Outline of research agenda to inform potential policy reconsideration in 2018 for PCV13 use among adults

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Key questions to be answered before 2018 review

- **Is PCV13 use preventing disease among adults ≥65 years old?**
- **To what extent are the observed benefits driven by adults PCV13 use (direct effects) vs. pediatric PCV13 use (indirect effects)?**
- **What benefits would we expect from continued PCV13 use among adults?**

Is PCV13 use preventing disease among adults ≥65 years old?

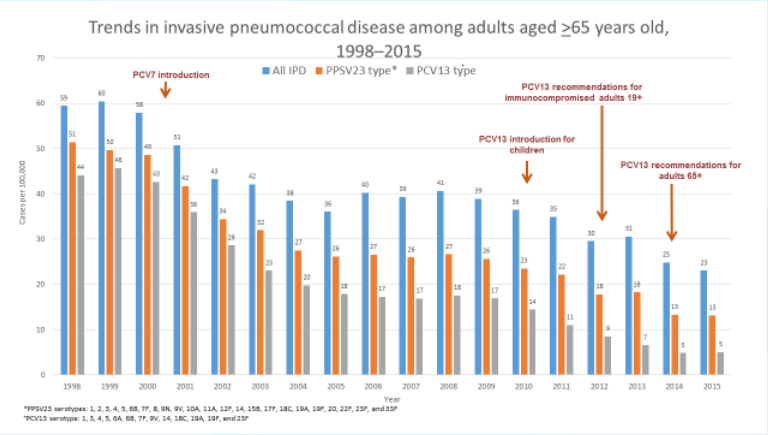
- **Monitoring impact of new recommendations in the vaccine target age group:**
  - Changes in IPD burden before and after PCV13 recommendation
  - Changes in pneumococcal pneumonia burden before and after PCV13 introduction
  - Uptake of vaccine among adults ≥65 years old
  - Effectiveness of PCV13 and PPSV23 against IPD among adults ≥65 years old (case-control study)

To what extent are the observed benefits driven by adults PCV13 use (direct effects) vs. pediatric PCV13 use (indirect effects)?

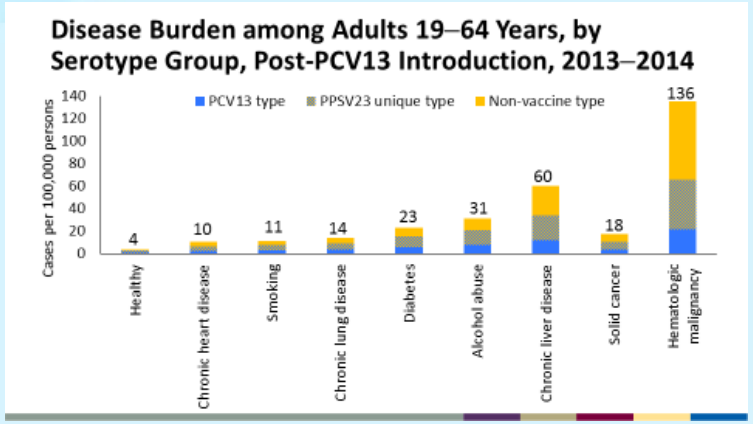
- **Monitoring impact of PCV13 use in children on adult disease burden (PCV13 indirect effects)**
  - Changes in IPD and pneumonia among adults ≥65 years old before and after PCV13 introduction for children and before PCV13 recommendations for adults
  - Changes in IPD and pneumonia among adults <65 years old without current PCV13 indications
- **Circulation and transmission of PCV13 types in a setting of herd effects**
  - Colonization studies among children
  - Colonization studies among adults
- **Continue to monitor disease trends through 2018 and estimate contribution of direct vs. indirect effects to observed reductions in IPD and pneumonia**
  - Mathematical model to estimate the contribution of direct vs. indirect effects
  - Estimate expected reductions through indirect effects only vs. observed through direct + indirect effects
  - Estimate expected direct effects given PCV13 coverage among adults ≥65 years old

Impact on IPD observed to date

- **Changes in PCV13-type IPD burden among adults ≥65 years old**
  - PCV13-type IPD rates declined through 2014 due to indirect PCV13 effects
  - No additional declines observed in 2015
  - PCV13-types account for 22% of IPD in 2015 compared to 43% pre-PCV13



- **Continued monitoring of disease trends among adults <65 years old is needed to evaluate the impact of herd effects**
  - PCV13-type IPD burden continues to decline among adults without current indications for PCV13 use
  - PCV13-types account for 24% of IPD in 2014 compared to 48% pre-PCV13 among adults without indications for PCV13



PCV13 Effectiveness Evaluation among Adults 65 years or older: case control study

- **Objectives**
  - Evaluate the effectiveness of
    - PCV13 against PCV13-serotype invasive pneumococcal disease.
    - PCV13 and PPSV23, when given in series
  - Evaluate risk factors for IPD among adults ≥65 years old in a setting of PCV13 and PPSV23 use
- **Cases:**
  - IPD among adults ≥65 years old identified through Active Bacterial Core surveillance
  - Pneumococcal isolate available for serotyping
- **Controls**
  - Identified using the commercial database ReferenceUSAGov (InfoGroup)
  - 4 controls per case matched on age group and zip code
- **Vaccination histories**
  - Identify all medical care encounters & providers in the last 6 years, during interview
  - Attempt to contact any providers/clinics who may have provided vaccines to the participant

PCV13 Effectiveness Evaluation among Adults 65 years or older: case control study

- **Progress to date:**
  - Enrolled 200 cases and 520 controls
  - Pneumococcal serotyping ongoing to determine the number of vaccine-type (VT) cases
- **Sample size estimates**
  - At ~30% PCV13 coverage, 46 VT cases needed to demonstrate a VE of 75%
- **Timelines**
  - Enrollment started ~November 2015
  - Estimated end of enrollment - winter 2017-2018

Ongoing studies to monitor PCV13 impact on pneumococcal pneumonia

- Assessing the impact of PCV13 on all-cause pneumonia hospitalizations (CDC)
- Population-based surveillance for non-invasive pneumococcal pneumonia (CDC)
- Population-based surveillance for PCV13-type pneumococcal pneumonia (University of Louisville, Pfizer)

Assessing the Impact of PCV13 on All-cause Pneumonia Hospitalizations

- **Objectives**
  1) Measure the impact of PCV13 introduction in children on pneumonia hospitalizations across age groups (PCV13 indirect effects)
  2) Estimate additional impact of the 2014 adult PCV13 recommendation on pneumonia hospitalizations among adults ≥ 65 years of age (PCV13 direct effects)
- **Objective 1: PCV13 indirect effects**
  - **Data Source**: Statewide Inpatient Data from 2004-2014
  - **Methods:** Time-series analysis using "synthetic controls" to adjust for unmeasured confounding (e.g. changes in coding practices, change in healthcare seeking behavior)
- **Objective 2: PCV13 direct effects**
  - **Data Source**:
    - Statewide Inpatient Data from 2004-2016 (collaboration with AHRQ to improve timeliness of data)
    - CMS part A/B data: 2008-2016
  - **Methods:** Time-series analysis using "synthetic controls" to adjust for unmeasured confounding with two intervention points (2010 and 2014)
- **Outcome**
  - All-cause community-acquired pneumonia and pneumococcal pneumonia hospitalizations
  - Classification algorithm based on discharge codes

Surveillance for non-invasive pneumococcal pneumonia

- **Objectives**
  - Conduct population-based surveillance for noninvasive pneumococcal pneumonia, 2013 and onward
  - Measure burden of non-invasive pneumococcal pneumonia in adults
  - Measure the potential impact of adult PCV13 recommendations
- **Case definition**
  - Positive pneumococcal urine antigen test (UAT) from Jan 2013 onward
  - Hospitalized adult (≥18 years) and resident of surveillance area
  - Clinically or radiographically-confirmed pneumonia documented in medical record
  - No evidence of invasive disease
- **Catchment area** (15.6 million persons)
  - Included hospitals offering the urine antigen test
  - Adjustments made to account for the following
    1. Not all “at risk” patients tested by UAT at hospitals offering it
    2. Not all hospitals in catchment area offer UAT

Population-based surveillance for PCV13-type pneumonia

- **University of Louisville Pneumonia study**
  - Objective: To estimate the incidence and outcomes of hospitalized CAP among adults ≥18 years old in 9 adult hospitals
  - Active prospective population-based cohort (estimate incidence using US Census denominators)
  - Inclusion criteria: pulmonary infiltrate on chest x-ray + ≥1 of the following: cough/sputum, or fever/hypothermia or leukocytosis/leukopenia and no alternative diagnosis
- **SSUAD study**
  - To estimate proportion of adults CAP caused by PCV13 serotypes among adults ≥18 years old in 20 hospitals
  - Active prospective hospital surveillance
  - Inclusion: presented with suspected pneumonia and positive chest x-ray for CAP and discharge diagnosis of CAP
  - Serotype-specific urine antigen detection (SSUAD) test positive

Ramirez JA Personal communication

Challenges with monitoring impact on pneumonia

- **All-cause CAP**
  - Non-specific endpoint may limit the ability to detect reductions of small magnitude
  - Replacement with non-vaccine types may wash out the effects
  - Changes from ICD9 to ICD10 overlap with vaccine introduction period
- **Pneumococcal CAP**
  - UAT does not distinguish pneumococcal serotypes: replacement with non-vaccine types may wash out the effects
  - UAT sensitivity 50-80% among non-bacteremic patients: may underestimate burden
  - PPV23 receipt prior to UAT or carriage may influence test results
- **PCV13-type CAP**
  - SSUAD not commercially available; results limited to one study
  - Does not detect non-PCV13 serotypes
  - PPV23 receipt prior to UAT or carriage may influence test results

Adult pneumococcal colonization study

- **Objectives**
  - Define prevalence and serotype distribution of S*. pneumoniae* carriage in seniors
  - Assess risk factors for colonization
  - Provide baseline data to assess the impact of the new ACIP recommendation on carriage rates through later carriage studies
- **Study population**
  - Age 65 years or older enrolled at outpatient clinics, senior centers
  - Not severely immunocompromised
  - Both NP and OP swabs obtained
  - Vaccination history collected
- **Enrollment to date**
  - N=2,773 participants enrolled across 4 US states
  - Target: N = 3,353
- **Timelines**
  - June 2015 - December 2016

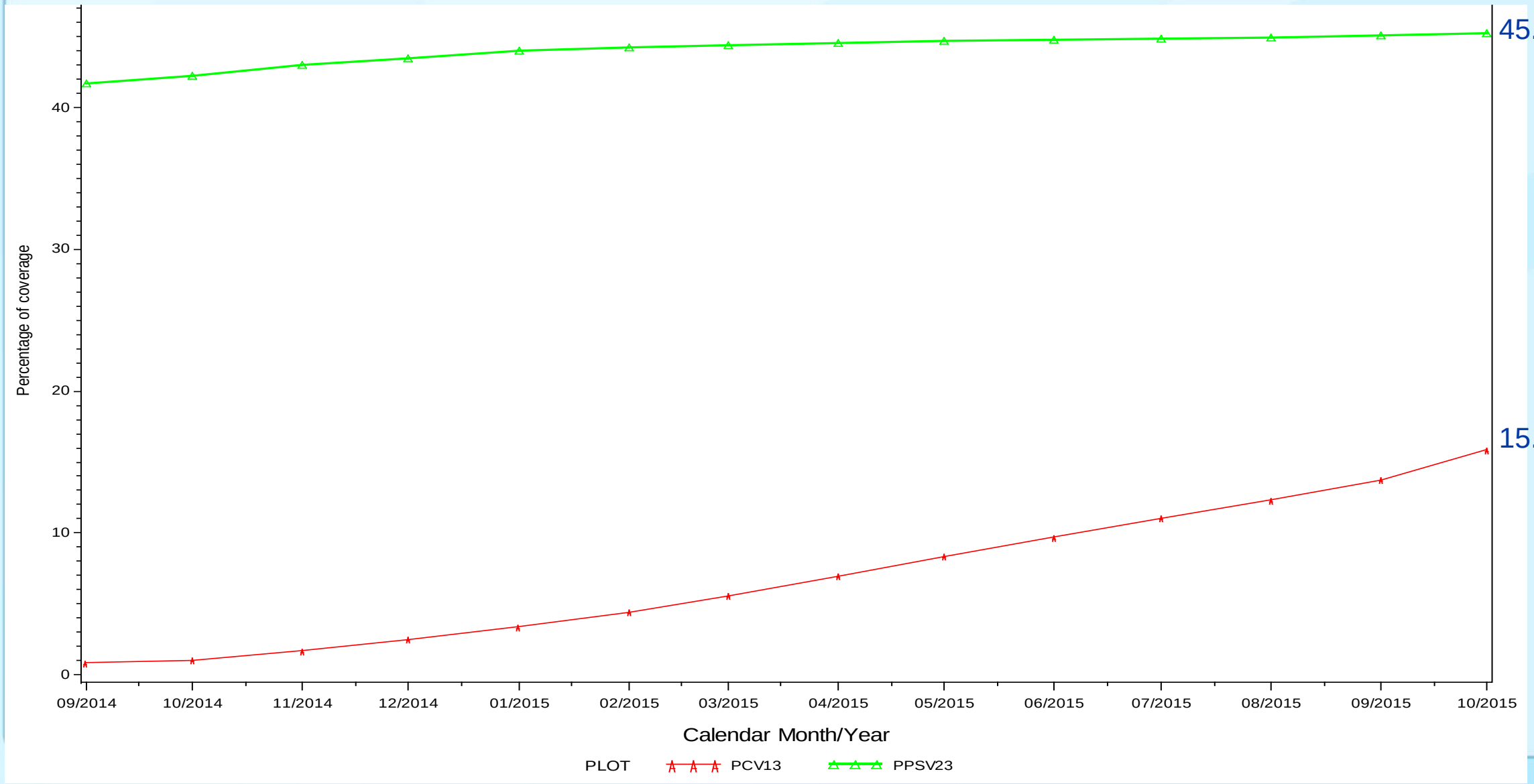
Monitoring vaccine uptake of PCV13 and PPSV23 in the target population of adults ≥65 years old

- **PPSV23 coverage has been assessed through National Health Interview Survey (NHIS)**
  - PPSV23 coverage has been relatively stable through 2014 (59.7%-62.3%)
  - Current survey question does not distinguish between PCV13 and PPSV23

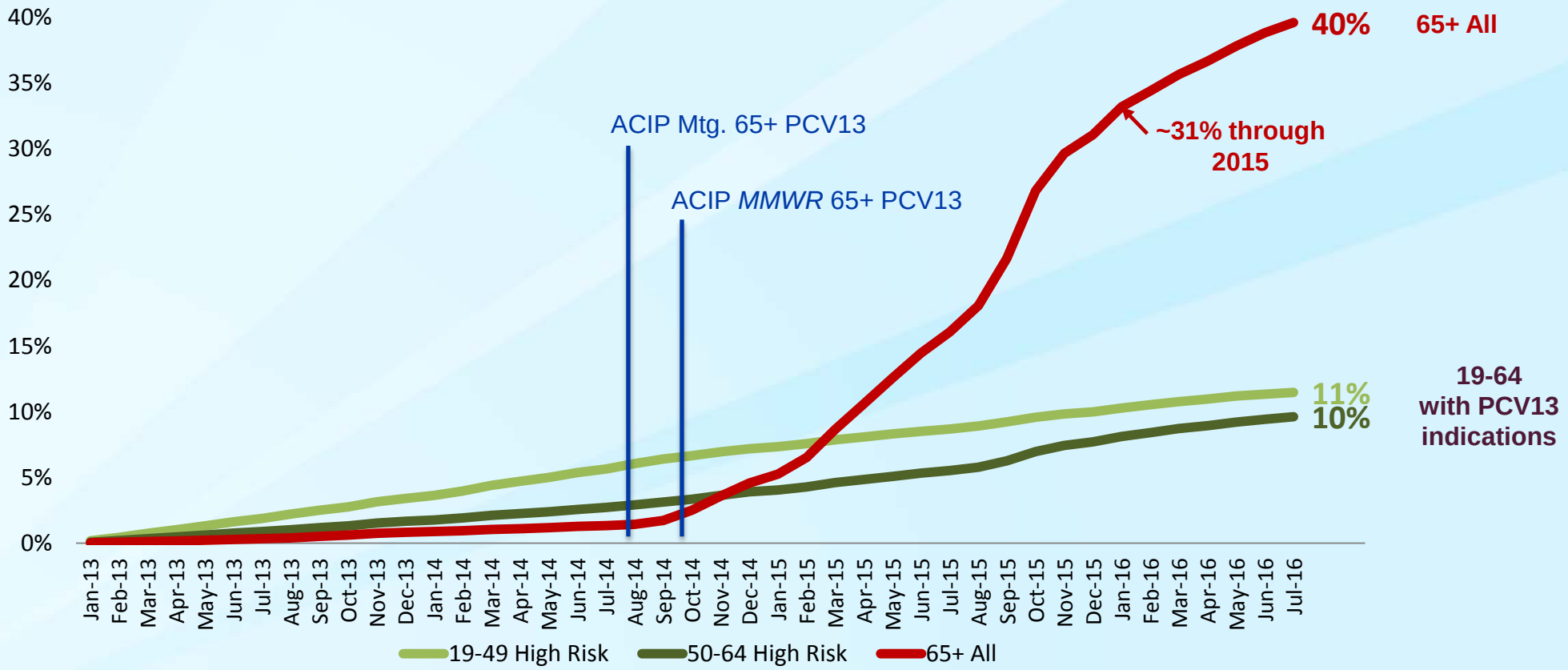
- **PCV13 and PPSV23 coverage assessment since 2014 recommendations**
  - CMS data for PCV13 and PPSV23 claims to estimate coverage among Medicare part B beneficiaries
  - Analysis of vaccine sales and IMS claims to estimate PCV13 coverage[1,2]

[1] *QuintilesIMS, Anonymized Patient-Level Data (APLD), Oct 2016 (includes diagnostic and prescription utilization claims for PCV13)*
[2] *Pfizer, Inc. internal sales data for PCV13, Oct 2016*

PCV13 and PPSV23 Cumulative Uptake, Adults ≥65 years old, CMS Claims Data Through Oct 2015



Estimated PCV13 Adult Cumulative Uptake by Risk and Age Group, IMS Claims Data Factored to Adjust to Total Sales, Jan 2013—Jul 2016



Slide courtesy of Pfizer

What benefits would we expect from continued PCV13 use among adults?

- Mathematical model to evaluate impact changes in adult recommendations would have on adult disease burden given observed and expected herd effects through pediatric PCV13 program
- Evaluate various policy options, including removal of PCV13 recommendation vs continued use
- Parameters/data inputs:
  - Estimate relative contribution of direct vs indirect effects on adult disease burden
  - VT IPD burden (by age and risk group)
  - VT CAP burden (by age and risk group)
  - PCV13 coverage in adults
  - VE against VT IPD and VT CAP
  - Duration of protection
- Outcomes for each policy option vs current recommendation
  - Public health impact (cases prevented for each outcome)
  - Cost-effectiveness

Next Steps

- **Update ACIP on the changes in vaccine-preventable disease burden among adults due to PCV13 direct and indirect effects during the next 2 years**
- **Update ACIP on the results of the ongoing studies**
- **These data should inform revisions as needed to the proposed adult PCV13 recommendations in 2018**
  - Declining burden of PCV13-type disease among adults <65 years old due to indirect effect of vaccinating children may signal that PCV13 is no longer needed
  - Revised cost effectiveness evaluation incorporating changes in disease burden, uptake, and the cost of the vaccines will help align this recommendation with other adult vaccines in use

Discussion/Questions to ACIP:

- Is the proposed research agenda appropriate to help determine if potential policy change is needed in 2018?
- What additional information will the committee need to help determine in 2018 whether continued PCV13 use in adults is warranted?