccines were administered. There are other high risk groups that also receive this vaccine, but statistics on population and coverage rates are unavailable. The total minimum estimate is that 4.2 million Pneumococcal vaccines

were administered in 2016. This represents the second largest vaccine market in Canada.

**200 Thousand Annual Shingles Vaccines**

Zostavax is another story altogether however. It is only recommended for those over 50 years of age. Further it is an expensive vaccine at approximately $210 for the dose and can only be received once. And Ontario is the **only province that publicly funds** this vaccine for 65 to 70 year olds only. According to the Zostavax website only 2 million doses have been distributed in Canada since it was introduced in 2009. Averaging the 2 million doses over 8 years means 200,000 per year.

One third of all AEFI reports in the usually quiet 3rd quarter were for Zostavax. This is probably due to seniors being administered this vaccine along with their annual flu shot in September. One can only assume the high number of AEFI reports are because this is a highly reactogenic vaccine. And as we shall see, it also has high vaccine failure rates resulting in shingles infections and related syndromes. We discussed this in previous *Vaccine Safety Reports* and recorded our suspicions, now verified in the CV AEFI 2016 quarterly reports.

## Smidgens of Data in the Reports

Though there is little information divulged in the brief CV Quarterly reports, some comments give us clues as to which populations were suffering serious adverse reactions. With investigation we can tracked down what was actually occurring.

The Q2 and Q3 reports both note **drug ineffectiveness** as a frequently reported Adverse Event. This term is a way of saying the vaccine failed and the infection being vaccinated against occurred anyway. This is the first time we have seen this noted in quarterly reports.

Here's the damning Q2 report quote: "*The most frequently reported AEFIs (serious and non-serious) were **all indicative of lack of effectiveness /vaccination failure**. These cases were due to incomplete vaccination or had limited information for assessment.*"

Here's the Q3 report on the same subject: "*The most frequently reported AEFIs (serious and non-serious) included pyrexia [fever], injection site erythema [inflammation], pain in the extremity, and **drug ineffectiveness**.*"

There is no indication in the report as to which vaccines led to the notable number of vaccine failures, nor how many vaccine failures were reported. We searched the 2016 CV database for pneumococcal, varicella and influenza reports assuming these were the likely culprits.

## Varicella Zoster Vaccines

Zostavax (shingles) and Varicella (chicken pox) vaccines were searched. Both of these vaccines attempt to curb chicken pox or shingles caused by the varicella-zoster virus (or human herpes virus type 3). This virus is an intercellular pathogen, that is, once a person has been exposed to this virus and illness symptoms disappear, the virus retreats into the ganglia (nerve cell clusters) in the central nervous system and the sensory system. If reactivated the virus results in shingles and various eye, ear, face, mouth and throat syndromes.

Zostavax is a one-dose, live-virus vaccine administered by subcutaneous injection. It can be received only once and its efficacy wanes rapidly, so timing is important.

In pre-license trials efficacy averaged 50%. For those in their 60's efficacy was 64%, in their 70's down to 38% and for those over 80 only 18%. Also of interest is that *herpes zoster (vaccine strain)* has been added as an adverse event to the product monograph. This was detected in post-market surveillance (although not by Canadian surveillance systems).

## 2016 Varicella Zoster AEFI Reports

Searching the 2016 CV database confirmed our suspicions with 121 AEFI reports for vaccines containing the varicella-zoster antigen. Only a handful of the 121 reports were for Merck's chicken pox vaccines—Varivax and ProQuad (MMR+V)—**3 of which listed either chicken pox or shingles illness** in children.

All the rest of the AEFI reports in this search were for Merck's shingles vaccine, Zostavax. One death was reported. There were only 11 reports where the words "drug ineffective" or "vaccine failure" were cited amongst other adverse events. However, there were **34 adverse events of herpes zoster** (HZ) including 19 listed as herpes zoster (shingles), 8 ophthalmic HZ (blindness), 5 face paralysis, 2 oticus HZ (deafness) and 4 throat, mouth, tongue or jaw complications. All 34 of these Zostavax reports plus the 3 chicken pox vaccine reports means a total of **37 reports or 31% were indicative of lack of effectiveness/vaccine failure.**

## New Developments in the News

Of interest in regard to the types of injuries described in the CV reports, on May 1st, 2018, Potts Law Firm in Houston, Texas issued a **press release**:

"*The first Zostavax shingles vaccine lawsuit was filed today since the vaccine's maker, Merck, requested that the exponentially growing number of cases being filed against it be consolidated into one Court. The lawsuits filed across the nation have alleged that Merck's blockbuster shingles vaccine causes viral injuries*

*such as loss of eyesight, complete and permanent hearing loss, and the very virus it was designed to prevent, shingles.*

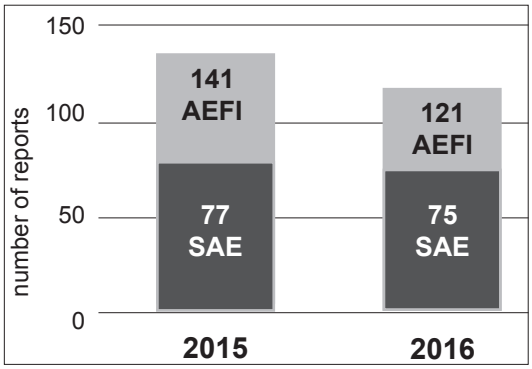
*...The number of lawsuits regarding Zostavax has risen quickly forcing Merck to request that the cases be consolidated into a Multi-District Litigation in front of one District Judge. Thousands more lawsuits are expected to be filed in the coming months.*

*"The Multi-District Litigation is inevitable," said Adam T. Funk, Partner at the Potts Law Firm in the firm's Houston office. Funk added, "Our firm represents a growing number of clients who have been severely damaged due to this vaccine and their lawsuits are being filed rapidly. Zostavax ruined a great many Americans' lives when it did exactly the opposite of what it was intended to do and infected thousands with the shingles virus."*

*Over 36 Million Americans were injected with Zostavax since it was approved by the FDA in 2006. Despite earning Merck as much as $685 Million a year, the vaccine's sales quickly dropped after the U.S. Center of Disease Control recommended in 2017 that adults ask for Shingrix instead of Zostavax. Shingrix was manufactured by GlaxoSmithKline and approved by the FDA only a few days before the CDC made its recommendation."*

However no safety signals have been reported by the Canada Vigilance surveillance system despite the high volumes of Zostavax AEFI reports in Canada that clearly indicate activation/re-activation of the varicella-zoster virus.

**Zostavax 2015 & 2016: 262 AEFI & 152 SAE reported by Canada Vigilance**




Even more surprising, Canada has made no recommendation for preferential use of Shingrix as the USA has, even though Canada licensed Shingrix before the USA and also served as one base for clinical trials, as this October 2017 GSK press release explains:

*"The approval of SHINGRIX in Canada, the first received worldwide, was based on a comprehensive Phase III clinical trial program evaluating its efficacy, safety and immunogenicity involving more than 37,000 people. GSK's global clinical trial program for the vaccine includes involvement of 31 trial sites and over 2100 participants across Canada."*

Shingrix is not a live vaccine. It is a genetically modified (GM), non-live, subunit recombinant vaccine with a patented adjuvant, AS01B. See below product monograph information graphic.

The GM **antigen** is derived from hamster ovaries. So yet another animal DNA product injected into humans, supposedly "purified" of animal cells, although this purification process has proved questionable with other vaccines. This raises the specter of retroviruses and cancer, compounded by the fact the antigen is injected into the elderly who have weakened immune systems.

The **adjuvant** is basically a combination of two lipid surfactants (like squalene or Polysorbate 80—which this vaccine also contains). For a complete discussion of safety risks of injecting surfactants into humans see the articles on our website, ***Polysorbate 80 Risks*** and ***A Glimpse into the Scary World of Vaccine Adjuvants.***

Shingrix cost in Canada is $150 per dose which will likely limit the market as no public funding for this vaccine is in place anywhere (yet).

We will reserve our opinion on the safety and efficacy of this new vaccine for at least 5 years as it comes into use in the real world. Adverse events may be even more problematic than those of Zostavax.

See **Dr. Brownstein, MD on Shingrix** safety and efficacy.

**Shingrix Product Monograph** (Excerpts)

**Pharmacuetical Information:**

The antigen in SHINGRIX is a truncate of the VZV gE expressed in Chinese Hamster Ovary cells presented in the form of a sterile white lyophilized powder. After purification, the non-infectious gE antigen component is formulated with excipients, filled into vials and lyophilized.

**Nonmedicinal Ingredients**:

Cholesterol, dioleoyl phosphatidylcholine, dipotassium phosphate, disodium phosphate anhydrous, polysorbate 80, potassium dihydrogen phosphate, Quillaja saponaria Molina, fraction 21 (QS-21), 3-O-desacyl-4'-monophosphoryl lipid A (MPL), sodium chloride, sodium dihydrogen phosphate dihydrate, sucrose, water for injections

## Pneumococcal Vaccines

There are two pneumococcal vaccines in common use in Canada today:

- PCV13—Pfizer's Prevnar®13, a pneumococcal 13-valent conjugate vaccine used for babies and children under 18 years old and as a booster dose in senior populations, and
- PPV23—Merck's PNEUMOVAX®23, a pneumococcal polysaccharide 23-valent vaccine used for adults & most high risk children.

These vaccines are used to control ***Invasive Pneumococcal Disease or IPD*** caused by the bacteria *Streptococcus pneumoniae*. IPD expresses clinically in different syndromes including (though not limited to) Pneumonia in the lungs, Sepsis (Bacteremia) in the blood and Meningitis in the central nervous system/ brain.

Since 2001 all provinces and territories have offered one dose of PPV23 to those 65 and older and to adults with chronic medical conditions at no cost. It is now also available to immunocompetent people less than 65 in long-term care facilities and to high risk children older than 2 years of age.

The 7-valent conjugate vaccine (PCV7) was incorporated in routine childhood schedules across Canada from 2002 through 2006. In response to the rise in IPD rates in babies and children in 2007, a 10-valent vaccine (PHiD10) was briefly offered from 2008-2010 in 5 provinces prior to the introduction of the 13-valent conjugate vaccine in a nationwide campaign.

PCV7 is no longer available in Canada. PHiD10 (also referred to as PCV10) is available but rarely used here, although it is widely used in Europe and elsewhere. PCV13 was incorporated into the routine schedule for all Canadian children in 2010 and 2011. Most provinces use a 3-dose schedule at 2, 4 and 12 months for infants. PEI offers a 4th dose to high risk infants at 6 months. NWT and Nunavut offer a 4-dose schedule to all babies at 2, 4, 6 & 18 months.

### 2016 Pneumococcal AEFI Reports

There were 98 AEFI reports for pneumococcal vaccines in the 2016 CV database search we performed. There were 40 reports for children, 3 of unknown age, 58 for adults. Of the reports, 14 listed **vaccine failure/drug ineffectiveness** along with other adverse events as follows:

- 27 reports of pneumococcal **pneumonia**: 7 cases in older adults, 17 cases in children ranging in age from 4 months to 4-1/2 years, & 3 of unknown age.
- 13 cases of pneumococcal **bacteremia**: 1 in a 42 year old and 11 cases in children ranging in age from 4 months to 19 months, & 1 of unknown age.
- 4 cases of pneumococcal **meningitis:** all in children ranging in age from 3 months to 25 months.
- 3 cases of serious IPD **ear infections** in children from 3 to 19 months old.
- 2 reports for children that only listed the adverse event as a *pneumococcal infection* and did not specify clinical syndrome.

In the 37 cases of pneumococcal infections in children listed above, 13 babies were less than a year old and would therefore fall into the category of incomplete vaccination (less than 3 doses) mentioned in the Q2 report comments. Nevertheless, we see 37 reported cases for babies, 8 for adults and 4 of unknown age for a total of **49 cases (50% of all reports) indicative of vaccine failure/drug ineffectiveness** related to pneumococcal vaccines in use in Canada in 2016.

### 2016 Influenza AEFI Reports

We found one AEFI report for Influenza vaccines that listed vaccine failure along with influenza as adverse events. However there were 8 other reports that listed influenza as an adverse event. The cases ranged in age from 15 years to 72 years. Therefore of the total 110 AEFI reports only **9 (8%) Influenza reports were indicative of vaccine failure**.

### 95 Total CV 2016 Vaccine Failure Reports

Adding the 9 Influenza reports, 37 Varicella Zoster reports and the 49 Pneumococcal reports results in a total of **95 AEFI reports that were indicative of vaccine failure/drug ineffectiveness or 19% of the total 493 AEFI reports for the year.**

We did not search all vaccines, so other reports may have also included this information. Regardless, it is no wonder the CV surveillors felt constrained to report vaccine failure in their quarterly vaccine safety summaries.

## Why Vaccines Fail

Vaccines are intended to control or eradicate various communicable illnesses in the population. Vaccine testing is done by the vaccine industry, either by the manufacturers themselves often through hire of testing firms that carry out trials that meet regulator's pre-license testing requirements or through industry grants to academics and medical professionals in universities and hospitals. The days of government testing are long gone in most developed nations including Canada.

## Efficacy & Effectiveness

These two terms are often used interchangeably in medical literature. However they were intended to have distinct meanings. The intent of the original scheme of vaccine testing was that pre-license Phase I randomized, controlled trials or RTCs would measure the actual efficacy of the vaccine. **Efficacy** is defined as the per cent reduction in disease incidence in a vaccinated group compared to an unvaccinated group under optimal (i.e., controlled) conditions.

RTCs are both expensive and time consuming and often conveniently deemed "unethical". Animal studies that could serve as valid proxies for human experiments are rarely performed in Phase I trials. Today, animal studies are largely performed by independent (not vaccine-industry funded) research scientists.

The next step in vaccine testing were to be pre-licensure Phase II and post-licensure Phase III trials. These trials show **Effectiveness:** defined as the ability of a vaccine to prevent *outcomes of interest* in a *real world* setting. These studies use larger populations, have less strict eligibility requirements and are of longer duration than Phase I trials. **Outcomes of interest** include vaccine safety (adverse event reporting and monitoring) and the incidence, severity of disease and hospitalizations in vaccinated populations compared to the control group. This studies were also intended to assess benefits versus risk and include cost calculations.

Far too many effectiveness studies are poorly designed. They often contain bias in choice of subjects and/or controls, are not properly blinded, are done with small populations that limit statistical significance of results, rarely use real saline placebos and thus have no true control groups (so establish nothing), make no attempt to medically monitor or examine adverse events that occur in formerly healthy subjects, have time lines that are too short to effectively evaluate adverse events and have **defined away the significance and causality of these events**.

Industry gives two definitions of **Vaccine Failure**. Both assume that seroconversion equals protection.

**Primary vaccine failure** is failure to seroconvert after vaccination. Up to 10% of the vaccinated do not seroconvert, depending on the particular vaccine and the age and health of the vaccinated population.

**Secondary vaccine failure** is waning immunity after seroconversion. Vaccine immunity wanes at different rates depending on the vaccine. 10 years is given as the upper limit before some vaccines lose their 'protective' ability, some wane in as little as 2–3 years.

## Immunogenicity Measures Effectiveness

In fact, we have devolved to the point that vaccine effectiveness, licensing, and vaccine policy is being determined almost solely by immunogenicity.

This **2018 UK study** published in *Lancet*, substantiates this concern as well. In the discussion section they state, *"Extended **PCV vaccines have been licensed on immunogenicity alone** and thus there is an established precedent for using immunogenicity studies to inform vaccine policy."*

Closer to home, the **National Advisory Committee on Immunization** (NACI) provides medical, scientific, and public health advice on the use of vaccines in Canada. In a **2015 PPV23 revaccination statement** they specifically state (regarding PPV23 vaccine in Section IV: Vaccines), *"**Efficacy**–Direct and Indirect No study found; **Effectiveness** No study found; **Immunogenicity** A total of 10 studies were reviewed..."* The statement then goes on to discuss the 10 immunogenicity studies where antibodies are measured as a basis for their policy decision.

**Immunogenicity** of a vaccine is determined by measuring seroconversion. Seroconversion refers to the levels of antigen-specific antibody titers found in a subject's blood after vaccination.

Unfortunately however, the antibodies produced by seroconversion are only ***surrogates of protection,*** meaning they may protect against a disease. It is well documented that some people have high titer levels, yet still succumb to the infection and others with low titer levels do not succumb to the infection at all. **In other words, antigen levels do not necessarily correlate to protection.** They are only a *surrogate* for actual immunity.

Additionally the titer levels required to produce the assumed 'protective' effect differ for all vaccines. The level of titers is often not even established before the vaccine is licensed. For example the post-licensure **Pneumovax23 product monograph** clearly states in **Section 14.2 Immunogenicity:** *"The levels of antibodies that correlate with protection against pneumococcal disease have not been clearly defined."*

In a like manner, the **Prevnar 13 product monograph** references the WHO standard for the concentration of antigens produced and then states, *"This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis."* So much for ***correlates to protection***.

## Noninferiority Testing

Building on seroconversion as a basis for "efficacy/

effectiveness" of vaccines, regulators have allowed the industry to use **noninferiority (NI) testing** in establishing the protective effect of a new vaccine.

Rather than actually testing a new vaccine for efficacy or effectiveness against a well-chosen control group in Phase 1, II or III Trials, the antigen levels produced by a previous vaccine that did employ controlled trials is used as a baseline. If the antigen levels (quantity of antigens) found in the new vaccine fall within a certain margin of those produced by the previous vaccine, then the new vaccine is considered "non-inferior".

Most NI trials choose a 10% margin. This means the new vaccine can produce up to 10% fewer antigens and still be considered "non-inferior" (even though it obviously IS inferior). Some NI trials use even larger margins. This 2014 European article titled ***Comparing vaccines: A systematic review of the use of the non-inferiority margin in vaccine trials*** explains,

*"Among the 143 studies using an NI margin...66% used a margin of 10%, 23% used margins lower than 10% and 11% used margins larger than 10% (range 11.5–25%)",* and *"As observed, 85% of the studies did not discuss the method of margin determination; and 19% of the studies lacked a confidence interval or p-value for non-inferiority."*

The second requirement of noninferiority testing is to assure that the vaccine antigens can actually kill the targeted bacteria (quality of the antigens) through a process called opsonophagocytosis.

For a real world example of noninferiority testing, the **product monograph for Prevnar 13** is explicit that NI testing was used to estimate 'efficacy' of this new vaccine. It references the WHO standard for the concentration of antigens produced. Then it goes on to explain, *"the main mechanism of protection against pneumococcal disease...can be measured by an opsonophagocytosis activity assay (OPA). The percentage of subjects with an OPA titre ≥ 1:8 is used for comparison between vaccines,* ***although the data to support the OPA titre ≥1:8 as a marker of protection are currently insufficient.***"

An interpretation of the actual noninferiority testing described in the monograph for Prevnar 13 is found in the **2010 licensing information** from the American counterpart to NACI, the Advisory Committee on Immunization Practices (ACIP), as follows:

*"Among infants receiving the 3-dose primary series, responses to three PCV13 serotypes (the shared serotypes 6B and 9V, and new serotype 3)* ***did not meet*** *the prespecified, primary endpoint criterion…however, detectable OPA antibodies to each of these three serotypes indicated the presence of functional antibodies…After the fourth dose, the IgG geometric mean concentrations (GMCs) were comparable for 12 of the 13 serotypes;* ***the noninferiority criterion was not met for serotype 3****."*

Importantly, most children in Canada receive only 3 doses of this vaccine, so antigen levels of 3 serotypes are not protective for them. Further, Serotype 3 was one of the three new serotypes targeted by PCV13 due to the rise in the number of cases of IPD caused by this serotype.

"*But never mind that 3 serotypes at 3-doses are not protective and one, serotype 3 failed noninferiority testing altogether, we'll license the vaccine anyway*," seems to be the attitude of the regulators and their experts. "*After all, the 3 serotype antigens did pass the OPA*." Even though the OPA was an "unproven marker of protection" and even if the antigens could kill the bacteria there were not enough of the antigens produced to do so effectively according to their own "*primary endpoint criterion*."

We will soon see what a short-sighted policy decision this was since serotype 3 infection is, of course, not being controlled well by this vaccine or the previous one, PPV23 which also targeted serotype 3.

Speaking of PPV23, the United Kingdom's Joint Committee on Immunization or JCVI (counterpart to NACI in Canada and ACIP in the USA) had a similar go-round with this vaccine. In March of 2011, **the JCVI recommended** the PPV23 program for seniors be suspended. They found the vaccine effectiveness (VE) "poor"—VE of 23% over 6 years and estimated VE at 1% after 6 years. Revaccination was not an option due to "lack of improved, and possibly an impaired response to revaccination." They considered the use of PCV13 in adults but found "no conclusive evidence currently" that it "would be more effective in older adults."

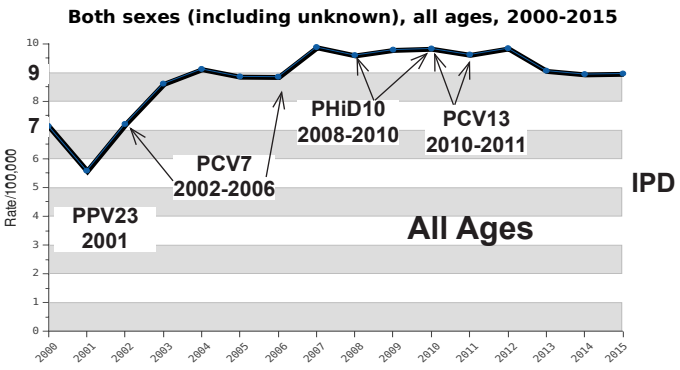
The UK **Department of Health asked** for views of interested stakeholders before they cancelled the program. As a result, the **JCVI issued a new recommendation** in July of 2011. Their comment on the manufacturer Sanofi's submission is particularly interesting. They concluded it provided a "*selective interpretation of evidence*" and while "*many data had been provided on the* ***immunogenicity of PPV23, these cannot be used to predict clinical outcome reliably, due to the lack of an established correlate of immune response with protection.***" However, they reinstated the program based on a "new, extended" epidemiological and cost-benefit analysis that found a VE of 48% for 2 years following vaccination and "cost effective".

# A Deeper Look at Pneumococcal Vaccines

In Canada the rate and number of IPD cases is tracked by the **Canadian Notifiable Diseases Database** (CNDD). Invasive Pneumococcal Disease (IPD) was added as a notifiable disease in 2000. Below are the downloaded 2000–2015 IPD **rate charts for various age groups**. Notes on dates of implementation of publicly funded routine vaccination programs across Canada have been added.

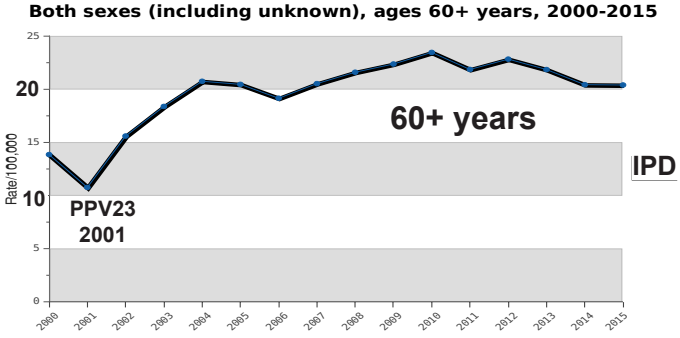
One can see from the **All Ages** chart that the overall rate of IPD for all ages **has not diminished** since introduction of the pneumococcal vaccines. It has increased from 5.5 cases per 100,000 population in 2001 to 9 cases per 100,000 population in 2015.

**Rate per 100,000 of reported cases over time in Canada**



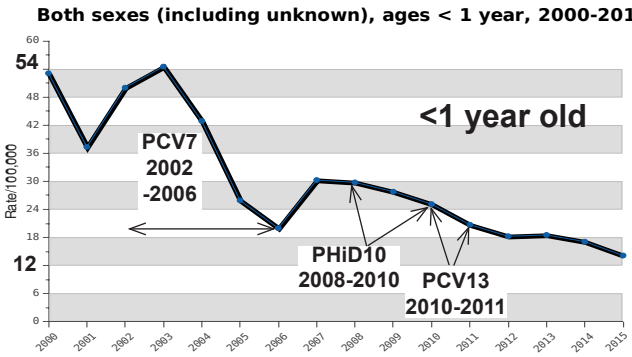

When we look at charts for specific age groups we see this increase is driven by adults over 60 years old. The 60+ chart shows a fairly steady rise of IPD case rates from a low of 11 cases/100,000 in 2001 to 20 cases/100,000 in 2015, a doubling of the rate of IPD in the elder population despite PPV23 vaccine use.

**Rate per 100,000 of reported cases over time in Canada**

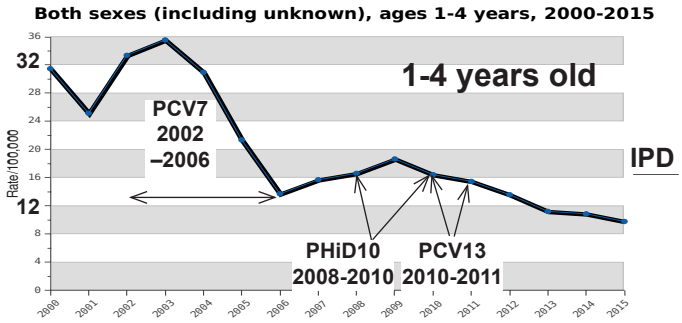



In counter-balance to the rate increase in elders, the youngest children have seen declines in IPD, after an initial increase from 2001–2003. In infants less than one year old rates have fallen from 53/100,000 in 2000 to 14/100,000 in 2015. In toddlers and children from 1 through 4 years old rates have fallen from 32 in 2000 to 11/100,000 in 2015. No other age groups have seen such steep declines.

**Rate per 100,000 of reported cases over time in Canada**




**Rate per 100,000 of reported cases over time in Canada**




The decline in rates after introduction of PCV13 is much less dramatic than that which followed the introduction of PCV7. This is because the PCV7 antigens for the 7 serotypes causing the largest burden of IPD disease in these age groups were effective. Whereas the 3 antigens added to PCV13 were directed at less burden of disease and were also not as effective (as we saw in the discussion of noninferiority testing).

The Notifiable Disease charts can be configured for either population-based case rate or number of cases reported. In terms of case numbers reported, in babies and children less than 5 years old, numbers of reported cases were almost halved over the 16 year period of these charts.

In the 60+ age group, the opposite has occurred. The number of reported cases went from 437 in 2000 to 1,641 in 2016. Numbers of reported cases increased almost 4 times. We will explore this further.

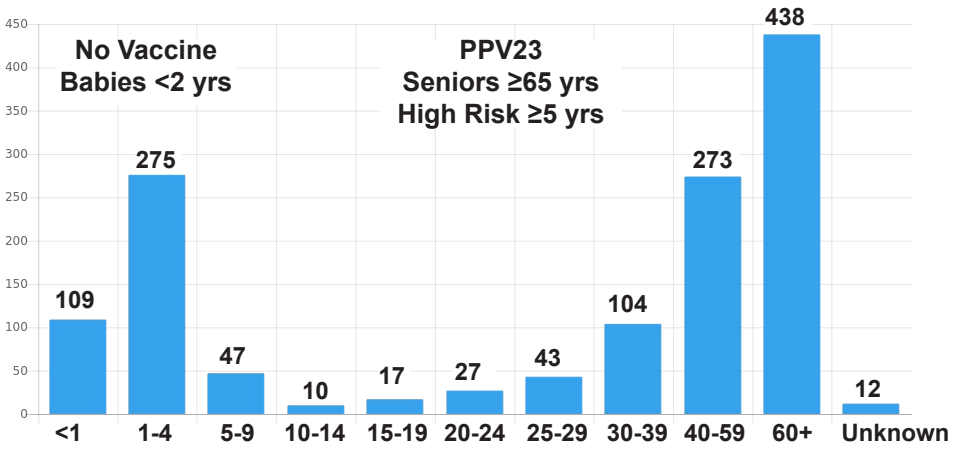
Whether looking at rates or case numbers, the rise in IPD in those over the age of 60 years really puts in question the effectiveness of the PPV23 vaccine in controlling IPD in older Canadians. Many thoughtful research scientists have spoken to this, as we will see.

The info-graphic on the next page examines in more detail the changes in case numbers in all age groups. The discussions there and which follow explain that changes in disease epidemiology following introduction of vaccines are well documented in medical literature.

## Notifiable Diseases Charts: Number of reported IPD Cases by Year & Age Group

(Numbers of cases added)

### **Year 2000** IPD Reported Cases—**1357**



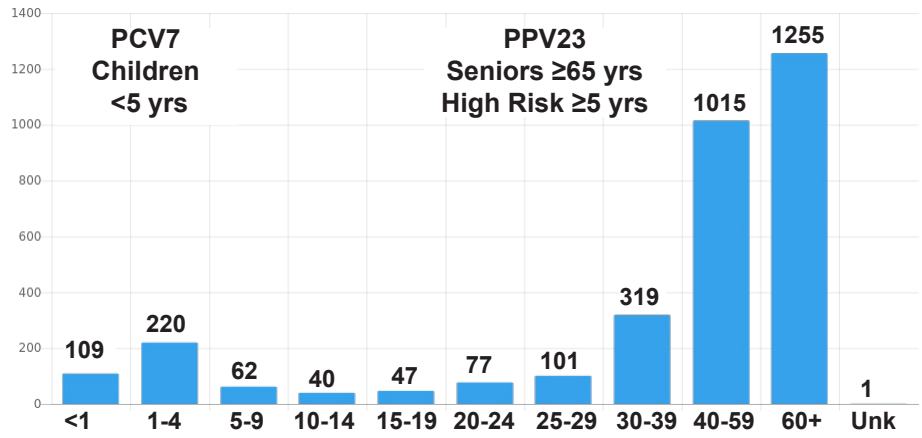

Note: The number of cases scale on this chart is much smaller the scales used on the charts below.

In 2000, no routine childhood vaccine programs were in place for IPD.

It was a fairly rare disease with 430 cases reported in children <5 years old and 438 cases in seniors over 60 years old.

In 2000, 23-valent PPV23 was being used for seniors and high risk groups over the age of 5. By the next year it was being used in all Provinces/Territories in Canada for seniors & any high risk groups > 5 years old.

### **Year 2007** IPD Reported Cases—**3247**

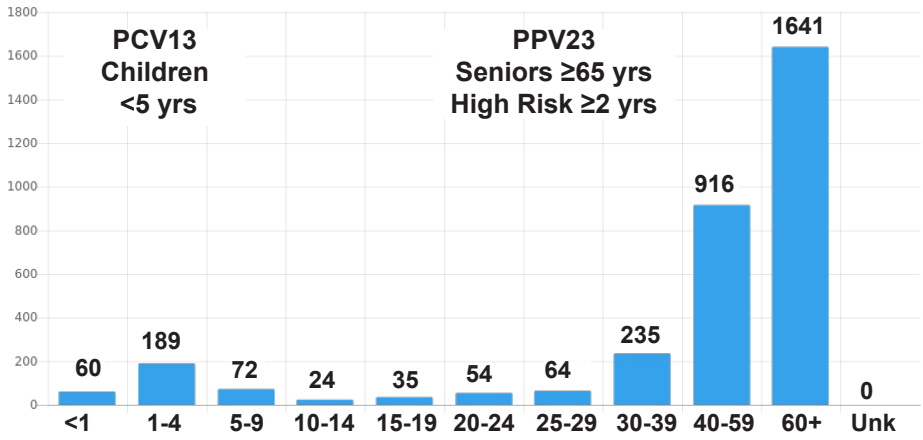



Since PPV23 was not effective in children less than 2, the first childhood vaccine–PCV7–was developed and phased in between 2002 and 2007.

By 2007, PCV7 was in use for all Canadian babies. Note the number of cases of IPD had not changed from the pre-vaccine era (2000) for children <1 year old. Case numbers for children aged 1–4 decreased from 275 to 220 for 55 fewer reported cases of IPD in this age group.

Meanwhile increases of IPD in all other age groups occurred. This is partly explained by a phenomena called **Epidemiological Shift**, which occurs when vaccine programs target young age groups and disease shifts to older ages. The shift, evident in all ages over 5, is especially pronounced in the 3 oldest age groups. The number of cases of IPD in the 30-39 year age group tripled from 2000 numbers, almost quadrupled for the 40-59 year age group and tripled for the 60+ group.

### **Year 2016** IPD Reported Cases—**3290**




PCV13 was introduced in 2010/11 for children less than 5 years old. By 2016, a significant decline from 2007 numbers is seen in babies <1 year old (45% decline). The 1–4 age group shows a 14% decline. However the 5–9 year group shows a 16% increase in cases compared to 2007. All other age groups show small declines from 2007, except 60+ which showed a 31% increase from 2007 case numbers.

**Comparing the reported case numbers for the entire span from 2000 (the pre-PCV vaccine era) to 2015**, only in the two youngest age groups have cases declined. Cases in 30–39 group increased 126%, 40–59 group increased 236% and the 60+ increased 275%. Obviously the pneumococcal vaccines are not having the desired effect in older populations.

Searching the medical literature verifies that the effectiveness of PPV23 for both elders and others considered at high risk for IPD has always been debatable.

This entire problem began when the PPV23 was licensed in the late 1970s based on 3 studies of healthy adults in South Africa and Papua New Guinea.

A 2002 UK paper titled, ***Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials***, explains as follows: *"The modern pneumococcal vaccine has now been licensed for two decades, yet the debate over its efficacy persists. Part of the reason for the controversy is that the current vaccines were not subjected to randomized controlled trials before their release. It is therefore crucial, despite assertions to the contrary that the new protein-conjugated pneumococcal vaccines* [PCV for children] *are properly evaluated."*

The explanation of why these three baseline studies were inappropriate follows: [emphasis ours]

*"Three studies have shown that the vaccine is effective ...in unique populations of healthy young adults at high risk for pneumococcal infection, such as South African gold miners and New Guinea highlanders. These subjects are capable of mounting a vigorous antibody response to the polysaccharide vaccine. They are also exposed to respiratory irritants (mining dust or fireplace smoke), which increases the risk of developing pneumonia. Finally, they share close living and sleeping quarters, which enables easy spread of a virulent strain of* Streptococcus pneumoniae *in the community.* ***This set of unusual circumstances is ideal for demonstrating the potential efficacy of the pneumococcal vaccine.***

***In more commonly encountered circumstances the vaccine is not effective.*** *Adults with immunosuppressing conditions, and many with chronic medical disorders, are unable to mount an adequate antibody response to the vaccine. Antibody response and vaccine efficacy are also reduced in the elderly, especially after age 75, and wane more quickly. Furthermore, since pneumonia in the elderly is usually caused by aspiration of oropharyngeal secretions, pneumococcal vaccine may prevent infection with* **S. pneumoniae** *but not pneumonia of other causes. Thus in non-epidemic situations the vaccine may be less effective in preventing pneumococcal infections. Even if the vaccine were effective, vaccinating millions of people in the UK in the hope of preventing perhaps 60% of the 7 cases of pneumococcal bacteraemia/100,000 persons is of dubious value."*

This paper is one of 6 meta-analyses papers that were published between 1998 and 2003 on the PPV23 vaccine. They all reached the same conclusion: the PPV23 vaccine was not effective in preventing invasive pneumococcal pneumonia in adult populations.

A 2009 Swiss study titled ***Efficacy of pneumococcal vaccination in adults: a meta-analysis*** concluded there is **no evidence of vaccine protection in trials of higher methodological quality** and *"Pneumococcal vaccination does not appear to be effective in preventing pneumonia, even in populations for whom the vaccine is currently recommended."*

The John Hopkins Medical School has an overview, reference article for medical professionals titled, ***Pneumococcal Vaccine: Vaccinate! Revaccinate??***. It states: *"**It should be noted that vaccination does NOT reduce pneumonia.** A meta-analyses shows no decrease in pneumonia incidence as a result of vaccination, however it has been shown to be about 60-70% effective in preventing invasive disease (meningitis, bacteremia)."*

The article is quoting this 2003 retrospective study, ***Effectiveness of Pneumococcal Polysaccharide Vaccine in Older Adults.*** This study found *"receipt of the pneumococcal vaccine was associated with a significant reduction in the risk of pneumococcal bacteremia...but* ***a slightly increased risk of hospitalization for pneumonia****. Pneumococcal vaccination did not alter the risk of outpatient pneumonia or of any case of community-acquired pneumonia, whether or not it required hospitalization..."*

The study concluded, "*These findings support the effectiveness of the pneumococcal polysaccharide vaccine for the prevention of bacteremia, but they suggest that* ***alternative strategies are needed to prevent nonbacteremic pneumonia, which is a more common manifestation of pneumococcal infection in elderly persons****."*

## Revaccination of PPV23 Vaccinees

The John Hopkins Medical School advice page also discusses revaccination with PPV23 and does not recommend it for seniors ≥65 for the same reasons the UK JCVI rejected it. (See page 11.) We especially note this statement:

*"However, the relationship between antibody titer and protection from invasive disease is not certain (i.e., higher antibody level does not necessarily mean better protection), so the ability to define the need for revaccination based only on serology is limited."*

This brings to mind the 2016 Canadian NACI recommendation to revaccinate seniors with PCV13. This followed the same ACIP recommendation in the USA. If the use of serology—that is immunogenicity studies that measure antibody titers—is a "limited

basis" for determining the need to revaccinate, why did NACI use just such immunogenicity studies for their recommendation?

Just like the older controversy surrounding the effectiveness of PPV23, revaccination of the older population with PCV13 has been a subject of debate. A number of studies in various countries have questioned the effectiveness of revaccinating with PCV13. (References to 4 studies are found in the Spanish article linked below.) We must note that studies most referenced to show effectiveness of PCV13 in older adult populations were 1) "placebo" controlled with another vaccine, 2) healthy subject biased, 3) sponsored by vaccine manufacturers or conducted by researchers who worked for manufacturers and thus had definite conflict of interest. Many of these studies also say that since PCV7 vaccines reduced incidence of IPD by these serotypes in older populations, that PCV13 will do the same. A completely unsubstantiated opinion as will be seen in the following section.

Here is the Abstract description of a 2011 retrospective analysis of PCVs used in adults, ***The Potential Role for Protein-Conjugate Pneumococcal Vaccine in Adults: What Is the Supporting Evidence?***

*"Vaccination with protein-conjugate pneumococcal vaccine (PCV) provides children with extraordinary protection against pneumococcal disease, although the protective effect may be blunted by the emergence of replacement strains. Studies in adults have compared PCV with pneumococcal polysaccharide vaccine (PPV) using surrogate markers of protection, namely, serum anticapsular IgG antibody and opsonic activity. Results suggest that PCV is at least as effective as PPV for the strains covered,* **but a definitive and consistent advantage has not been demonstrated.** *Unfortunately, persons who are most in need of vaccine do not respond as well as otherwise healthy adults to either vaccine. Newer formulations of PCV will protect against the most prevalent of the current replacement strains, but replacement strains will create a moving target for PCVs. Unless an ongoing trial comparing 13-valent PCV with placebo (not to PPV) demonstrates a clearly better effect than that seen in the past with PPV, cost-effectiveness considerations are likely to prevent widespread use of PCV in adults."*

The current **CDC vaccine price list** shows PCV13 adult dose at more than double the cost of PPV23 adult dose, $113 to $49 respectively.

One wonders if NACI and ACIP will reconsider the decision to revaccinate PPV23 vaccinees with PCV13 especially in light of more recent studies. For example, consider this large study from Spain (published in 2018), ***Evaluating clinical effectiveness of 13-valent pneumococcal conjugate vaccination against pneumonia among middle-aged and older adults in Catalonia.*** Abstract details:

**Background**

Benefits using the 13-valent pneumococcal conjugate vaccine (PCV13) in adults are controversial. This study investigated clinical effectiveness of PCV13 vaccination in preventing hospitalization from pneumonia among middle-aged and older adults.

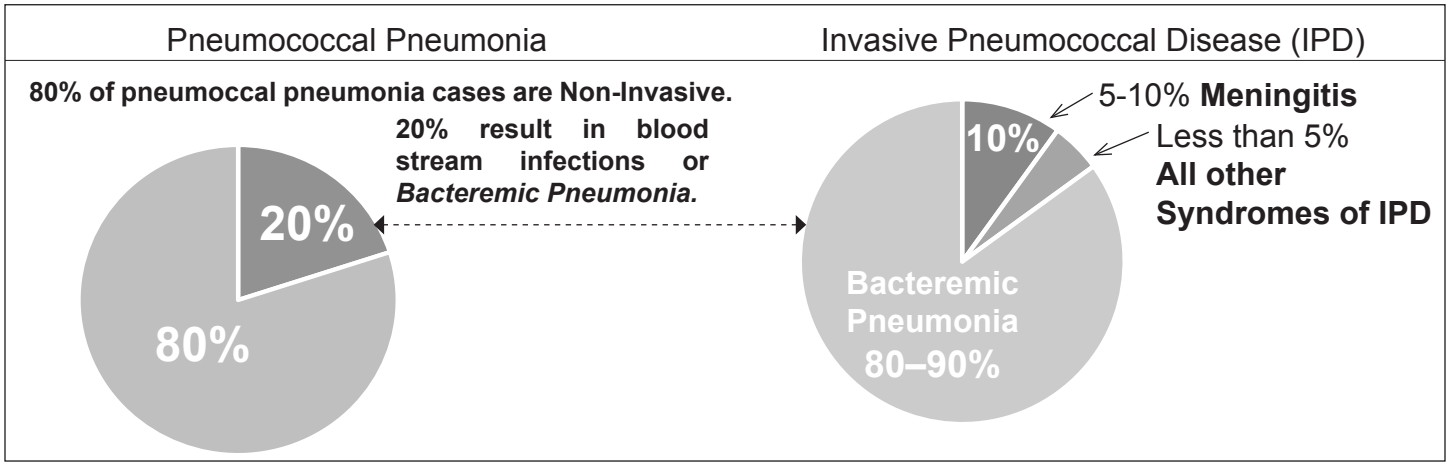
***Conclusion***

Our data does not support clinical benefits of PCV13 vaccination against pneumonia among adults in Catalonia.

In fact this study found that PCV13 vaccination did *"not alter significantly the risk of pneumococcal pneumonia or all-cause death"*, but was ***"significantly associated with an increased risk of all-cause pneumonia"*** for the 6,900 adults in the study.

Considering the data and opinions in this section, is it any wonder we see IPD incidence continuing to rise for Canadian seniors?

The graphic below shows per cent of pneumococcal pneumonia cases that lead to IPD and IPD incidence by syndrome.



| Vaccine | Serotypes in Pneumococcal Vaccines | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 4 | 9V | 6B | 14 | 18C | 19F | 23F | 1 | 5 | 7F | 3 | 6A | 19A | 2 | 8 | 9N | 10A | 11A | 12F | 15B | 17F | 20 | 22F | 33F |
| Pneu-C-7 [1] | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | | | | | | | | | | | | | | | | |
| Pneu-C-10 | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | | | | | | | | | | | | | |
| Pneu-C-13 | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | | | | | | | | | | |
| Pneu-P-23 | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |

## National Laboratory IPD Surveillance

In order for reported cases of IPD (whether pneumonia or other syndromes) to appear on the Notifiable Disease Database charts we looked at previously, 88% of the 2016 cases were tested for IPD serotypes to confirm they are indeed cases of IPD.

The chart above is from the ***Canadian Immunization Guidelines***. It shows the serotypes that the antigens in each vaccine target. Pneu-23 (PPV23)—the adult vaccine, used for decades—contains antigens for all serotypes except 6A. Pneu-C-7 (PCV7) is no longer available in Canada, however all of its serotype antigens are contained in the 3 other pneumococcal vaccines. Pneu-C-13 (PCV13) is the currently mandated childhood vaccine.

The various IPD cases arising from the 92 (so far discovered) serotypes of the bacteria *Streptococcus pneumoniae* are tracked and reported on annually by the *National Laboratory Surveillance of Invasive Streptococcal Disease* program. These annual reports are no longer posted on-line! Only the **2016 Executive Summary** of the report is posted with an email link to request copies of the full report. Earlier National Laboratory annual IPD reports (2010–2014) are linked at the bottom of a different web page titled, ***Invasive Pneumococcal Disease,*** (along with many other IPD-related publications).

The chart below is from the latest 2016 Report (using 2015 data). It confirms the large decreases in IPD in children under 5 and the steady increase in all other age groups. (Our notes are added in red.) Keep in mind when looking at this chart that the less-than-5-year-old line represents around 5% of the total population of Canada and the greater-than-5-year-old line represents the other 95% of the population.

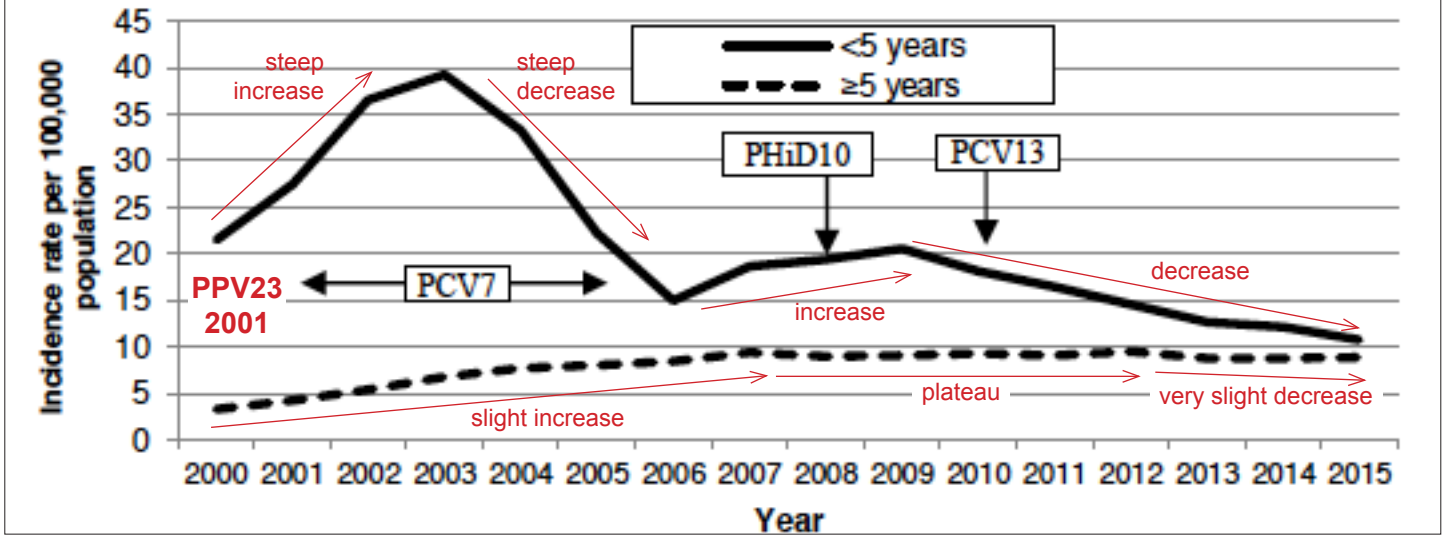
## Serotype Replacement

The text in the report accompanying the chart below explains that *"...after the introduction of vaccination programs, pediatric IPD increased due to serotype **replacement** among pneumococcal infections with increases in non-PCV7 serotype infection such as 7F & 19A."*

The steep increase in IPD from 2000 to 2003 in young children (<5) shown on the chart below is what the statement above is in reference to. Also note the increase from 2006 to 2009 in young children. The slight increase from 2000 to 2007 in the older population after both PPV23 and PCV7 programs is also evidence of this phenomenon.

Serotype replacement is a well known occurrence when vaccinating against bacterial infections. When certain serotypes are suppressed through vaccination, other serotypes arise to replace them and continue as a cause of the targeted disease. As replacement occurs,

**Figure 1. Annual incidence of IPD in Canada, 2000-2015**



more vaccines with antigens against the new serotypes must be developed. Hence the 10-valent vaccine (PHiD10 or PCV10) included 3 more serotypes—1, 5 & 7F—to combat serotype replacement after introduction of PCV7. Then PCV13 vaccine was developed to combat 3 more serotype replacements—3, 6A & 19A. More about serotypes 3 & 19A in a moment.

As this **2016 article in the *Journal of Clinical Microbiology*** explains:

*"Like many bacteria, the pneumococcus can import DNA from other strains or even species by transformation and homologous recombination, which has allowed the pneumococcus to evade clinical interventions such as antibiotics and pneumococcal conjugate vaccines (PCVs)…*

*As a result of this recombination-mediated shuffling of serotype and genotype, when PCVs were introduced, the population already contained potential vaccine escape variants, some of which have subsequently become common and important causes of disease."*

Bacterial vaccines for Hib and meningococcal diseases are another example of serotype replacement occurring not only within bacterial strains, but also influencing colonization of other bacterial species in the population. All leading to the need for more vaccines. See the *Vaccine Merry-Go-Round* re-printed on the last page of this report.

There are numerous studies that acknowledge serotype replacement after PVC7 vaccination programs. The two below are case studies from pediatric hospitals in the US and Canada.

A 2012 US study titled, ***The Changing Epidemiology of Invasive Pneumococcal Disease***, collected data for a 14 year span (pre- and post-vaccine) from hospital records of children who had been diagnosed with IPD. It cites epidemiological shift to older age groups, worsening symptoms, and serotype replacement:

- In the pre-vaccine era, 54% of children with IPD were less than 2 years of age, 27% were between 2 and 4 years, and 20% were older than 5.
- The proportion of children with IPD younger than 2 years decreased after PCV7 introduction to 43%, but the proportion of disease among children 5 years or older increased to 28%, shifting the median age of children with IPD from 19 months to 27 months.
- There was an increase in the proportion of children with IPD who had one or more underlying chronic medical conditions: 1.6% during the pre-vaccine period versus 7.5% in the vaccine period.
- Immune-compromising conditions were noted more frequently in the vaccine era: 14.5% vs. 5.5%
- While meningitis rates remained stable, and bacteremia decreased from 37% to 25%, IPD associated with pneumonia increased substantially from 29% to 50%, primarily due to an increase in complicated pneumonia (17% to 33%).
- 28% of the children with IPD were fully immunized with PCV7 (4 dose schedule) in the vaccine period, 48% had received from 1 to 3 doses of PCV7.
- Non-vaccine serotypes 7F, 19A, 22F and 3 emerged as the dominant serotypes in the post-vaccine period.

And finally the author notes:

"*It is of note that the emergence of non-PCV7 serotypes has been associated with a shift to a greater proportion of IPD occurring in older children. We observed increases in the age of children with bacteremia and pneumonia (both complicated and uncomplicated). Chibuk et al noted a similar increase in the age of children with complicated pneumonia in Canada.*"

The Chibuk reference above is to this 2010 case study, ***Pediatric complicated pneumonia and pneumococcal serotype replacement***, which also found, *"Recent studies have described an increase in the incidence of complicated pneumonia in children, primarily caused by Streptococcus pneumoniae…In patients where serotype data was available, non-vaccine pneumococcal serotypes accounted for 67%…of cases in the post-PVC7 era versus 14% …in the pre-PCV7 era"*

## Serotype Resurgence

There is another statement in the information presented with the Annual Incidence chart on the previous page that also bears examination:

"*However, a troubling increase of PCV13 serotypes in children <2 years of age has been driven by the* ***resurgence*** *of serotypes 3 and 19A in this age group since 2014."*

The causes of **resurgence** are not well understood, While resurgence continue to be debated in the medical literature, its existence is not in question.

It is resurgence of serotypes that are vaccinated against that lead to reports of **vaccine breakthroughs and failures**. The resurgence in Canada of the two PCV13 serotypes, 3 & 19A, mentioned above is being seen in other countries with mass vaccination programs as well.

A 2016 case study from Portugal, ***Pneumococcal pneumonia vaccine breakthroughs and failures after 13-valent pneumococcal conjugated vaccine***, describes 19 cases of IPD pneumonia in

which 9 children were not vaccinated and 10 children were. Of those 10 vaccinated children, 6 had 4 doses, 3 had 3 doses and only 1 had 2 doses of PCV13. The *Summary of Key Points* cites the same PCV13 **serotypes 3 & 19A** that the Canadian report cites:

- *In the last years, we have witnessed a change in the epidemiological pattern of pneumococcal invasive disease in children, particularly after the introduction of pneumococcal conjugated vaccines (PCV).*
- *PCV are highly effective, but some cases of vaccine failure and vaccine breakthrough have been reported.*
- *We describe four cases of Streptococcus pneumoniae serotype 3 vaccine failure and three cases of vaccine breakthrough (2 with serotype 3 and 1 with serotype 19A).*
- *This work represents additional insight in PCV13 efficacy and can be useful in Public Health policies, i.e., maintaining an effective surveillance on pneumococcal invasive disease, in order to better understand the mechanisms involved in vaccine failures and breakthroughs.*

## Serotypes in Canadian IPD

The *Executive Summary* in the 2016 National Laboratory IPD Surveillance Report also contains the information that 70% of IPD cases reported in Canada are caused by vaccine serotypes (VT) and 30% are caused by non-vaccine serotypes (NVT).

Table 3 below is from the 2016 report. Note the 2 rows *PPV23All* and *NVT* (circled on the left) and their values in the *All Ages* column (circled at the far right). This shows the 69%/31% breakdown of all VT (vaccine targeted serotypes) versus NVT (non-vaccine serotypes).

It also brings us to a major question regarding herd immunity and distinguishing which vaccines are responsible for antigens that are targeting any particular serotype. The 2016 IPD Surveillance Report says in the Executive Summary:

*"Continued declines of PCV7 and PCV13 serotypes in seniors ≥65 years of age, as well as lower case rates in this age group, indicate indirect reduction of disease* ***most likely through herd immunity effects.****"*

There are a number of problems with this statement. First, the "lower case rates" referred to are actually a reduction of 0.8 (less than one case per 100,000) for 60+ age group from 2014 to 2015 case rates. See Table 1 below from the 2016 report.

Second problem, Table 1 is the same table that appeared in the 2015 report, (Yet the "herd immunity

**Table 3. Pneumococcal Vaccine Serotypes 2016** Per cent and (number of cases)

| Vaccine* | Age Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | <2 years | 2-4 years | 5-14 years | 15-49 years | 50-64 years | ≥65 years | All Ages** |
| PCV7 | 3.6%(6)*** | 3.3%(3) | 10.9%(10) | 19.2%(130) | 11.0%(86) | 6.7%(72) | 10.6%(308) |
| PCV13 | 15.5%(26) | 15.2%(14) | 19.6%(18) | 20.2%(137) | 23.4%(183) | 18.6%(201) | 20.0%(581) |
| PCV13 All | 19.0%(32) | 18.5%(17) | 30.4%(28) | 39.4%(267) | 34.4%(269) | 25.2%(273) | 30.6%(889) |
| PPV23 | 45.8%(77) | 38.0%(35) | 38.0%(35) | 41.2%(279) | 39.5%(309) | 36.3%(393) | 38.9%(1130) |
| PPV23 All | 64.9%(109) | 55.4%(51) | 68.5%(63) | 80.4%(544) | 73.5%(575) | 60.1%(650) | 68.7%(1997) |
| NVT | 35.1%(59) | 43.5%(40) | 31.5%(29) | 19.4%(131) | 26.1%(204) | 38.4%(416) | 30.5%(887) |
| Total | (168) | (92) | (92) | (677) | (782) | (1082) | (2906) |

**Table 1. Annual incidence of IPD cases in Canada by age group, 2009–2015**

| Year | Age Group (Years) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | <1 | 1-4 | 5-9 | 10-14 | 15-19 | 20-24 | 25-29 | 30-39 | 40-59 | 60+ | All Ages |
| 2009 | 27.8 | 18.7 | 5.7 | 1.6 | 1.8 | 2.4 | 3.4 | 5.5 | 8.9 | 22.3 | 9.8 |
| 2010 | 25.1 | 16.4 | 4.7 | 1.8 | 1.2 | 1.9 | 3.1 | 5.2 | 9.0 | 23.4 | 9.8 |
| 2011 | 20.7 | 15.4 | 5.2 | 2.4 | 1.6 | 1.4 | 3.0 | 5.3 | 9.1 | 21.6 | 9.6 |
| 2012 | 18.3 | 13.6 | 4.3 | 2.5 | 1.6 | 2.5 | 4.0 | 5.1 | 9.1 | 22.7 | 9.8 |
| 2013 | 18.6 | 11.3 | 3.8 | 1.5 | 1.2 | 1.5 | 2.8 | 4.5 | 8.4 | 21.7 | 9.1 |
| 2014 | 17.4 | 11.0 | 3.7 | 1.1 | 1.0 | 1.6 | 2.6 | 4.4 | 8.6 | 21.1 | 8.9 |
| 2015 | 14.5 | 9.9 | 3.8 | 1.2 | 1.5 | 1.8 | 2.7 | 4.5 | 9.0 | 20.3 | 9.0 |
| 2016 | 17.1 | 14.2 | 5.0 | 1.6. | 1.6 | 2.0 | 3.2 | 5.7 | 10.25 | **22.3** | 9.1 |

statement" did not appear in that report.)There is no data for 2016 incidence rates in this IPD report because the *Notifiable Diseases Database* had not been updated since 2015. It was updated in June of 2018, so we now know the 2016 case rate of those 60+ was 22.3. We added the 2016 rates for all age groups below Table 1 so it is easy to see the **case rate increased in this age group** as it did in every other group in 2016. In fact for the 60+ age group the rate is the same as it was in 2009 before PCV13 was introduced. Some herd immunity!

Third problem, the serotype rates are for 2016. Why did the authors of this report feel the need to make this statement based on comparing data from 2 different years?

Fourth and biggest problem, Table 3 is very strange. For any particular age or for All Ages if you add the first and second row numbers you get the third row, labelled *PCV13 All*. If you add this row to the fourth row *PPV23* you get the values in the fifth row *PPV23All*. This fifth row contains the actual IPD incidence numbers and percent of cases in an age group that have vaccine targeted serotypes (VT). The final row are the number of cases in any age group of IPD that have non-vaccine targeted (NVT) serotypes.

So here is the question. A case of IPD comes into the lab and they isolate serotype 4 as the cause. How can the lab possibly distinguish whether that case of IPD is caused by a serotype from PCV7 or PCV 13 or PPV23 since all these vaccines contain this serotype?

The table is an artificial construct. Few conclusion can actually be drawn from it. Especially a conclusion that assumes a decline that is found in serotypes targeted by all three vaccines are the result of "likely herd immunity" from the childhood vaccines. This is especially the case with PCV7, a vaccine no longer available in Canada and that hasn't been used for almost 10 years. Any immunity it offered to children who received it would have waned by now, so it could hardly be conferred as 'herd immunity' to others no matter what their age.

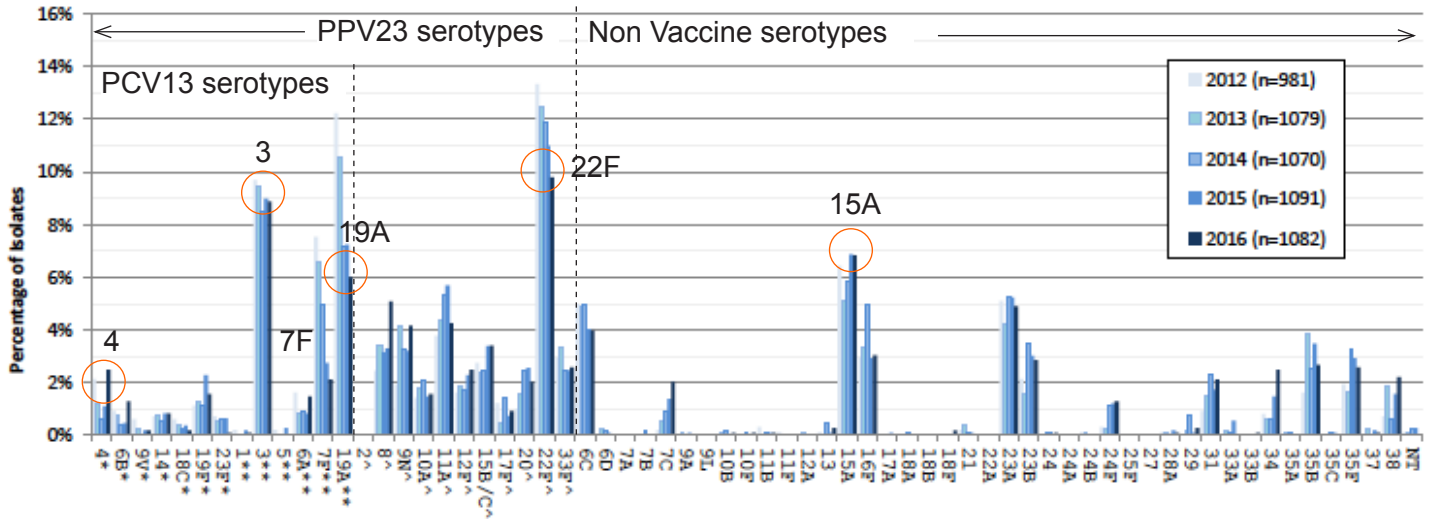
And what about increases? The text accompanying Table 3 reports on PCV7 serotypes saying, "large increases from 2012 to 2016 have been seen in 15–49 year olds from 7.7% to 19.2% and in the 50–64 year olds from 5.6% to 11%." How can these increases in IPD cases from the 'PCV7 vaccine serotypes' be related to a vaccine that is no longer in use? In reality the increases should be related to PCV13 serotypes and/or PPV23 serotypes common with PVC13 since both vaccines are in use in Canada today.

Certainly the reference to PCV7 serotypes should be dropped from all the current tables and discussions. It is an artifact of the 2002–2009 original childhood vaccine campaign and only bears relevance to those years.

Figure 17 below from the 2016 IPD Report shows the five year changes in serotypes in ≥65 age group. We have added red text, lines and arrows to show the 2 vaccines that contain the antigens for these serotypes. We have also circled and labeled certain serotypes for their role in 2016 cases of IPD as follows:

- **Serotype 22F** was the largest contributor to IPD in this age group in 2016. It is a PPV23 serotype.
- **Serotype 3** is the 2nd largest contributor. It is both a PCV13 and a PPV23 serotype. It has declined minimally since 2015 or from 2012 for that matter. We know that PCV13 is not particularly effective in controlling Serotype 3 and that it is resurgent.
- **Serotype 15A** is a non-vaccine serotype (NVT) and is the 3rd largest contributor to IPD.

**Figure 17. Invasive *S. pneumoniae* serotypes in ≥65 year olds**



- **Serotype 19A** is the 4th largest contributor. It is both a PCV13 and a PPV23 serotype and shows strong decline from 2012 when it was the 2nd largest contributor.
- The rapid increase of **Serotype 4** is attributed to an outbreak of IPD in the homeless community in Western Canada. It is a PCV13 and a PPV23 serotype. No "herd immunity" for these folks.

The declines in serotypes targeted by both PPV23 and PCV13 childhood vaccines are not particularly striking except for 19A & 7F. 19A has not seen steady declines in all age groups however. In 2–4 year olds it increased from 17.6% in 2013 to 25% in 2014. Surely this age group would be expected to benefit from decreases due to 'herd immunity' effects far more than the ≥65 year olds due to contact rates among children.

## Global Comparisons

The table below compares the five most predominant serotypes for all age groups using published 2015 data from three locations—Canada, Europe and New Zealand. These were the only IPD Surveillance Reports from government sites with enough information on prevalent serotypes to make useful comparisons.

We used the **2015 ECDC European IPD Report**, the **2015 Canadian IPD Report** and the **2015 New Zealand IPD Report** for data. The table represents a total of just over 24,000 reported cases of confirmed IPD in the three locations combined.

In the table, of the 15 most prevalent IPD serotypes in all three locations, 14 are serotypes targeted by vaccines (VT) and one is a non-vaccine targeted serotype (or NVT).

### NVT Serotype 6C

Serotype 6C was **discovered** in 2007. It is the 91st pneumococcal serotype and is the result of **replacement** of serotype 6A contained in the PCV13 vaccine.

### PPV23 Serotypes: 22F & 8

- **Serotype 22F** is among the **top three** most prevalent serotypes in all locations. It is first in Canada despite years of vaccinating seniors ≥65 and all high risk groups over 2 years of age (and more recently all residents of long term care facilities regardless of age). In Europe it is 3rd and in new Zealand it is 2nd. Most European countries do not routinely vaccinate seniors with PPV23, nor does New Zealand. The UK and Ireland are exceptions in Europe.
- **Serotype 8** in two locations, first in Europe and fifth in Canada (again despite widespread vaccination with PPV23 as detailed for 22F).

The prevalence of these specific vaccine-targeted (VT) serotypes harkens back to the concerns raised by medical professionals on the lack of effectiveness of the PPV23 vaccines in controlling IPD pneumonia. Globally IPD pneumonia is the most common clinical manifestation of IPD found in adults and children, So it stands to reason that many of the total 24,000 IPD cases for all ages reflected in the table would be IPD pneumonia cases.

### PCV13 Serotypes: 3, 19A & 7F

Almost all of the European countries, routinely vaccinate children with either PCV10 (Synflorix®) or PCV13. New Zealand routinely vaccinates children with PCV10. Canada routinely vaccinates with PCV13. All PCV serotypes are also PPV23 serotypes.

- **Serotype 3** occurs commonly in all three locations. In Canada and Europe serotype 3 is the 2nd most common serotype. In New Zealand it is 4th.
- **Serotype 19A** is the most common serotype in New Zealand and 3rd in Canada, 5th in Europe.
- **Serotype 7F** is the 3rd most common in New Zealand and 4th in Canada.

Again despite years of vaccination programs for children with PCV13 and adults with PPV23, which both contain these serotypes, the effectiveness of the vaccines is called into question. Considering the revelation that PCV13 was licensed despite its failed noninferiority testing for serotype 3 protection, we do not find it surprising that it is currently one of the most common IPD serotypes found globally.

## Serotype 3 in 2016 Canadian IPD cases

The 2016 IPD report shows a total of 2906 confirmed cases of reported IPD. Serotypes 3 and 22F were most prevalent, accounting for 9% of cases each.

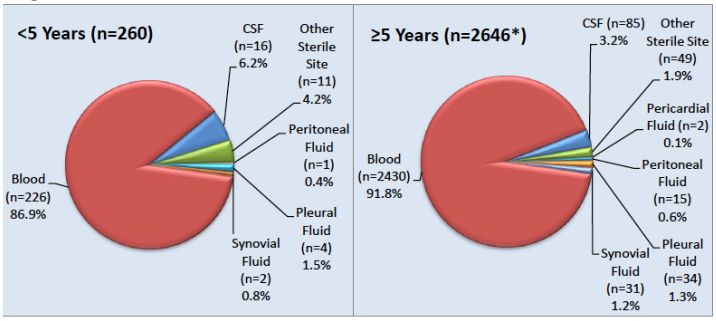
The vast majority of samples confirming these cases of IPD were taken from blood as shown above in the pie charts in Figure 3 from the report. The red portion of the pie charts are blood samples. Blood samples that

**2015 Most Common IPD Serotypes (with % of cases) in order of prevalence**

| | | | | | |
|---|---|---|---|---|---|
| Europe | ^8 (12%) | **3** (12%) | ^22F (7%) | ^12F (7%) | **19A** (7%) |
| Canada | ^22F (9.7%) | **3** (9.1%) | **19A** (7.2%) | **7F** (5.6%) | ^8 (5.3%) |
| New Zealand | **19A** (21%) | ^22F (9.3%) | **7F** (8.8%) | **3** (7.6%) | *6C (8%) |

^PPV23 only **PPV23/PCV13** *6C is an NVT

**Figure 3. Clinical isolation sites in 2016**




confirm *Streptococcus pneumoniae* bacteria are alive in the patent's blood stream are designated as cases of bacteremia. The bacteria can enter the blood during IPD infections, for example, from IPD pneumonia or IPD meningitis. A portion of patients may respond to bacteremia with toxic shock (sepsis).

The second most common location (blue in the pie charts) were from CFS—cerebrospinal fluid found in the brain and spine. These samples would confirm cases of IPD caused meningitis. Pleural fluid samples would confirm cases of IPD caused pneumonia including complicated pneumonias. Samples from other sterile sites would indicate everything from septic arthritis to bacterial peritonitis to fluid build-up surrounding the heart.

The four charts that follow are from the 2016 Report. They show the serotypes found in blood (Fig 4), CSF (Fig 5), pleural fluid (Fig 6), and all other sterile sites (Fig 7). On these charts, we have added notation of non-vaccine targeted serotypes (NVT) to the right of the dotted line and vaccine targeted serotypes (VT) to the left. Serotype 3 is specifically noted due to its high prevalence on all charts.

**Figure 4 Blood**: The most prevalent vaccine-targeted serotype is 22F followed closely by serotype 3. Together these account for almost 18% of samples. Serotype 4 is the third highest serotype due to that outbreak of IPD in homeless populations. Also of note, vaccine-targeted (VT) serotypes are the most abundant in this chart compared to the other three charts.

**Figure 4. Serotypes of invasive *S. pneumoniae* from blood in 2016**

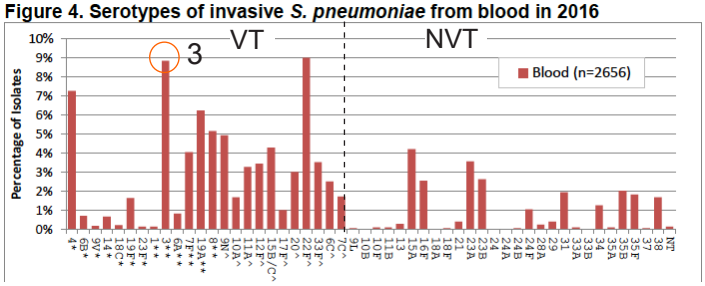



**Figure 5 Cerebrospinal Fluid:** Serotype 3 is the most prevalent, followed closely by NVT 23B. These two serotypes account for over 20% of IPD meningitis cases and are targeted by both PCV13 & PPV23. The two other high VT serotypes are 15B/C and 22F, both PPV23 vaccine-targeted serotypes.

**Figure 5. Serotypes of invasive *S. pneumoniae* from CSF in 2016**

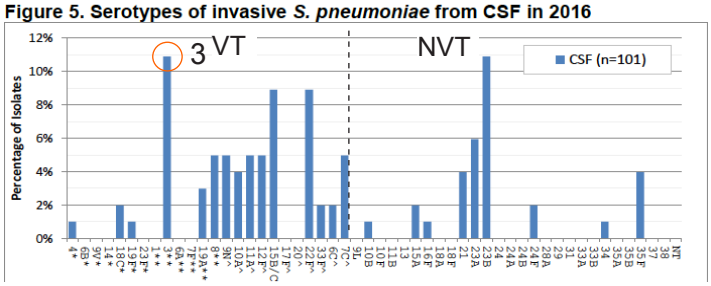



**Figure 6 Pleural Fluid:** Serotype 3 is far and away the most common cause of invasive pleuritiss. It accounts for 29% of these cases.

**Figure 6. Serotypes of invasive *S. pneumoniae* from pleural fluid in 2016**

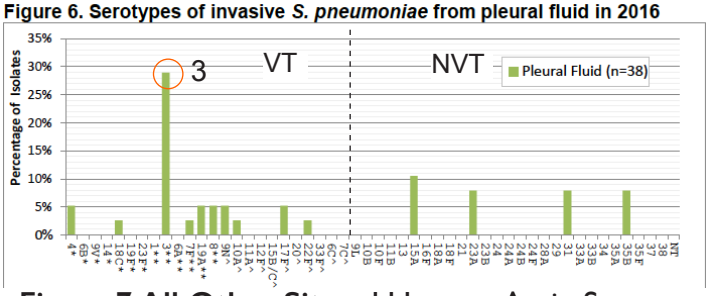
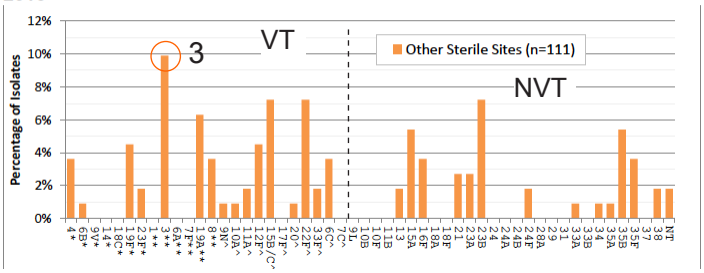



**Figure 7 All Other Sites:** 111 cases. Again Serotype 3 is prominent, accounting for almost 10% of cases. Also of note, this chart has the most number of NVTs.

**Figure 7. Serotypes of invasive *S. pneumoniae* from other sterile sites in 2016**




It is fairly evident from these charts that vaccine campaigns are failing to control Serotype 3 and 22F and that NVT 23B is of particular concern in meningitis.

## NVTs on the rise

As explained in the **microbiology article** quoted in the previous discussion on replacement:

*"Use of a 7-valent pneumococcal conjugate vaccine (PCV7) and subsequent 13-valent (PCV13) formulations has been followed by a precipitate reduction in IPD due to vaccine serotypes (VTs) in the United States…PCVs are plainly an effective selective pressure on the pneumococcal population. The response to that pressure has been notable for the increase in prevalence of nonvaccine serotypes (NVTs)."*

The 2016 IPD report has both a table and graph that track the prevalence of NVTs over a 5-year period 2012-2016. These are shown below.

For *All Ages* in that 5-year period NVTs have increased as a per cent of all isolates from 24.2% to 30.5%. This is in response to the PCV13/PPV23 vaccine programs as coverage of the population has increased and booster doses have been added.

NVT distribution in the various age groups is uneven. Although in 2012 the distribution was more even than 2016, ranging from a low of 17% to a high of 29%. In 2016 the range has broadened from a low of 19% to a high of 43.5%.

That highest concentration of NVTs at 43.5% is found in 2–4 year olds. Seniors are next at 38.4%. Babies under 2 years next at 35.1%. These are the three most targeted populations for the pneumococcal vaccines– PCV13 for infants and babies and PCV23 with PCV13 boosters for the elderly.

In Canada, approximately 80% of children are vaccinated with the full 3-dose schedule of PCV13 and approximately 40% of seniors are vaccinated with PPV23; not to mention the 17% of chronically ill in all age groups over 2 years of age. These coverage statistics are obviously providing "effective selective pressure on the pneumococcal population."

**Figure 22. Trends of non-vaccine serotypes (NVT)**

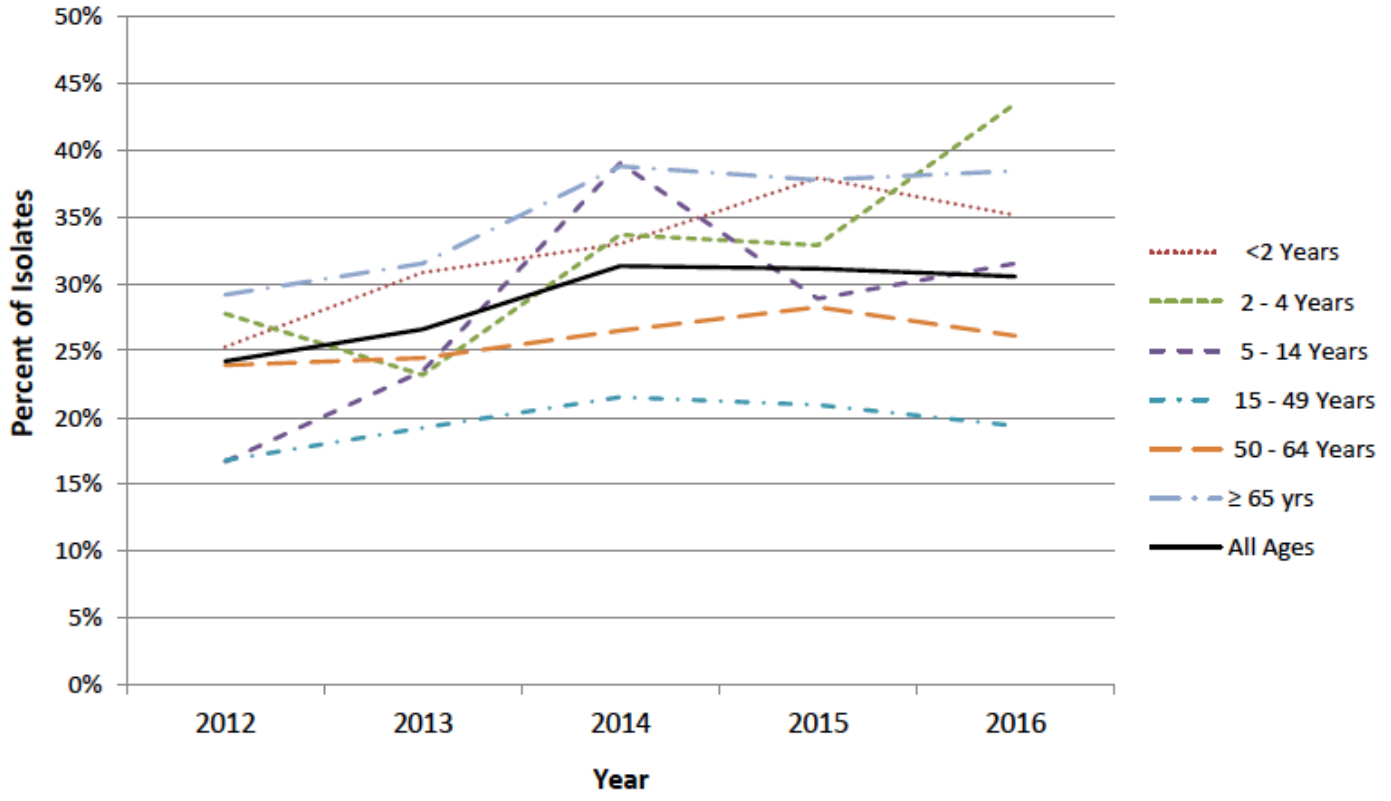



**Table 8. Non-vaccine serotype (NVT) isolates**

| | Age Group | | | | | | |
|---|---|---|---|---|---|---|---|
| Year | <2 years | 2-4 years | 5-14 years | 15-49 years | 50-64 years | ≥65 years | All Ages** |
| 2012 | 25.3% (43)* | 27.8% (40) | 16.7% (17) | 16.8% (111) | 23.9% (178) | 29.2% (286) | 24.2% (685) |
| 2013 | 30.8% (53) | 23.2% (22) | 23.5% (19) | 19.2% (107) | 24.4% (177) | 31.5% (340) | 26.6% (728) |
| 2014 | 33.0% (59) | 33.6% (37) | 39.0% (32) | 21.5% (115) | 26.5% (197) | 38.8% (415) | 31.3% (870) |
| 2015 | 37.9% (58) | 32.9% (25) | 28.9% (28) | 20.9% (128) | 28.2% (219) | 37.8% (412) | 31.1% (876) |
| 2016 | 35.1% (59) | 43.5% (40) | 31.5% (29) | 19.4% (131) | 26.1% (204) | 38.4% (416) | 30.5% (887) |

## Through the Looking Glass

The more one investigates the pneumococcal vaccines, the easier it is to see that replacement and resurgence in fact defeat vaccine campaigns or, as the industry sees it, require more and 'better' vaccines to control disease.

Researchers from Utah have published a compendium of much cited case studies on the result of the PCV7 & PCV13 campaigns on populations in Utah. They arrive at the same conclusion that investigations into PPV23 arrived at for older populations: **pneumococcal vaccination does not control pneumonia incidence in young populations. Rather it increases hospitalization for uncomplicated and complicated pneumonias.** Controlling pneumonia, the great global killer, is still touted as one of the main reasons for these vaccine campaigns.

This is not to say that these vaccines have not reduced IPD meningitis and bacteremia in targeted populations. Below is a chart from one of the Utah case studies (2013) showing the incidence of IPD syndromes in hospitalized children (<18 yrs) before and after the PCV7 vaccine campaign [arrows added].

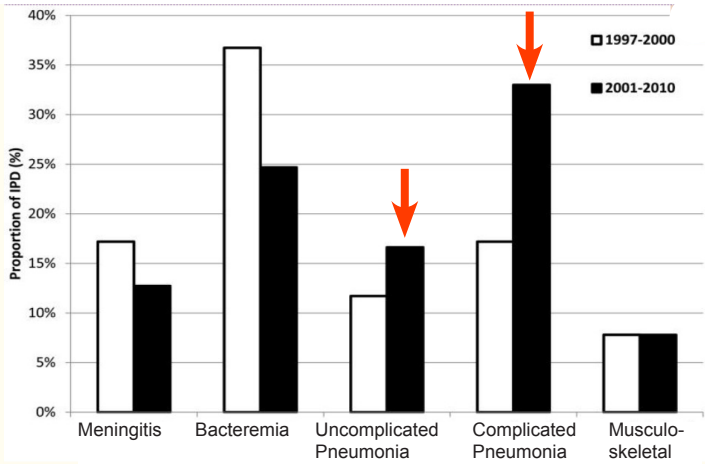



Figure 1: Proportion of IPD attributed to clinical syndromes in Utah during the pre- (1997–2000) and post- (2001–2010 vaccine periods.

The ***Results*** portion of this study notes the shift of disease to older populations, the shift of disease to pneumonia cases and serotype replacement.

*"The median age of children with IPD increased from 19 months during the pre-vaccine period to 27 months during post-vaccine period with a larger proportion of IPD among children older than 5 years. The proportion of IPD associated with pneumonia increased substantially from 29% to 50%. This increase was primarily attributable to an increase in complicated pneumonia 17% to 33%. Non-vaccine serotypes 7F, 19A, 22F and 3 emerged as the dominant serotypes in the post-vaccine period. Of S. pneumoniae isolates collected from children <5 years of age, for which vaccine is recommended, 67% of IPD was due to serotypes [later incorporated] in PCV13 during 2005–2010."*

So in this group of Utah children, the age shifted from <2 year olds to 2-4 age group. This is the same shift we are seeing in Canada now with the post-PCV13 serotype replacement as the NVT graph on the previous page attests. We also can see this shift of proportion of cases in the 5-14 age group in both the table and the graph on the previous page.

The study above was pre-dated by a 2008 Case Study using the same Utah data and serotype specimens. It evaluated cases of pneumococcal necrotizing pneumonia (PNP), a particularly serious type of complicated pneumonia, and the serotypes associated with it. It found, that cases of **PNP in children increased from 13% pre-vaccine to 33% post vaccine and that serotype 3** was most often associated with PNP with 79% of patients developing necrosis (death of lung cells).

*"When compared with all other serotypes, serotype 3 was almost 15 times more likely to be associated with radiographic evidence of lung necrosis."* This statement attests to Serotype 3 being a most virulent serotype. Virulence of a microorganism is a measure of the severity of the disease it causes.

And they also found that, *"PCV-7 vaccination history was not different between children with and children without evidence of necrotizing pneumonia. However, more children with serotype 3 pneumonia had documentation of vaccination with at least 1 dose of PCV-7 (21%), compared with children with pneumonia due to other serotypes (6%) (P=.05)."* This statement links PCV7 vaccination to serotype 3 replacement and more serious disease.

In 2013 another case study in this series was published examining the incidence of IPD, its syndromes and serotypes in **infants less than 3 months old** and therefore unvaccinated. They conclude the following:

1) **IPD incidence did not change in this age group post vaccine** due to an increase in non-vaccine serotypes (i.e., replacement) which balanced the decrease in vaccine serotypes,

2) Incidence of IPD syndrome **bacteremia decreased** while **meningitis increased to 70% of cases**, and

3) Serotype 7F was the most common in these infant infections.

Unvaccinated infants under 3 months were one of the groups that was supposed to benefit from "herd immunity" with use of this vaccine. This was not the case with no change in incidence of IPD and the shift to

meningitis, the most severe category of IPD.

That the most prevalent NVT serotypes cause more serious disease is also spoken to in this **2009 German study** where they say, *"Serotype 7F has been reported to be associated with a higher risk of severe and fatal outcomes than other serotypes."*

And finally in the Utah series, the 2016 study titled ***Clinical and Epidemiological Evidence of the Red Queen Hypothesis in Pneumococcal Serotype Dynamics*** offers this conclusion:

*"This vaccine-driven example of human/bacterial coevolution appears to confirm the Red Queen hypothesis, which* ***reveals a limitation of serotype-specific vaccines and offers insights that may facilitate alternative strategies for the elimination of IPD."***

In the discussion they say:

*"As predicted by the Red Queen hypothesis, we observed clinical evidence suggestive of vaccine-induced selective pressure that resulted in serotype replacement in children following the introduction of both PCV7 and PCV13 within the US childhood immunization schedule…The effect was greatest in young children, who were also the population targeted for immunization. Serotype-specific immunization of children appears to be a powerful driver of serotype replacement within the pneumococcal population, leading to changes in the dominant types responsible for IPD both in immunized children and in nonimmunized populations."*

The Red Queen Hypothesis is based on Lewis Caroll's book *Through the Looking Glass* in which Alice encounters a world altogether different than what she is accustomed to. As the delightful explanation (linked above) of this hypothesis explains,

*"At the top of the hill, the Red Queen begins to run, faster and faster. Alice runs after the Red Queen, but is further perplexed to find that neither one seems to be moving. When they stop running, they are in exactly the same place. Alice remarks on this, to which the Red Queen responds: 'Now, here, you see, it takes all the running you can do to keep in the same place.'*

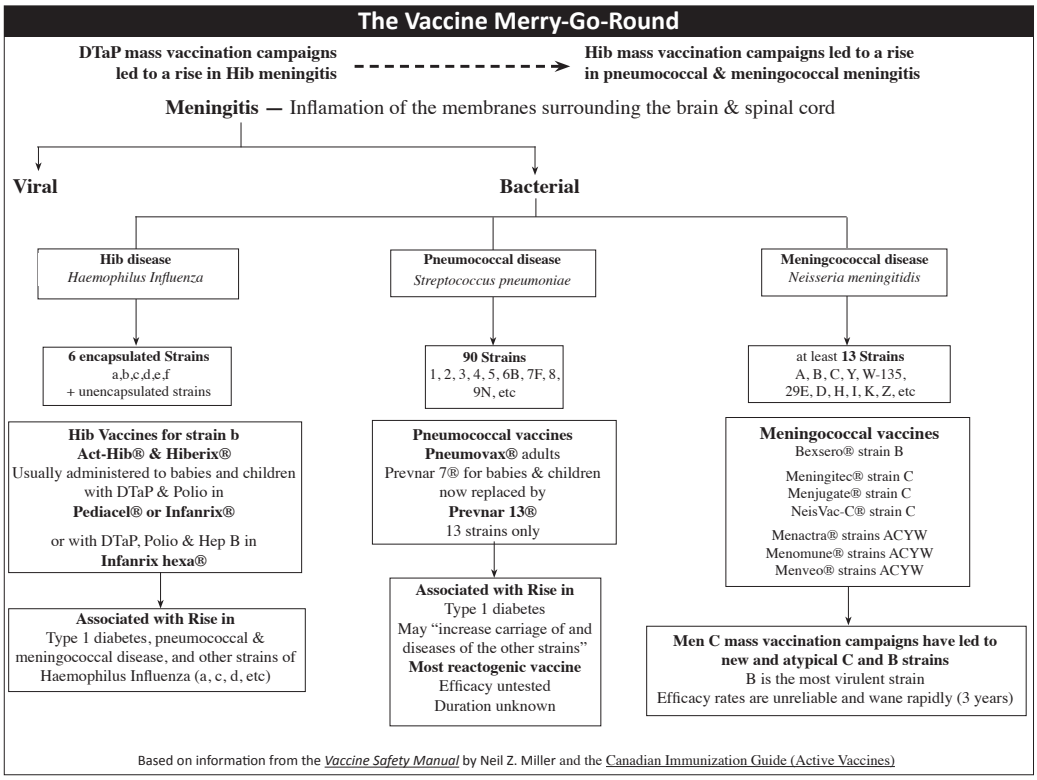
*And so it may be with coevolution."*

## Conclusion

And so it goes, running as fast as we can with *Streptococcus pneumoniae*, only to stay in one place developing more (ineffective?) vaccines.

Pneumococcal replacement serotypes always fill the gap when new vaccines are introduced. The non-vaccine serotypes that eventually predominate tend to be more virulent causing more serious outcomes. Resurgence of vaccine serotypes occurs. IPD incidence shifts away from vaccine-targeted young to older groups, especially the elderly, other immunocompromised populations and those who are chronically ill. All age incidence of IPD does not decline.

More vaccines cause new problems. The vaccine merry-go-round spins faster and faster. Adverse event data is obscured. Causality defined away. The policy makers crow at the reduction of IPD in targeted groups and ignore all else. Valid science is ignored, precaution out the window. Vaccines are declared a miracle as the health of the population declines. And so it goes...




Graphic originally published in the *VCC Vaccine Safety Report*, March, 2016.