Existing SARI Surveillance Systems for Influenza and Integration with SARS-CoV-2 Surveillance in the EMR

Eastern Mediterranean Region COVID-19 Vaccine Effectiveness Study; Using Test-Negative Design in Severe Acute Respiratory Infection (SARI), 15 December 2021

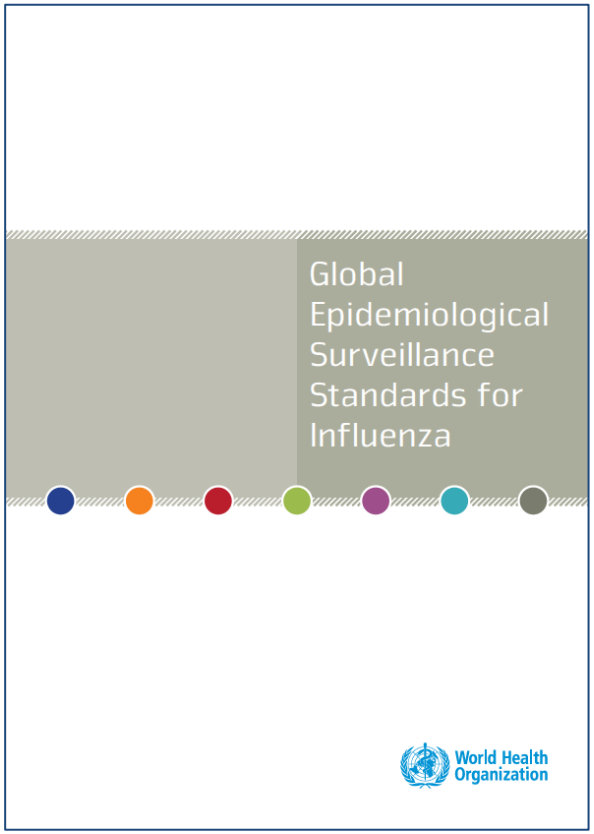
Infectious Hazards Prevention and Preparedness (IHP) Unit
WHO Health Emergencies Programme, WHO Regional Office for the Eastern Mediterranean

Outline

- Influenza sentinel surveillance in the EMR
- Integration of influenza and SARS-CoV-2 SARI sentinel surveillance
- Estimation of influenza vaccine effectiveness using a test-negative design from sentinel surveillance

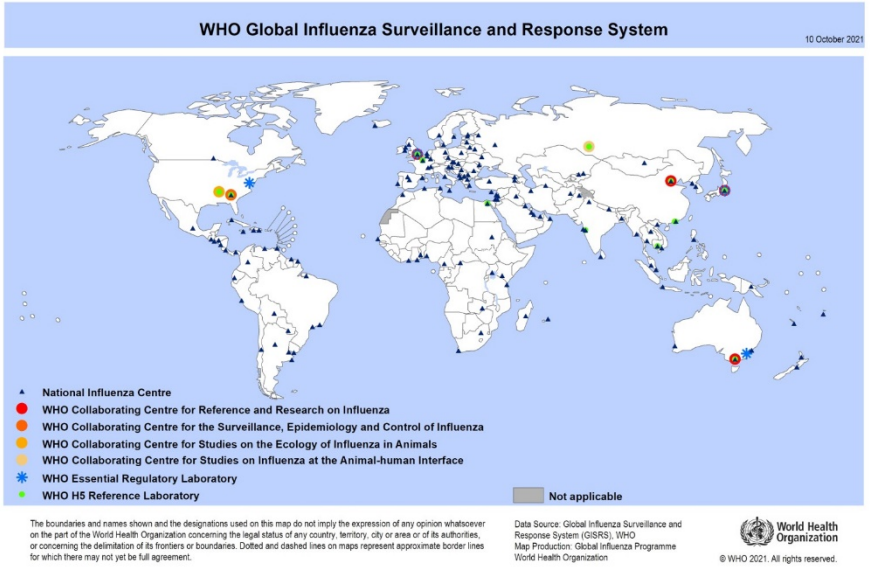
The Global Influenza Surveillance and Response System

GISRS is a system fostering global confidence and trust for over half a century, through effective collaboration and sharing of viruses, data and benefits based on Member States' commitment to a global public health model.



The foundation of GISRS is influenza sentinel surveillance among:

- Inpatients with Severe Acute Respiratory Infection (SARI)
- Outpatients with Influenza-Like Illness (ILI)



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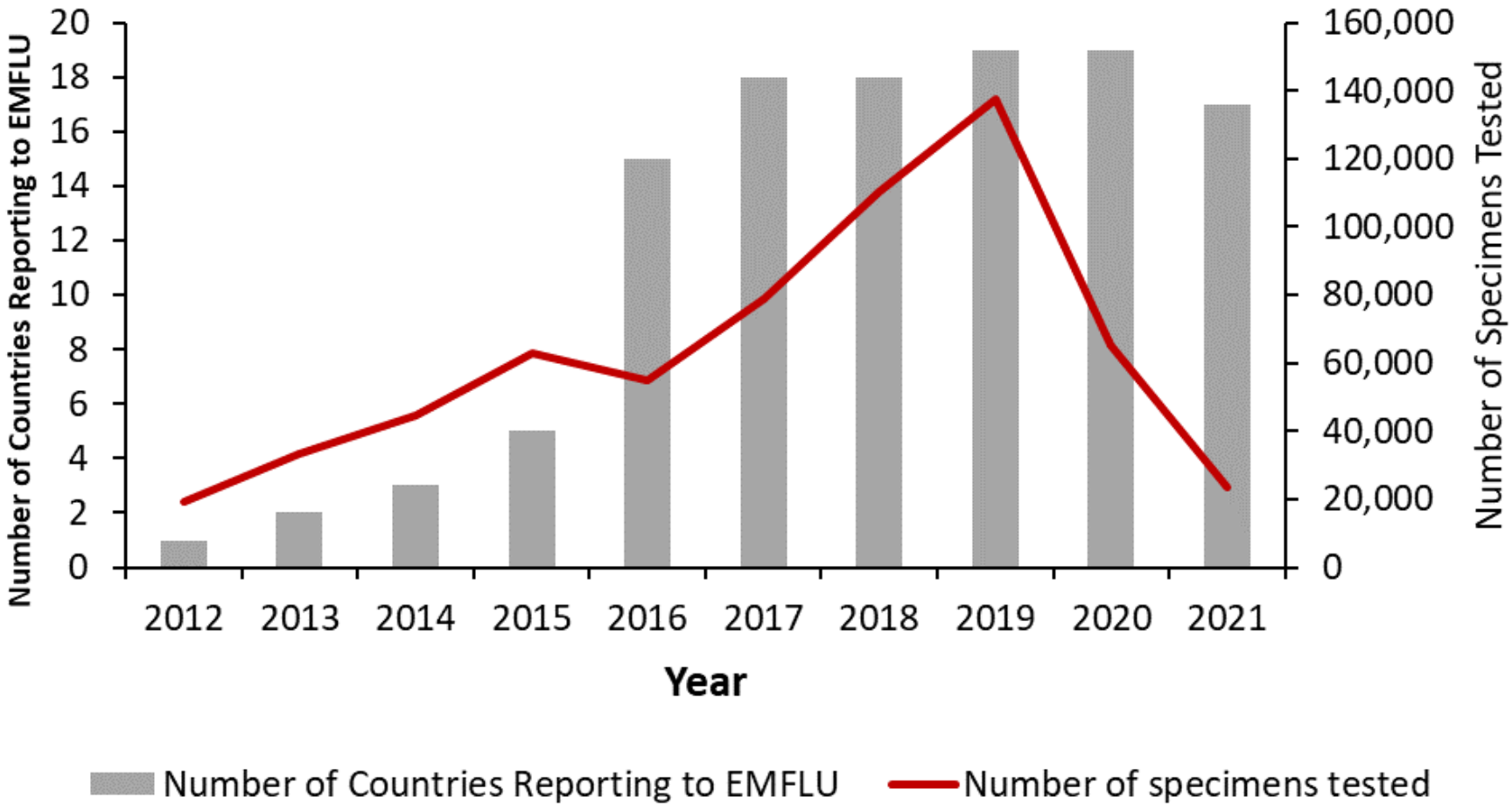
Number of influenza specimens tested and reported to FluNet/EMFLU and number of reporting countries, 2012-2021



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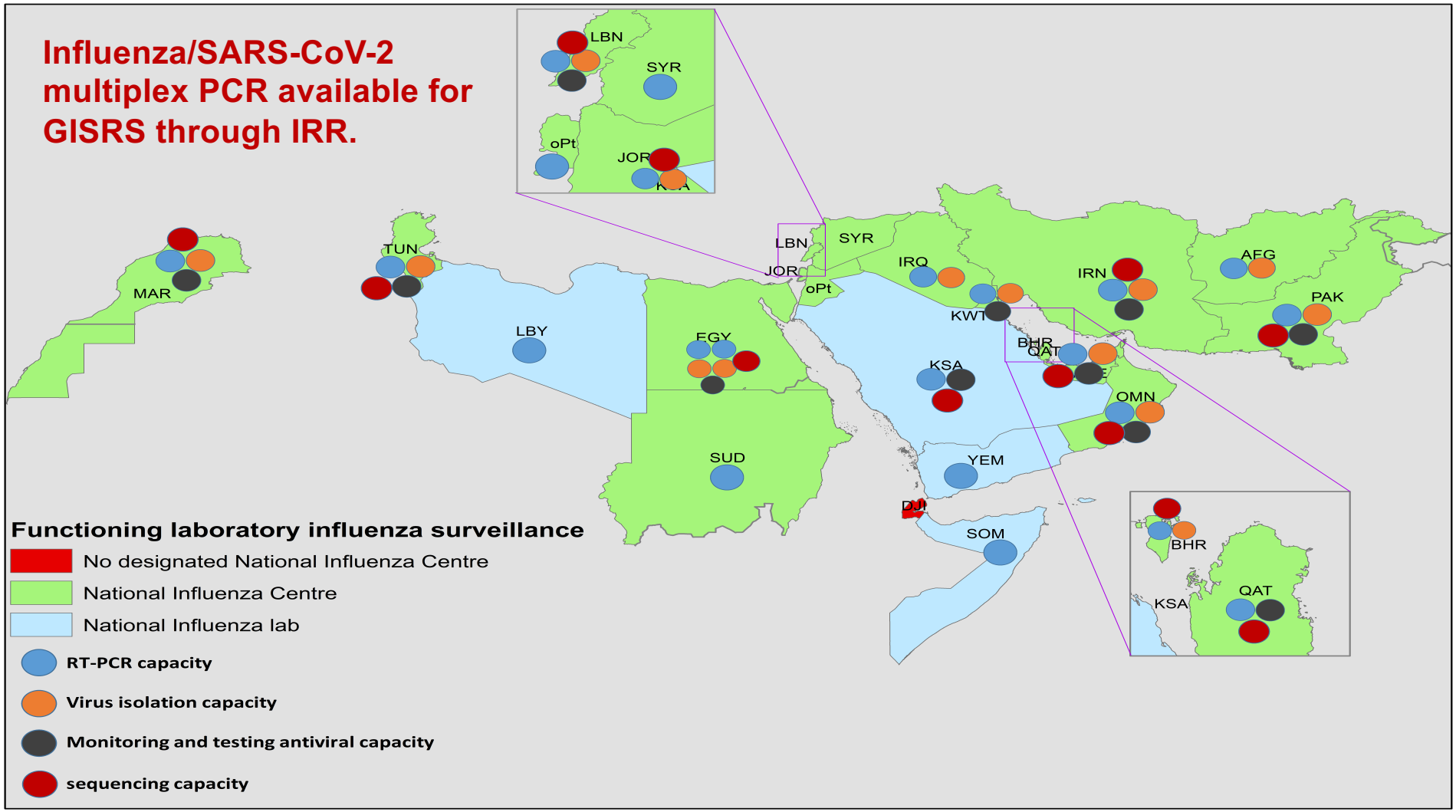
Status of influenza laboratory (SARS-CoV-2) capacity in EMR (October 2021)



The next evolution of GISRS is beyond influenza: GISRS+

Integration of surveillance for other respiratory pathogens is **NOT new** (e.g. RSV pilot studies)

COVID-19 pandemic accelerated the process and **highlighted the need for integration**

GISRS+ conceptualized for the **integration of surveillance for influenza and other respiratory viruses (ORVs)** with epidemic and pandemic potential

Priority currently given to the integration of **influenza** and **SARS-COV-2** in SARI/ILI sentinel surveillance

Integration of influenza and SARS-CoV-2 in sentinel surveillance under GISRS+

Nov. 2020

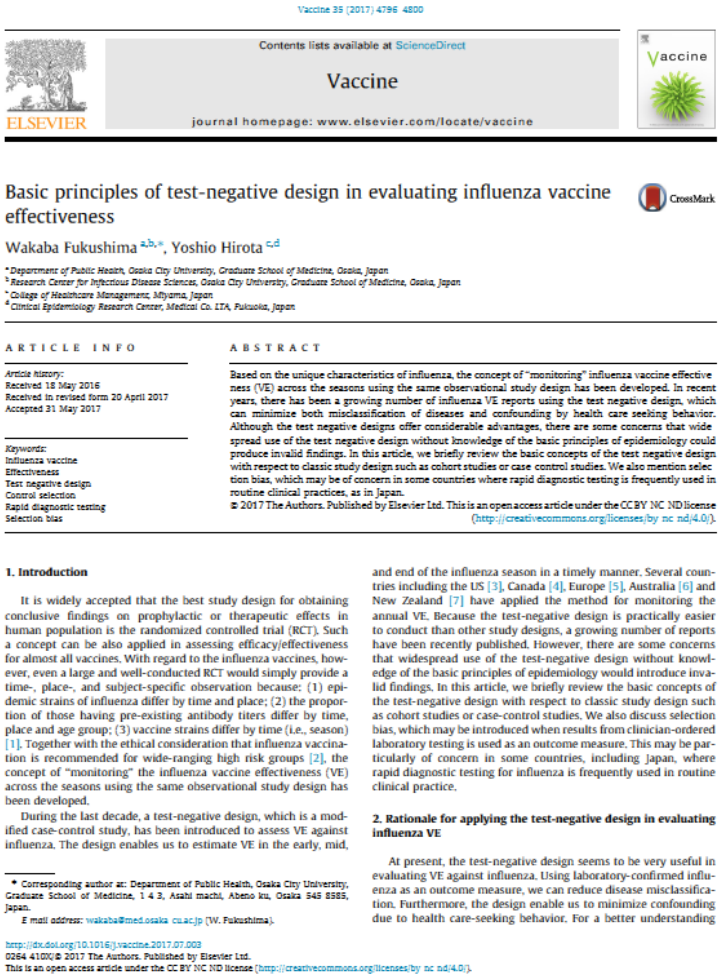
https://apps.who.int/iris/rest/bitstreams/1316069/retrieve

Feb. 2021

https://www.who.int/publications/i/item/WHO-2019-nCoV-genomic-sequencing-GISRS-2021.1

- Two eConsultations on the integration of influenza and SARS-CoV-2 surveillance
- Interim guideline: “Adapting the Global Influenza Surveillance and Response System to monitor influenza and SARS-CoV-2” (Oct. 2021)
- EMR operational plan for integrated SARI/ILI sentinel surveillance for influenza and SARS-CoV-2 developed and 5 countries in the EMR already implementing integrated surveillance and reporting influenza and SARS-CoV-2 data to GISRS

Test-Negative Design to Estimate Influenza Vaccine Effectiveness



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Basic principles of test-negative design in evaluating influenza vaccine effectiveness

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ABSTRACT

Based on the unique characteristics of influenza, the concept of "monitoring" influenza vaccine effectiveness (VE) across the seasons using the same observational study design has been developed. In recent years, there has been a growing number of influenza VE reports using the test negative design, which can minimize both misclassification of diseases and confounding by health care seeking behavior. Although the test negative designs offer considerable advantages, there are some concerns that widespread use of the test negative design without knowledge of the basic principles of epidemiology could produce invalid findings. In this article, we briefly review the basic concepts of the test negative design with respect to classic study design such as cohort studies or case control studies. We also mention selection bias, which may be of concern in some countries where rapid diagnostic testing is frequently used in routine clinical practices, as in Japan.

1. Introduction

It is widely accepted that the best study design for obtaining conclusive findings on prophylactic or therapeutic effects in human population is the randomized controlled trial (RCT). Such a concept can be also applied in assessing efficacy/effectiveness for almost all vaccines. With regard to the influenza vaccines, however, even a large and well-conducted RCT would simply provide a time-, place-, and subject-specific observation because; (1) epidemic strains of influenza differ by time and place; (2) the proportion of those having pre-existing antibody titers differ by time, place and age group; (3) vaccine strains differ by time (i.e., season) [1]. Together with the ethical consideration that influenza vaccination is recommended for wide-ranging high risk groups [2], the concept of "monitoring" the influenza vaccine effectiveness (VE) across the seasons using the same observational study design has been developed.

During the last decade, a test-negative design, which is a modified case-control study, has been introduced to assess VE against influenza. The design enables us to estimate VE in the early, mid, and end of the influenza season in a timely manner. Several countries including the US [3], Canada [4], Europe [5], Australia [6] and New Zealand [7] have applied the method for monitoring the annual VE. Because the test-negative design is practically easier to conduct than other study designs, a growing number of reports have been recently published. However, there are some concerns that widespread use of the test-negative design without knowledge of the basic principles of epidemiology would introduce invalid findings. In this article, we briefly review the basic concepts of the test-negative design with respect to classic study design such as cohort studies or case-control studies. We also discuss selection bias, which may be introduced when results from clinician-ordered laboratory testing is used as an outcome measure. This may be particularly of concern in some countries, including Japan, where rapid diagnostic testing for influenza is frequently used in routine clinical practice.

2. Rationale for applying the test-negative design in evaluating influenza VE

At present, the test-negative design seems to be very useful in evaluating VE against influenza. Using laboratory-confirmed influenza as an outcome measure, we can reduce disease misclassification. Furthermore, the design enable us to minimize confounding due to health care-seeking behavior. For a better understanding

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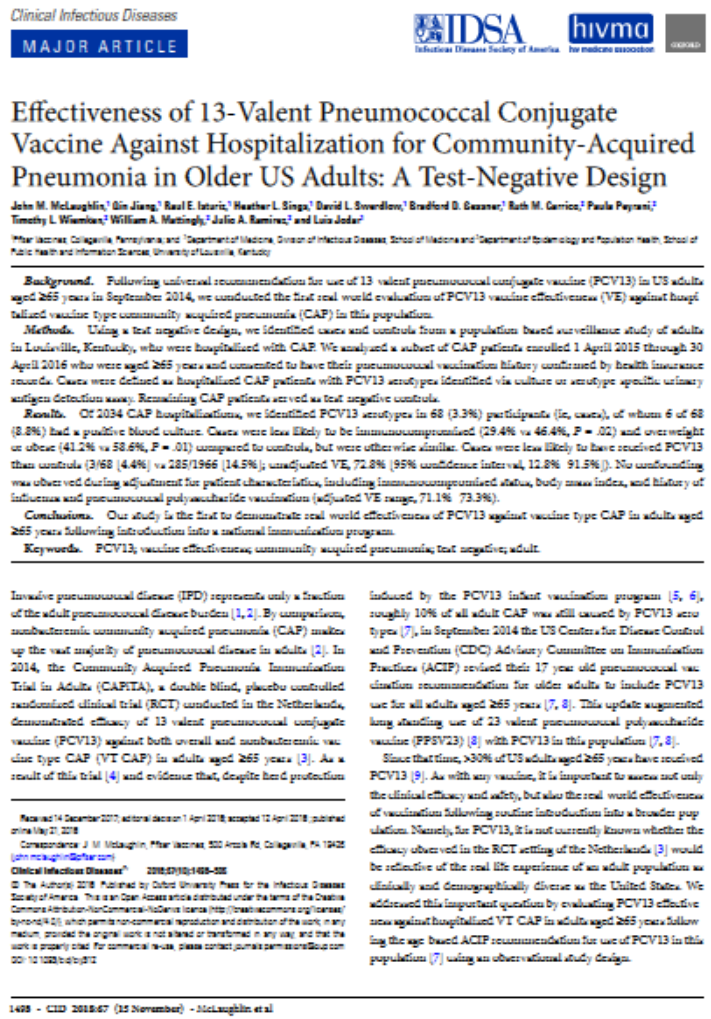
Test-Negative Design to Estimate Vaccine Effectiveness for Non-Influenza Pathogens



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Hospitalization for Community-Acquired Pneumonia in Older US Adults: A Test-Negative Design

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Background. Following universal recommendation for use of 13-valent pneumococcal conjugate vaccine (PCV13) in US adults aged ≥65 years in September 2014, we conducted the first real world evaluation of PCV13 vaccine effectiveness (VE) against hospitalized vaccine type community acquired pneumonia (CAP) in this population.

Methods. Using a test negative design, we identified cases and controls from a population based surveillance study of adults in Louisville, Kentucky, who were hospitalized with CAP. We analyzed a subset of CAP patients enrolled 1 April 2015 through 30 April 2016 who were aged ≥65 years and consented to have their pneumococcal vaccination history confirmed by health insurance records. Cases were defined as hospitalized CAP patients with PCV13 serotypes identified via culture or serotype specific urinary antigen detection assay. Remaining CAP patients served as test negative controls.

Results. Of 2034 CAP hospitalizations, we identified PCV13 serotypes in 68 (3.3%) participants (ie, cases), of whom 6 of 68 (8.8%) had a positive blood culture. Cases were less likely to be immunocompromised (29.4% vs 46.4%, $P = .02$) and overweight or obese (41.2% vs 58.6%, $P = .01$) compared to controls, but were otherwise similar. Cases were less likely to have received PCV13 than controls (3/68 [4.4%] vs 285/1966 [14.5%]; unadjusted VE, 72.8% [95% confidence interval, 12.8% 91.5%]). No confounding was observed during adjustment for patient characteristics, including immunocompromised status, body mass index, and history of influenza and pneumococcal polysaccharide vaccination (adjusted VE range, 71.1% 73.3%).

Conclusions. Our study is the first to demonstrate real world effectiveness of PCV13 against vaccine type CAP in adults aged ≥65 years following introduction into a national immunization program.

Keywords. PCV13; vaccine effectiveness; community acquired pneumonia; test negative; adult.

Invasive pneumococcal disease (IPD) represents only a fraction of the adult pneumococcal disease burden [1, 2]. By comparison, nonbacteremic community acquired pneumonia (CAP) makes up the vast majority of pneumococcal disease in adults [2]. In 2014, the Community Acquired Pneumonia Immunization Trial in Adults (CAPITA), a double blind, placebo controlled randomized clinical trial (RCT) conducted in the Netherlands, demonstrated efficacy of 13 valent pneumococcal conjugate vaccine (PCV13) against both overall and nonbacteremic vaccine type CAP (VT CAP) in adults aged ≥65 years [3]. As a result of this trial [4] and evidence that, despite herd protection induced by the PCV13 infant vaccination program [5, 6], roughly 10% of all adult CAP was still caused by PCV13 serotypes [7], in September 2014 the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) revised their 17 year old pneumococcal vaccination recommendation for older adults to include PCV13 use for all adults aged ≥65 years [7, 8]. This update augmented long standing use of 23 valent pneumococcal polysaccharide vaccine (PPSV23) [8] with PCV13 in this population [7, 8].

Since that time, >30% of US adults aged ≥65 years have received PCV13 [9]. As with any vaccine, it is important to assess not only the clinical efficacy and safety, but also the real world effectiveness of vaccination following routine introduction into a broader population. Namely, for PCV13, it is not currently known whether the efficacy observed in the RCT setting of the Netherlands [3] would be reflective of the real life experience of an adult population as clinically and demographically diverse as the United States. We addressed this important question by evaluating PCV13 effectiveness against hospitalized VT CAP in adults aged ≥65 years following the age based ACIP recommendation for use of PCV13 in this population [7] using an observational study design.

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Opportunity to estimate SARS-CoV-2 (and influenza) VE from integrated influenza and SARS-CoV-2 SARI sentinel surveillance systems

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Summary

- Influenza SARI/ILI sentinel surveillance established globally under WHO GISRS
- Influenza SARI sentinel surveillance established in several EM countries – however, SARI surveillance systems impacted by COVID-19 pandemic
- Integration of influenza and SARS-CoV-2 SARI sentinel surveillance recommended under WHO GISRS+ and already implemented in a few EM countries
- Integrated influenza and SARS-CoV-2 provides an opportunity for the estimation of SARS-CoV-2 (and influenza) VE using a well-established test-negative design.

Thank you

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