

Gaps in Influenza Clinical Research

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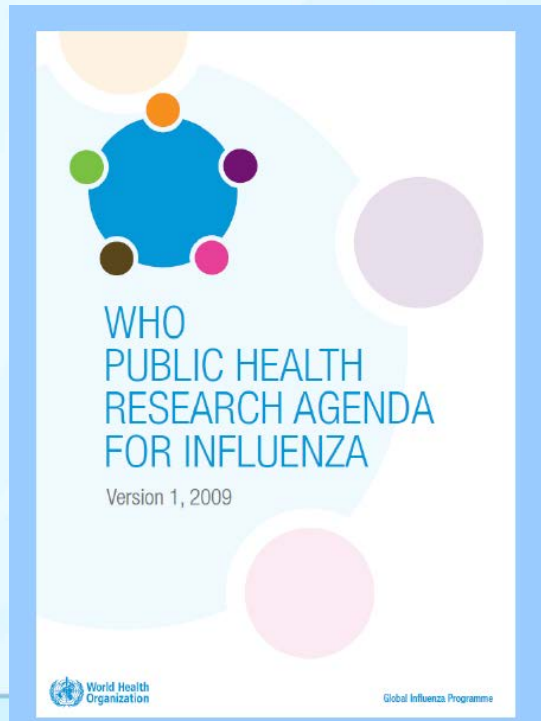


Outline

- 1. Global frameworks:**
 - 2010 Research Agenda
 - 2013 BRa Ve Agenda
- 2. Key gaps in clinical research**
- 3. Opportunities in Indonesia**

WHO Research Agenda for Influenza

- Published in Feb 2010
- Five streams
- 3-4 Areas of Focus for each stream



Clinical Areas of Focus in Research Agenda



- ❑ Disease burden
- ❑ Improve vaccines
- ❑ Reduce impact through public health policy
- ❑ Clinical aspects including risk factors, danger signs
- ❑ Clinical management
- ❑ Healthcare capacity and surge

Developments Since Research Agenda Established

□ Disease burden:

- WHO guidance for countries with difficulties in calculating population denominators.
- Large investment including in Indonesia to estimate morbidity and mortality rates.
- Recent global review (Peasah et al, 2013): per capita cost of an influenza case ranged from \$30 to \$64.

□ Improved vaccines:

- Quadrivalent vaccine (QIV): by incorporating both circulating influenza B lineages, vaccination with QIV reduces risk of dominant circulating B type virus not matching the vaccine strain selected.
- Live attenuated influenza vaccine (LAIV): easy administration suitable for mass immunization, cross-reactivity to drifted strains for broader coverage, contains four strains.

Developments since Research Agenda Established

□ Reduce impact:

- Since 2012, WHO recommends seasonal influenza vaccination for:

- **Highest priority:** Pregnant women
- **Priority** (in no particular order):
 - Children aged 6-59 months
 - Elderly
 - Individuals with specific chronic medical conditions
 - Health-care workers

Programmatic and research priorities for improving influenza immunization of pregnant women

Kevin A. Ault, MD; R. Phillips Heine, MD; Laura E. Riley, MD

For more than a decade, the American College of Obstetricians and Gynecologists (ACOG) and the Advisory Committee on Immunization Practices (ACIP) have recommended that pregnant women be routinely vaccinated against influenza. Since the Spanish flu pandemic of the early 20th century, it has been known that pregnant women are at increased risk for morbidity and mortality due to influenza.¹ The 2009 influenza pandemic confirmed these observations and greatly expanded our knowledge about influenza in pregnancy. The 21st century influenza pandemic also has led to an increased interest in improving uptake of influenza vaccination during pregnancy.

Multiple clinical research studies have been published over the past few years demonstrating that influenza vaccination during pregnancy is safe for both the mother and fetus.² Infants <6 months of

Despite evidence regarding the benefits of influenza immunization during pregnancy for both the pregnant woman and her infant, as well as reassuring safety data, influenza vaccination rates in pregnancy have lagged. The 2009 influenza pandemic was accompanied by increased maternal vaccination rates. In this article, we review programmatic and research priorities with regard to overcoming barriers to influenza immunization of pregnant women.

Key words: infants, influenza, maternal immunization, pregnancy, vaccination

age cannot receive influenza vaccination and these infants are at increased risk of severe illness and death from influenza. Maternal vaccination protects infants from influenza by passive immunization, ie, transplacental passage of antiinfluenza antibodies from the vaccinated mother to the fetus. These benefits are shown in Table 1 and addressed in detail in other articles in this supplement. Evidence of the protection against influenza in infants born to vaccinated pregnant women was a significant breakthrough when published in 2008.³ This work has been expanded to show protection against preterm and small-for-gestational-age infants.^{4,5}

Despite the long-standing recommendation from ACOG that pregnant women receive influenza vaccination during pregnancy, vaccination rates in this at-risk population have lagged well behind other high-risk groups. The 2009 H1N1 pandemic improved vaccination rates from <15% in 2008 to >50% in 2010.⁶ In a recent article from the Centers for Disease Control and Prevention (CDC), seasonal and monovalent H1N1 vaccination rates during pregnancy by state were reported for the influenza season of 2009 through 2010.⁶ During this influenza season, 2 different influenza vaccines were recommended for routine use during pregnancy. One vaccine was the monovalent H1N1 vaccine, and the other was the trivalent inactivated seasonal vaccine. Vaccination rates for the 2 different vaccines varied from 22–86% in the 24 states within this CDC report. Although much of this data is

encouraging, there is room for continued improvement (rates for selected states are in Table 2).

Overcoming programmatic barriers regarding influenza immunization during pregnancy

Table 3 enumerates programmatic issues regarding influenza immunization during pregnancy. Broadly, these issues fall into 3 categories: (1) novel strategies to encourage vaccination; (2) ongoing professional education targeted at obstetrical care providers; and (3) making influenza vaccination a routine item in women's health care.

Most providers are familiar with pamphlets as tools for patient education. There are also many contemporary examples of patient education materials on the Internet. One example of this is the website "Families Fight Flu" at www.familiesfightingflu.org. Families Fighting Flu is a volunteer child advocacy organization. This group also has a presence on social media sites such as Twitter and Facebook. Their website includes patient videos, reliable medical information, and print downloads.

Perhaps one of the most innovative programs concerning maternal health is Text4baby. This program is a voluntary text messaging service that provides pregnant women thrice-weekly pregnancy care messages. Remick⁷ has reported the initial results from this service as related to maternal influenza vaccination. Of the 96,070 pregnant women surveyed, 70% had received or were planning to receive their in-

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Vaccine Program Office, the Centers for Disease Control and Prevention, or the Food and Drug Administration.

Dr Ault has recently joined the medical advisory board of Families Fighting Flu. Families Fighting Flu is a nonprofit, 501(c)(3) volunteer-based advocacy organization dedicated to protecting the lives of children. Dr Ault is not paid for this role.

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Vaccine Research Gaps

- Pregnant women: highest priority for vaccination.
- Research shows that pregnant women more likely to be vaccinated if offered the vaccine by a health worker.
- But, vaccination rates in this group still low globally.

TABLE 1

Known benefits of maternal influenza vaccination

- Decreased respiratory illness among pregnant women³
- Decreased preterm births⁴
- Decreased small-for-gestational-age infants⁴
- Decreased influenza among infants <6 months of age³
- Decreased respiratory illness among infants <6 months of age³

Ault. Research priorities for improving influenza immunization of pregnant women. Am J Obstet Gynecol 2012.

Research priorities for influenza vaccination during pregnancy

- Vaccine safety
 - New adjuvants, geographic expansion of availability, new formulation and administration routes
- Vaccine acceptance
 - Evaluate interventions to increase vaccination rates, assess reasons for refusal, assess reasons for provider refusal
- Vaccine effectiveness
 - Assess outcomes (complications/deaths) due to influenza
 - Benefits to newborn, prevention of pneumonia and other co-morbidities

Developments since Research Agenda Established

□ Reduce impact:

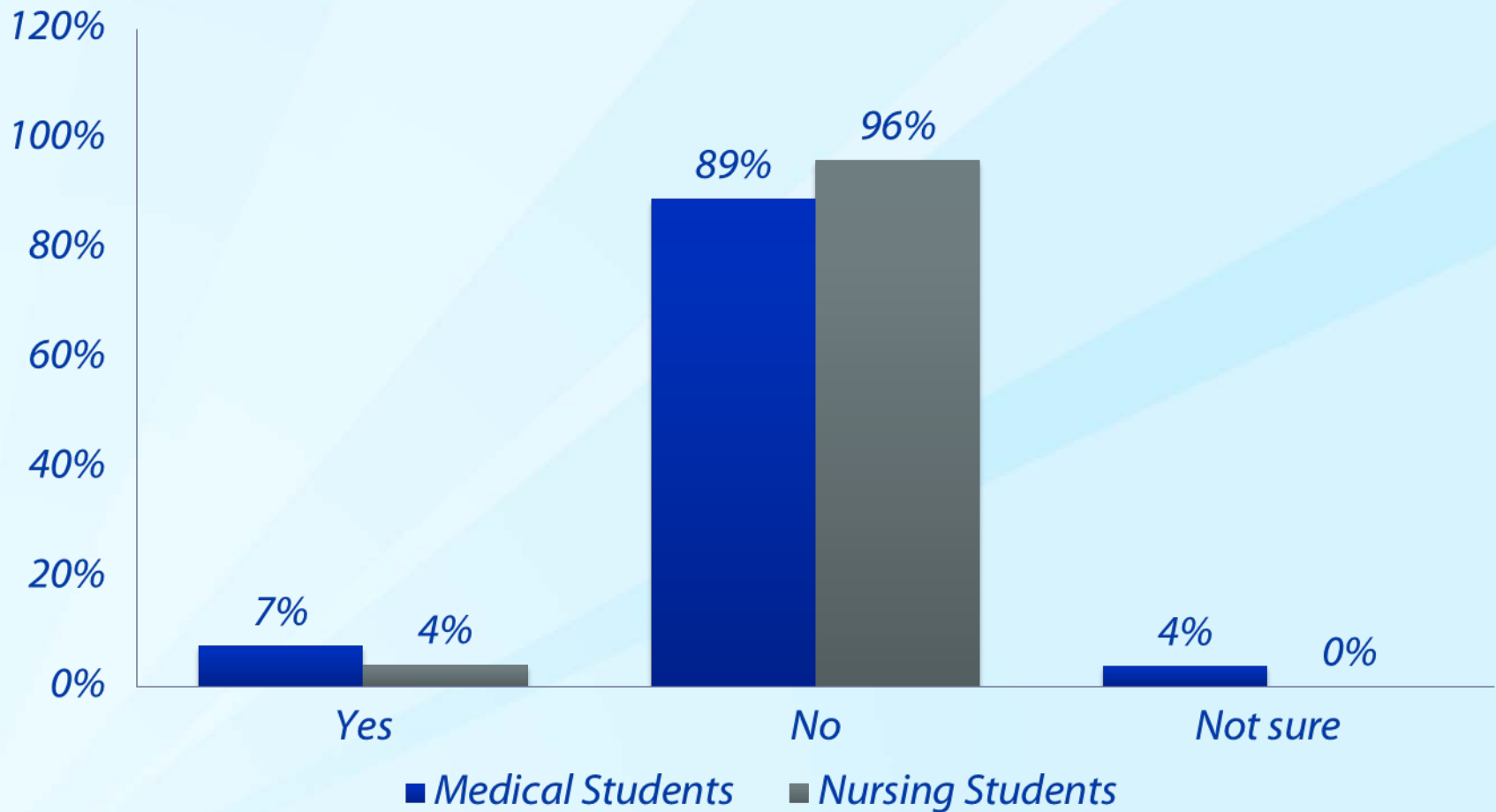
- Since 2012, WHO recommends seasonal influenza vaccination for:
 - **Highest priority:** Pregnant women
 - **Priority** (in no particular order):
 - Children aged 6-59 months
 - Elderly
 - Individuals with specific chronic medical conditions
 - Health-care workers
- Research to understand healthcare worker attitudes towards vaccination (occupational health): studies in Indonesia

Influenza Vaccination: knowledge, practices and attitudes among Indonesian medical and nursing students, 2014

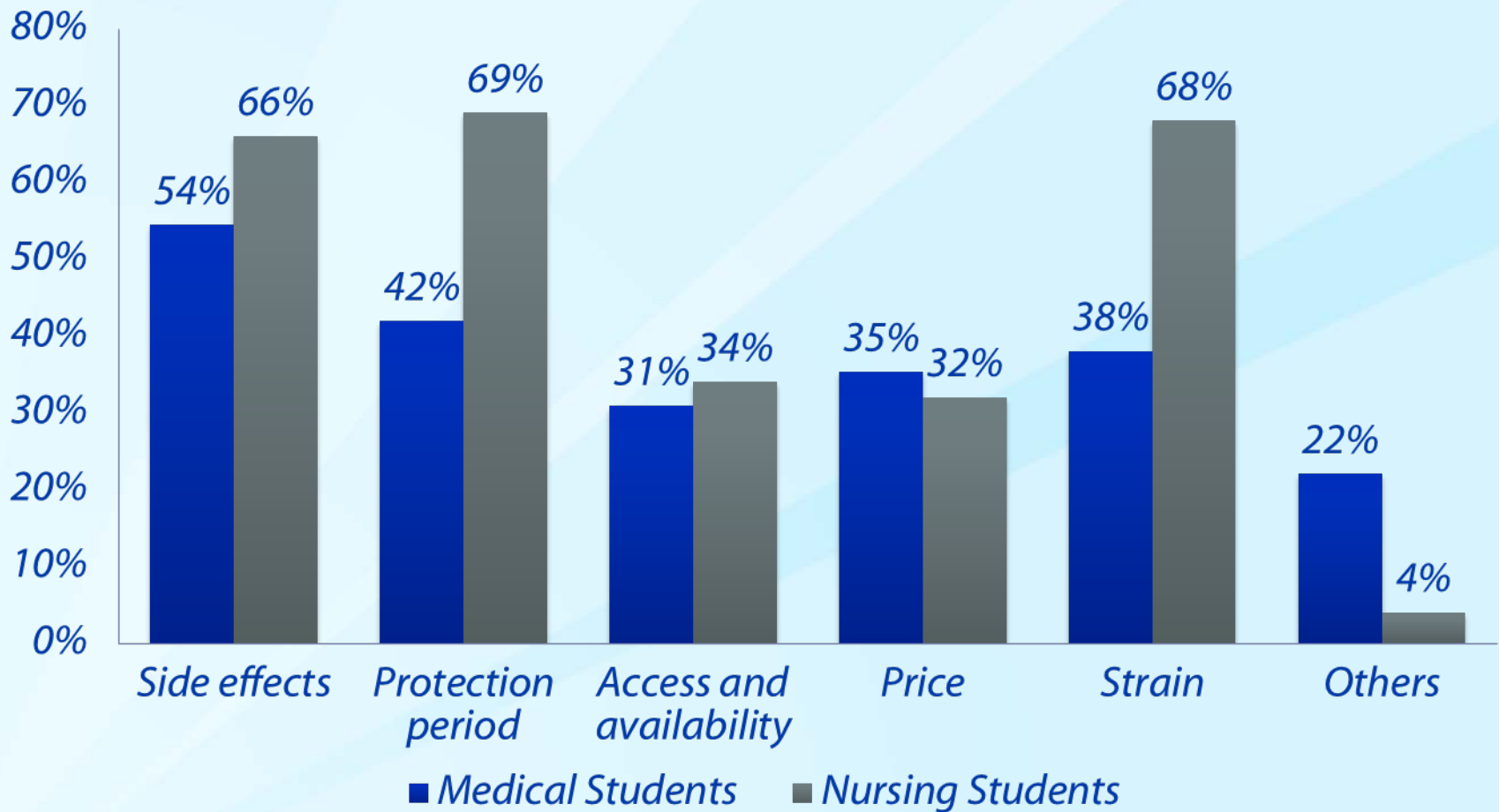
- Cross sectional study using random stratified sampling:**
 - 136 medical students of Atma Jaya Catholic University
 - 119 nursing students of St. Carolus Health Institute

- Conducted by medical students at Atma Jaya Catholic University with US CDC technical support.**

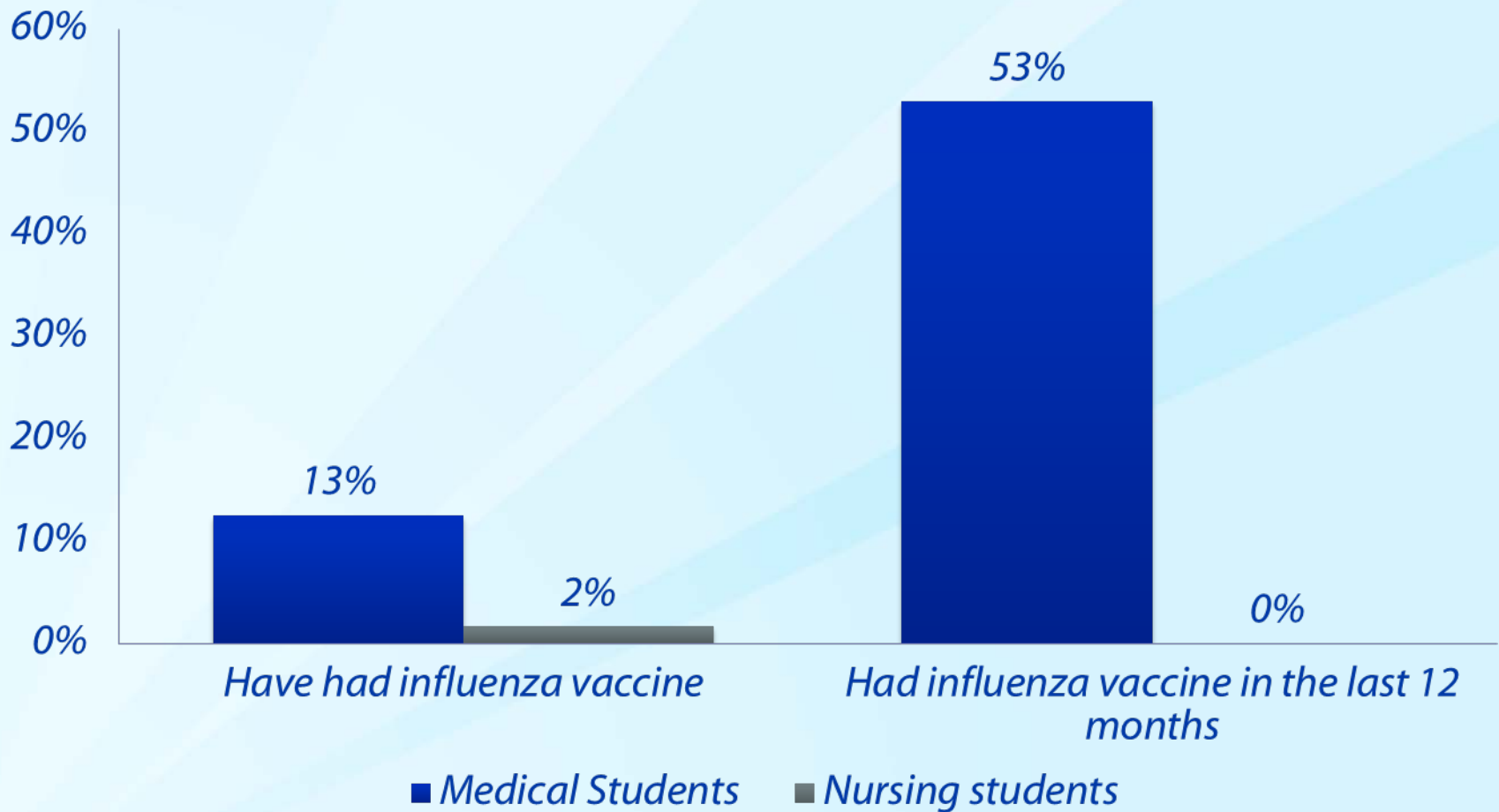
Did Students Have Enough Knowledge about Influenza Vaccine?



What Students Wanted To Know?



Influenza Vaccination Use



Recommendation

- Based on progress against the WHO Research Agenda for Influenza, develop an Indonesian national influenza research agenda.
 - Helps researchers and partners agree on current priorities and focus available resources to key questions.

Research needs for the Battle against Respiratory Viruses (BRaVe)

Background document
2013



**World Health
Organization**

http://www.who.int/influenza/patient_care/clinical/BRaVe_Research_Agenda_2013.pdf?ua=1

WHO: Research needs for the Battle against Respiratory Viruses (BRaVe)

Key objectives of this clinical research agenda are to:

- identify the specific research needed to improve medical and public health responses to RVIs and their sequelae over both the short-to-medium (1–5 years) and the medium-to-long (5–10 years) term;
- provide a framework – reflecting public health research priorities – for allocating research resources, including studies applicable in under-resourced countries and those addressing areas that have been relatively less studied (e.g. operational and social sciences research);
- facilitate discussion, coordination and interactions among fundamental and clinical investigators from both public and private sectors, funders, pharmaceutical industry representatives and public health professionals;
- highlight the need and the potential benefits of a multidisciplinary approach to addressing knowledge gaps in prevention and treatment of RVIs.

BRaVe: Influenza in context of other respiratory viruses

1. Defining the burden of disease
2. Understanding disease pathogenesis and host dynamics
3. Expanding treatment options
4. Improving SARI diagnosis and diagnostic tests
5. Improving clinical management of SARI and CAP
6. Optimizing public health strategies.

Box 3: Distribution of pathogens in children with lower respiratory infections/pneumonia

	(%) ^a (22)	(%) ^b (50)	(%) ^c (35)
Bacterial	18.4	51	
Selected bacteria			
<i>Mycoplasma pneumoniae</i>	7.9		9.8
<i>Haemophilus influenzae</i>	3.9		
<i>Chlamydomphila pneumoniae</i>	1.3		
<i>Streptococcus pneumoniae</i>			
Viral			
Selected			
		12	
	7.2		24.8
Mixed viral		20	
Mixed bacterial/viral		28.5	
Patient with 1 pathogen (either virus or bacteria)	47.2		
Patient with 2 pathogens (either virus or bacteria)	31.5		30.5
Patient with 3 or more pathogens (either virus or bacteria)	9.2		8.1

Improved understanding of virus–host interactions is fundamental to developing rational therapeutics & vaccines.

^a Age range of children: 1 month to 15 years old; ^b Age range of children: under 5 years old; ^c Age range of children: under 5 years old

Expanding Treatment Options

- In (H1N1) 2009 pandemic in Japan, the combination of early diagnosis, rapid testing and oseltamivir treatment, resulted in the lowest mortality rate in the world with influenza deaths in pregnant women.
- But, oseltamivir is not a cure, especially for seriously ill patients.
- Other neuraminidase inhibitors, including intravenous and long-acting inhaled formulations, are in clinical development, as are several agents with novel mechanisms of anti-influenza action (e.g. DAS181, favipiravir, nitazoxanide and AVI-7100).

Trials to assess value of available and new treatment options (especially in context of pandemic).

Disease burden and Vaccine Introduction in Indonesia

- Indonesia has long-established influenza surveillance (ILI and SARI).
 - Data can be used to inform vaccine target groups priorities and introduction.
 - Vaccine policy and introduction: pending.
- ➔ Research needed to demonstrate vaccine benefit in priority groups and to encourage policy development (eg Health workers, pregnant women, immuno-compromised).
- ➔ Influenza seasonality in different provinces: impact on vaccine timing & composition recommendations.

Other Research Opportunities in Indonesia

- Barriers to vaccine introduction or national recommendations.
- Provision of influenza vaccine to health workers in clinical facilities to achieve better occupational health status: JKN impact.
- Zoonotic viruses: analysis of live-bird market specimens testing positive for influenza A (but H5/H7 negatives) to determine subtypes circulating in birds. Potential future spill-over viruses into humans.

Thank you