ไข้หวัดใหญ่ในประเทศไทย

สมาคมไวรัสวิทยา (ประเทศไทย)

คำนำ

ก่อนการระบาดของไข้หวัดนก มีความตื่นตัวเกี่ยวกับโรคไข้หวัดใหญ่น้อยมากในประเทศไทย การระบาดใหญ่ทั่วโลก (pandemic) ครั้งสุดท้ายก็ได้ผ่านไปแล้วถึง 40 ปี ทำให้คนในสังคมส่วนใหญ่ไม่ได้มีประสบการณ์ตรง และไม่ได้ตระหนักถึงความร้ายแรงของปัญหา คนส่วนใหญ่จึงไม่รู้สึกว่าไข้หวัดใหญ่ไม่ใช่ปัญหาร้ายแรง นอกจากนี้ก็ยังมีความเชื่อกันว่าไข้หวัดใหญ่ไม่ใช่ปัญหาสำคัญของประเทศในเขตร้อน อย่างไรก็ตามในช่วงเวลาที่ผ่านมาเราไม่มีข้อมูลชัดเจนถึงขนาดของปัญหาของไข้หวัดใหญ่ จึงทำให้มีความเห็นที่แตกต่างกันถึงความสำคัญของปัญหาไข้หวัดใหญ่ แต่เมื่อเร็วๆนี้ได้มีการศึกษาในลักษณะ population-based ทำให้เราได้ข้อมูลชัดเจนว่าไข้หวัดใหญ่เป็นปัญหาที่สำคัญ และมีขนาดของปัญหาและความเสียหายทั้งต่อสุขภาพของประชาชนและต่อเศรษฐกิจใหญ่กว่าคนทั่วไปคาดไว้มาก สมาคมไวรัสวิทยามีความเห็นว่าข้อมูลเหล่านี้มีความสำคัญและสมควรเผยแพร่ในวงกว้าง เพื่อให้บุคลากรทางสาธารณสุขของประเทศรวมทั้งบุคคลทั่วได้ได้ตระหนักถึงปัญหานี้ รวมทั้งได้รวบรวมทบทวนข้อมูลความรู้เกี่ยวกับระบาดวิทยาของไข้หวัดใหญ่โดยเน้นข้อมูลของประเทศเพื่อให้ได้มีการนำข้อมูลนี้เผยแพร่เพื่อใช้ประโยชน์ในการร่วมกันควบคุมและป้องกันโรคนี้ต่อไป

สารบัญ

ระบาดวิทยาของไข้หวัดใหญ่

การเปลี่ยนแปลงของไวรัสไข้หวัดใหญ่

อาจกล่าวได้ว่าไวรัสไข้หวัดใหญ่มีการเปลี่ยนแปลงตัวเองอยู่ตลอดเวลา และการเปลี่ยนแปลงเป็นหัวใจของการดำรงอยู่และการแพร่ระบาดของไข้หวัดใหญ่ ทั้งนี้เนื่องจากทั้งธรรมชาติของไวรัสที่มีการกลายพันธุ์ได้ง่ายและความจำเป็นในการดำรงอยู่ที่ต้องอาศัยการเปลี่ยนแปลงเพื่อหลบหลีกจากภูมิคุ้มกันของผู้ติดเชื้อ [1]

การเปลี่ยนแปลงที่ทำให้ไวรัสสามารถหลบหลีกจากระบบภูมิคุ้มกันของมนุษย์ได้นั้นเกิดจากการกลายพันธุ์ของไวรัสในส่วนของโปรตีน hemagglutinin (HA) และ neuraminidase (NA) ไวรัสในแต่ละปีจะค่อย ๆมีการเปลี่ยนแปลงของลักษณะของแอนติเจน (สิ่งที่ระบบภูมิคุ้มกันจดจำ) ของไวรัส บนโปรตีน HA และ NA ไปทีละเล็กละน้อย ทำให้ระบบภูมิคุ้มกันของคนที่เคยติดเชื้อในปีก่อนๆไม่สามารถจดจำหรือรู้จักเชื้อที่เกิดใหม่ในปีหลังๆ และทำให้เกิดการติดเชื้อซ้ำได้ การเปลี่ยนแปลงดังกล่าวเราเรียกกันว่า antigenic drift

การเฝ้าระวังไข้หวัดใหญ่

เพื่อให้สามารถติดตามการเปลี่ยนแปลงของไวรัสไข้หวัดใหญ่ รวมทั้งติดตามสถานการณ์การระบาดของไข้หวัดใหญ่ทั่วโลกได้อย่างมีประสิทธิภาพและทันเวลา องค์การอนามัยโลกได้จัดตั้งระบบเฝ้าระวังขึ้นมาตั้งแต่ปี พ.ศ. 2480 โดยเป็นเครือข่ายความร่วมมือระหว่างประเทศ ปัจจุบันมีห้องปฏิบัติการร่วมอยู่ในเครือข่าย 114 แห่งใน 83 ประเทศ ซึ่งกรมวิทยาศาสตร์การแพทย์ก็เป็นหนึ่งในห้องปฏิบัติการในเครือข่ายนี้ โดยเข้าร่วมเครือข่ายมาตั้งแต่ปี พ.ศ. 2515

สำหรับในประเทศไทยกรมวิทยาศาสตร์การแพทย์ มีเครือข่ายในการเก็บตัวอย่างเพื่อเฝ้าระวังเชื้อไข้หวัดใหญ่ใน 4 ภาค ได้แก่ที่จังหวัด ตาก, หนองคาย, ชลบุรี, สงขลา และในส่วนกลางที่นนทบุรี นอกจากนี้ยังมีเครือข่ายห้องปฏิบัติการในจังหวัดต่างๆ 13 แห่ง ซึ่งได้เริ่มขึ้นเมื่อเกิดการระบาดของไข้หวัดนก และห้องปฏิบัติการเหล่านี้สามารถให้การวินิจฉัยทางห้องปฏิบัติการได้ทั้งไข้หวัดใหญ่และไข้หวัดนก

สายพันธุ์ของไวรัสไข้หวัดใหญ่ในประเทศไทย

เช่นเดียวกับในประเทศอื่นๆทั่วโลก สายพันธุ์ของไวรัสไข้หวัดใหญ่ในประเทศไทยก็มีการเปลี่ยนแปลงอยู่อย่างสม่ำเสมอ ตารางที่ 1 แสดงสายพันธุ์ของไวรัสไข้หวัดใหญ่ที่พบในประเทศไทยใน 5 ปีที่ผ่านมา (พ.ศ. 2546-2550) จะเห็นได้ว่าจะมีสายพันธุ์และ type/subtype ของไวรัสที่เด่นแตกต่างกันในแต่ละปี ซึ่งส่วนใหญ่จะเหมือนกับสายพันธุ์ของไวรัสที่ระบาดในภูมิภาคในปีนั้นๆ

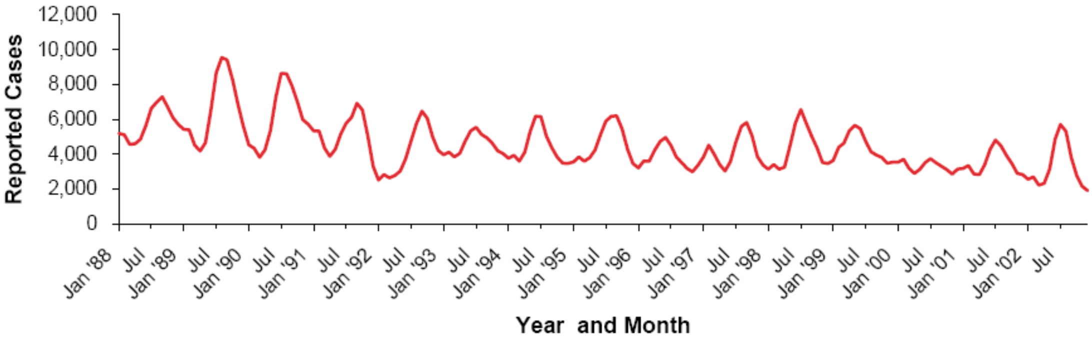
ตารางที่ 1 สายพันธุ์ของไวรัสไข้หวัดใหญ่ที่พบในประเทศไทย

ปี พ.ศ.	Type/sub type	%	สายพันธุ์
2550	A/H1H1 A/H3N2 B	2 88 10	
2549	A/H1H1 A/H3N2 B	73 10 17	A/New Caledonia/20/99 A/Wellington/1/2004 A/California/7/2004 B/Hong Kong/330/2001 B/Shanghai/361/2002 B/Hawii/33/2004 B/Malaysia/2506/2004
2548	A/H1H1 A/H3N2 B	6 60 35	A/New Caledonia/20/99 A/Wellington/1/2004 A/California/7/2004 B/Sichuan/379/99 B/Hong Kong/330/2001 B/Shanghai/361/2002 B/Malaysia/2506/2004
2547	A/H1H1 A/H3N2 B	48 38 15	A/New Caledonia/20/99 A/Fujian/411/2002 A/Wellington/1/2004 A/California/7/2004 B/Shanghai/361/2002 B/Hong Kong/330/2001 B/Sichuan/379/99
2546	A/H1H1 A/H3N2 B	0 4 96	 A/Fujian/411/2002 B/Sichuan/373/99

(ข้อมูลจากกรมวิทยาศาสตร์การแพทย์ และจาก WHO Global Atlas of Infectious Diseases: http://gamapserver.who.int/GlobalAtlas/home.asp)

ฤดูกาล

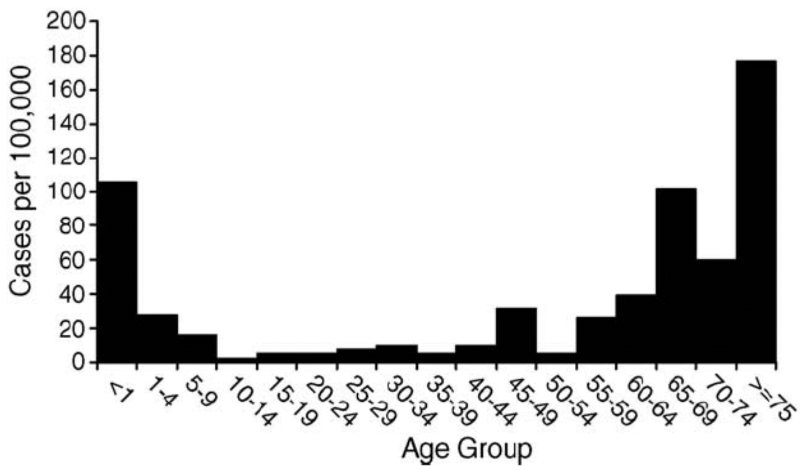
ไข้หวัดใหญ่เป็นโรคที่รู้จักกันดีในประเทศหนาวว่าเป็นโรคที่มาตามฤดูกาล โดยจะมีการระบาดในฤดูหนาว แต่สำหรับประเทศไทยที่มีความแตกต่างระหว่างฤดูกาลน้อยก็ทำให้บางคนอาจคิดไปว่าการระบาดอาจขึ้นกับฤดูกาลน้อยลง แต่ในความเป็นจริงแล้วข้อมูลที่ผ่านมามีความชัดเจนว่าในประเทศไทยก็มีลักษณะการระบาดที่ขึ้นกับฤดูกาลอย่างชัดเจนเช่นเดียวกัน โดยช่วงที่มีการระบาดมากที่สุดจะเป็นช่วงฤดูฝนและมีการระบาดต่อเนื่องไปในฤดูหนาวแล้วลดลงอย่างมากในฤดูร้อน ดังแสดงในรูปที่ 1 [2]



รูปที่ 1 แสดงความสัมพันธ์ของอัตราการรายงานโรคไข้หวัดใหญ่กับฤดูกาลในประเทศไทย (จาก Simmerman et al, 2006)

กลุ่มอายุ

ไข้หวัดใหญ่เป็นโรคที่พบในเด็กได้บ่อยกว่าผู้ใหญ่ และเป็นปัญหาสำคัญคือก่อให้เกิดภาวะแทรกซ้อนคือปอดอักเสบได้บ่อยในเด็กเล็กและผู้สูงอายุ [3] ข้อมูลในประเทศไทยจากการสำรวจที่จังหวัดสระแก้ว พบว่า 80% ของผู้ป่วยไข้หวัดใหญ่ที่มาตรวจที่แผนกผู้ป่วยนอกมีอายุต่ำกว่า 14 ปี และเมื่อดูการกระจายตามอายุของผู้ป่วยไข้หวัดใหญ่ที่มีปอดอักเสบ ก็จะเห็นชัดเจนว่าพบมากในกลุ่มเด็กต่ำกว่า 5 ขวบ และผู้ที่อายุมากกว่า 65 ปี ดังแสดงในรูปที่ 2 [4]



รูปที่ 2 การกระจายตามอายุของผู้ป่วยไข้หวัดใหญ่ที่มีปอดอักเสบ

ขนาดของปัญหาและความสูญเสียจากไข้หวัดใหญ่

ขนาดของปัญหา

มีความเข้าใจกันอย่างผิด ๆว่าไข้หวัดใหญ่เป็นโรคของประเทศหนาวและสำหรับประเทศในเขตร้อนอย่างประเทศไทย โรคไข้หวัดใหญ่ไม่ใช่ปัญหาทางสาธารณสุขที่สำคัญ เนื่องจากที่ผ่านมาเราไม่มีข้อมูลที่ชัดเจนถึงอัตราป่วยและขนาดของปัญหาจากโรคนี้ แต่เมื่อเร็ว ๆนี้ได้มีการศึกษาในพื้นที่จังหวัดสระแก้ว ทำให้ได้ข้อมูลที่ชัดเจนของอุบัติการณ์ และความสูญเสียที่เกิดขึ้นซึ่งมีขนาดใหญ่กว่าที่คาดคิดกันโดยทั่วไปมาก

ในระบบการเฝ้าระวังโรคของสำนักระบาดวิทยา กระทรวงสาธารณสุข มีการรายงานโรคที่มีลักษณะทางคลินิกเข้าได้กับไข้หวัดใหญ่ (influenza-like illness) ในปี พ.ศ. 2540 – 2547 มีรายงานโรคนี้เฉลี่ย 66/ประชากร 100,000 คนในแต่ละปี และในปี พ.ศ. 2542 มีรายงานโรคนี้ในผู้ป่วยที่รับไว้ในโรงพยาบาล 21/100,000 คน ซึ่งการที่มีสัดส่วนของผู้ป่วยที่รับไว้ในโรงพยาบาลสูงเมื่อเทียบกับอุบัติการณ์ทั้งหมดแสดงให้เห็นว่าการรายงานมีความโน้มเอียงที่จะรายงานเฉพาะรายที่มีอาการหนัก ทำให้อุบัติการณ์ดังกล่าวนี้น่าจะต่ำกว่าความเป็นจริงมาก [2]

ในปี พ.ศ. 2546-2547 มีการศึกษาในพื้นที่จังหวัดสระแก้วเพื่อประเมินอุบัติการณ์ของไข้หวัดใหญ่ โดยพบว่ามีอุบัติการณ์ของผู้ป่วยไข้หวัดใหญ่ที่มารับการตรวจรักษาที่แผนกผู้ป่วยนอกของโรงพยาบาล 1420 ราย / ประชากร 100,000 และมีผู้ป่วยไข้หวัดใหญ่ที่รับไว้เป็นผู้ป่วยในของโรงพยาบาล 18-111 ราย/ ประชากร 100,000 ในหนึ่งปี หรือคิดเป็นจำนวนผู้ป่วยทั้งประเทศ เป็นผู้ป่วยนอกมากกว่า 9 แสนรายต่อปี และผู้ป่วยในประมาณ 12,000 – 75,000 รายต่อปี [4]

อีกการศึกษาหนึ่งซึ่งทำในระดับชุมชนในจังหวัดสระแก้ว ในปี พ.ศ. 2546 ซึ่งทำให้ได้ข้อมูลของผู้ป่วยที่ไม่ได้ไปรับการตรวจรักษาที่โรงพยาบาล ในการศึกษานี้พบว่าอุบัติการณ์ของไข้หวัดใหญ่เป็น 5941 ราย / ประชากร 100,000 หรือคิดเป็นจำนวนผู้ป่วยทั่วประเทศเกือบ 4 ล้านรายต่อปี [5]

ความสูญเสียทางเศรษฐกิจ

ในประเทศพัฒนาแล้วความสูญเสียทางเศณษฐกิจที่สำคัญจากไข้หวัดใหญ่เป็นผลงานการหยุดงานของผู้ป่วย ในประเทศไทยแต่เดิมซึ่งเชื่อกันว่าไข้หวัดใหญ่ไม่ใช่ปัญหาสำคัญนั้นก็ทำให้คิดกันไปเองว่าความสูญเสียจากไข้หวัดใหญ่คงไม่มากนัก แต่จากการศึกษาโดยการสำรวจในจังหวัดสระแก้วพบว่าความเสียหายทางเศรษฐกิจจากไข้หวัดใหญ่นั้นมีขนาดใหญ่กว่าที่คิดกันทั่วไปมาก โดยเป็นการสำรวจจำนวนผู้ป่วยไข้หวัดใหญ่ที่มารับการรักษาในแผนกผู้ป่วยนอกและผู้ป่วยไข้หวัดใหญ่ที่มีปอดอักเสบและรับเป็นผู้ป่วยในของโรงพยาบาล ข้อมูลจากการศึกษานี้ทำให้ประมาณได้ว่าความสูญเสียทางเศรษฐกิจของทั้งประเทศจากไข้หวัดใหญ่นั้นอยู่ระหว่าง 23.4 ถึง 62.9 ล้านเหรียญสหรัฐ หรือประมาณ 750 – 2000 ล้านบาท โดยในจำนวนนี้ 43%

เป็นค่าใช้จ่ายทางตรงจากการรักษาพยาบาล ส่วนที่เหลือเป็นความสูญเสียทางอ้อม เช่นความสูญเสียที่เกิดจากการหยุดงาน [4]

ในอีกการศึกษาหนึ่งซึ่งทำการสำรวจในชุมชนซึ่งเป็นการประมาณจำนวนผู้ป่วยทั้งที่ไปขอรับการรักษาและที่ซื้อยากินเอง การศึกษานี้ได้ประมาณว่ามีจำนวนผู้ป่วยไข้หวัดใหญ่ทั้งประเทศเกือบ 4 ล้านราย ซึ่งพบว่าในการป่วยแต่ละครั้งมีค่าใช้จ่ายเฉลี่ย 663 บาท ซึ่งเมื่อคูณกันแล้ว ก็จะทำให้เป็นความสูญเสียทางเศรษฐกิจสูงถึงประมาณ 2600 ล้านบาทต่อปี [5]

ตารางที่ 2 แสดงอุบัติการณ์ของไข้หวัดใหญ่และความสูญเสียทางเศรษฐกิจในประเทศไทย

กลุ่มผู้ป่วย	อุบัติการณ์/100,000	จำนวนผู้ป่วยทั่วประเทศ (แสนคน)	ความสูญเสียทางเศรษฐกิจ (ล้านบาท)
ผู้ป่วยปอดอักเสบที่รับไว้ในโรงพยาบาล [4]	18 - 111	0.12 – 0.75	137 – 940
ผู้ป่วยนอก [4]	1420	9	560 – 1000
ผู้ป่วยในชุมชน [5]	5941	40	2600

บรรณานุกรม

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The cost of influenza in Thailand

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Abstract

The cost of influenza in less wealthy tropical countries is needed to inform national vaccine policy decisions. Between September 2003 and August 2004, we prospectively identified hospitalized pneumonia cases and outpatients with laboratory confirmed influenza in a Thai province. Disease incidence, patient interviews, medical record reviews, and data from a national health survey were used to calculate direct and indirect costs which were extrapolated to the Thai population. Influenza was identified in 80 (11%) of 761 hospitalized pneumonia inpatients with projected annual incidence of 18–111/100,000 population. Influenza was confirmed in 23% of 1092 outpatients with an estimated annual incidence of 1420/100,000 population. Influenza was estimated to cause between US$ 23.4 and US$ 62.9 million in economic losses with lost productivity accounting for 56% of all costs. The burden of influenza in Thailand is greater than previously appreciated, particularly in young children and the elderly. The impact and cost-effectiveness of influenza vaccination for high-risk groups merits further investigation.
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Keywords: Influenza; Cost of illness; Thailand

1. Introduction

Influenza is a vaccine preventable infectious disease that causes morbidity in all age groups and appreciable mortality, especially in the elderly, young children, and those with underlying illness [1]. In the temperate climates of Europe and North America, seasonal influenza epidemics are associated with substantial illness, death, and significant economic losses due to direct medical costs and absenteeism from the workplace [2–4], while new data suggest that influenza is also an important cause of illness in Hong Kong and Singapore [5,6]. Recent studies have identified a significant disease burden and cost of influenza in young children [7–9], a finding which contributed to the US Advisory Committee on Immunization Practices recommendation for influenza vaccination of all healthy children aged 6–23 months [10].

In developed economies, influenza may cause 10–12% of all absence from work [11] and while direct medical costs are substantial, the primary economic impact of influenza is from lost wages due to sickness absence [12,13]. In the United States during 1976–1999, influenza was associated with 88,479–225,985 hospitalizations and between 7608 and 72,399 (mean 34,470) deaths each year, the majority of these

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in elderly persons [10,12,14,15]. In 1981 the US Office of Technology and Assessment estimated that influenza caused US$ 1–3 billion in direct costs and US$ 10–15 billion in lost earnings [16]. In countries where the vaccine is commonly used, influenza vaccination has been shown to reduce absenteeism and healthcare costs in working adults [17,18], and is cost-effective in the elderly [19,20]. In Taiwan, influenza vaccination has been found to reduce hospital admissions and length of stay and results in savings in healthcare costs at least three times greater than the costs of vaccination [21,22]. The burden of influenza in Hong Kong has been found to be comparable to temperate regions [6,23]. Fitzner et al. concluded that influenza vaccination in Hong Kong was cost-effective for the individual but not was not cost-effective from the societal perspective [24].

Thailand is a middle-income country with an annual per capita income of US$ 2287, a 2004 population of 65,112,652 million persons and a strong public health infrastructure [25]. Thailand has a policy of introducing new vaccines only after careful consideration of the evidence of disease burden, and the potential cost and benefit from such vaccines. In the past, influenza vaccine has been underutilized with fewer than 100,000 doses distributed to less than 1% of the population annually [26]. Compared to other routinely provided vaccines, the inactivated influenza vaccine is relatively expensive at approximately US$ 6 per dose. However, if the disease burden and economic cost of influenza are found to be substantial, Thailand's growing economy may allow the country to consider targeted influenza vaccination to reduce the incidence of severe complications from influenza and the associated costs. In addition to improving health status and possibly reducing costs, the introduction of influenza vaccine should improve Thailand's preparedness for a possible influenza pandemic [27]. Therefore, the objectives of this study were to estimate the incidence and the direct and indirect cost of influenza-associated hospitalized pneumonia and outpatient febrile respiratory illness in Thailand.

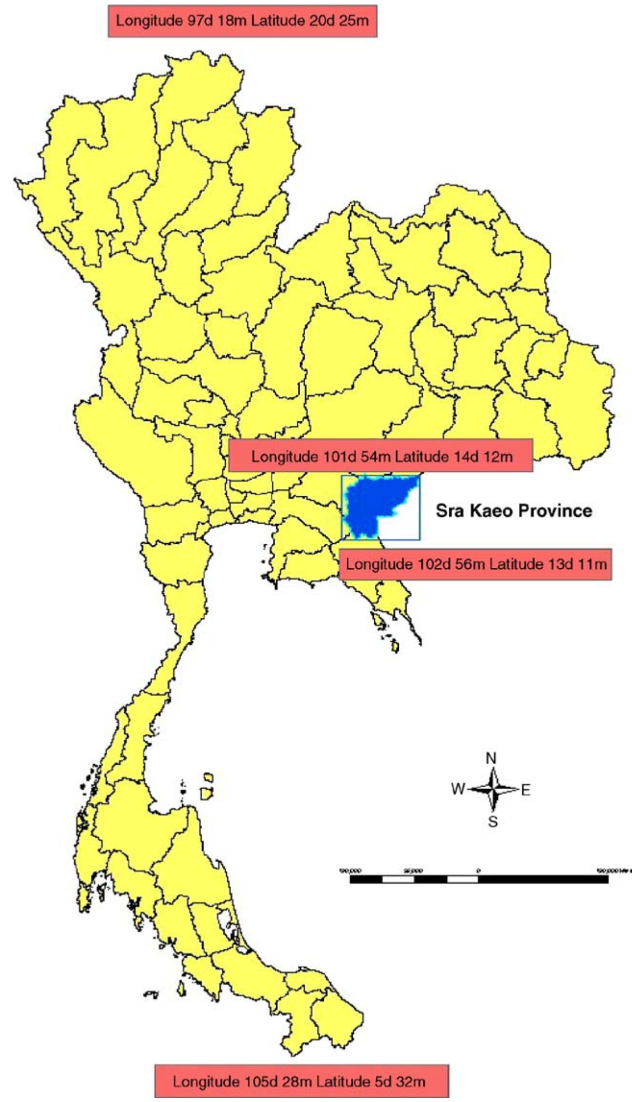

Fig. 1. Thailand and Sa Kaeo province.

2. Methods

We prospectively identified all hospitalized pneumonia patients using an active, population-based surveillance system carried out through collaboration between the Thailand Ministry of Public Health (MOPH) and the US Centers for Disease Control and Prevention (CDC) in Sa Kaeo province in eastern Thailand [28] (Fig. 1). Sa Kaeo is a rural province located about 200 km east of Bangkok with a population of 438,557 and an age distribution that is the same as the national population [25]. Sa Kaeo has a population density of 75 persons per km^2 compared to 110 per km^2 for all of Thailand outside of Bangkok [25]. The per capita annual GDP of Sa Kaeo province is US$ 914. During 2004 the mean daily temperature in Sa Kaeo province was 27.52 °C with 1211 mm of total rainfall while the mean daily temperature across all of Thailand was 24.7°C and an average of 1438 mm of fell over all of meteorological stations in Thailand [29].

Patients with signs and symptoms of pneumonia and a chest X-ray were enrolled from all hospitals in the province, including six district hospitals, a large provincial hospital and single military hospital. Pneumonia patients were recruited as part of a comprehensive study of respiratory pathogens. Within 48 h of admission and after informed written consent was obtained, a nasopharyngeal swab specimen was collected. The specimen was then split into aliquots and kept frozen at −70 °C until tested at the Thai National Institute of Health (NIH) laboratory by viral tissue cell culture according to established methods [30]. The swab specimen was also tested by RT-PCR, and paired sera were assayed to detect a 4-fold rise in influenza hemagglutinin inhibition (HI) antibodies at CDC in Atlanta, GA, USA [31,32].

To estimate the burden of influenza pneumonia, we calculated a baseline incidence using laboratory confirmed influenza pneumonia cases from our study as a lower limit and made adjustments based on other studies of the study population to estimate an upper limit. For example, primarily due to difficulty in obtaining parental consent we enrolled 151 of 648 (23%) of children <5 with pneumonia while 601 of 1363 (44%) of eligible pneumonia patients from all other age groups were enrolled. We also used data from a community survey on health-seeking behavior in Sa Kaeo to adjust for the approximately 20% of pneumonia cases who seek care outside of a Sa Kaeo province hospital facility [33]. The resulting incidence range was applied to the 2004 population to estimate the number of hospital admissions due to influenza pneumonia.

The average length of hospitalization for influenza pneumonia was multiplied by the routine service cost per day by hospital type obtained from the Thailand MOPH. A medical records review of 78 of 80 influenza pneumonia cases hospitalized during 1 year was conducted to determine ancillary medical care costs such as pharmacy and laboratory investigations, and therapeutic interventions. One elderly patient with multiple, severe pre-existing comorbidities and a 255 day length of stay for nursing care of decubitus ulcers was removed from the cost analysis. A second patient's medical record was not able to be located.

Routine service costs and ancillary costs were summed to obtain the total cost per influenza pneumonia hospitalization. This figure was multiplied by the lower and upper limits of the estimated number of influenza pneumonia hospital admissions. Because laboratory confirmation of influenza pneumonia was not available for 1–2 months after hospital discharge, prospective data on household expenditures associated with hospitalized influenza pneumonia were not available. Instead, data on household expenditures resulting from management of lower respiratory infections in the 2004 National Health and Welfare Survey were used to estimate these costs. The Thailand National Health and Welfare surveys are conducted by the National Statistical Office (NSO) and focus on illness experience, health care utilization of Thai households. The National Health and Welfare Survey employ a two-stage sampling design with the 75 provinces and the Bangkok metropolitan area as the primary strata. Household blocks and villages are the secondary sampling units for municipal and rural areas, respectively. From 109,966 enumeration blocks and villages nationwide, 1932 were randomly selected for systematic sampling of households. More than 67,000 members from 26,520 households were interviewed by National Statistical Office staff in the 2004 National Health and Welfare Survey.

To examine the burden and cost of influenza managed in the outpatient department we enrolled patients of all ages with influenza like illness (ILI) from September 1, 2003 to August 31, 2004. Influenza like illness was defined using the WHO criteria of fever greater than 38 °C and either cough or sore throat [34]. Patients were enrolled during two randomly selected clinic days per week at five of eight public hospital outpatient departments (OPD) in Sa Kaeo province. After obtaining informed consent, the QuickVue® (Quidel Company) Influenza Test was used by research nurses trained to perform the test according to the manufacturer's instructions [35]. This rapid test has a reported sensitivity of 77% and a specificity of 96% when compared to tissue cell culture in Thailand [36]. Nasopharyngeal swabs were also collected and tested by cell culture and RT-PCR as described for pneumonia patients above. Demographic and risk factor data were collected from all ILI patients.

All patients who tested positive using the rapid test were provided a simple diary to record health care utilization and household costs associated with the illness. A research nurse completed a structured interview with each influenza positive patient 3 weeks after enrollment. Participants were asked about household expenditures required to manage their illness including transportation costs to the clinic. To estimate the number of outpatient visits due to laboratory confirmed influenza in Thailand, we calculated the proportion of all outpatients in Sa Kaeo province who had laboratory confirmed influenza by either RT-PCR or cell culture. We multiplied this figure by the number of all outpatient visits in the public and private healthcare sectors estimated from the 2004 National Health and Welfare Survey.

Table 1
Routine service cost and ancillary cost by institution type. Mean and 95% CI

	Routine service cost per OPD visit (US$)	Routine service cost per inpatient day (US$)	Ancillary cost for OPD visit due to influenza (US$)	Ancillary cost per pneumonia inpatient day (US$)
Health center	1.41[a]	N/A	2.31[c]	N/A
District hospital	5.31 (4.03–6.56)	28.08 (21.21–34.97)	3.10 (7.21–9.08)	94.62 (0–308.41)
Provincial hospital	9.59 (7.21–11.97)	31.10 (24.72–37.51)	3.10 (7.21–9.08)	94.62 (0–308.41)
Other public hospital	11.67[a]	37.33[a]	3.10 (7.21–9.08)[d]	94.62 (0–308.41)[d]
Private clinic	1.82[a]	N/A	4.64[e]	N/A
Private hospital	9.59 (7.21–11.97)[b]	31.10 (24.72–37.51)[b]	4.64[f]	141.92[f]

[a] Data from the International Health and Policy Program, MOPH, Thailand. No confidence intervals calculated [66].
[b] Cost was assumed to be equal to that of provincial hospital.
[c] Cost assumed to be 0.75 that of district and provincial hospital.
[d] Ancillary cost assumed to be equal at public hospital facilities.
[e] Ancillary cost assumed to be 1.2 times that of public hospital OPD clinics.
[f] Ancillary cost assumed to be 1.5 times that of public hospitals.

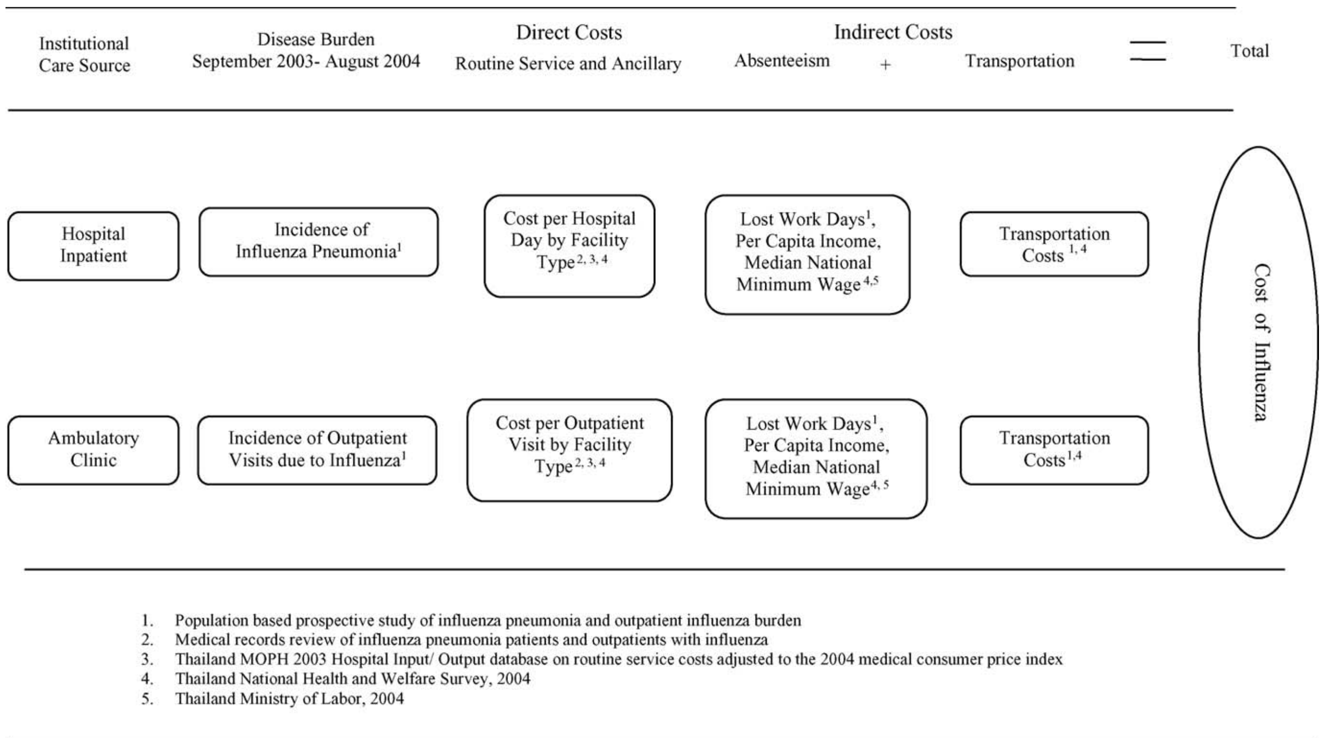

Fig. 2. Components and data sources for estimating influenza disease burden and cost.

We estimated the routine service costs per outpatient visit by type of facility (i.e. health center, district, provincial, and university hospitals) using the annual report of the national health care system costs and services delivered (input-output database) provided by the Thailand MOPH. Ancillary medical costs were obtained by a medical records review of a random sample of 50 influenza positive outpatients (Table 1). The routine service cost and mean ancillary cost per visit were summed and this figure was multiplied by the estimated number of influenza visits by facility type to calculate a total cost to the healthcare system for influenza managed in the outpatient setting in Thailand (Fig. 2, Table 2).

We estimated lost productivity due to influenza among outpatients by first calculating the proportion of influenza infections that occurred in the 0–14, 15–59 and ≥60 age groups in Sa Kaeo. For patients age ≥15 years, we multiplied the mean days of lost work due to influenza reported by Sa Kaeo outpatients by the estimated number of outpatient department visits due to influenza in Thailand in this age group. For the 0–14 age group, we multiplied the mean days of lost work reported by caregivers of influenza positive children by the number of OPD visits due to influenza infection in this age group. We assumed that elderly persons with influenza infection also required care and applied the same figure in this group. We used an average of 23.6 work days per month to account for a 6-day work week and Thai national holidays and adjusted for employment rates by age group from the National Health and Welfare Survey. We then multiplied lost work days by the median national minimum daily wage of US$ 3.38 obtained from the Ministry of Labor and by the average per capita daily income of US$ 6.15 derived from the National Health and Welfare Survey to generate a range [37]. We estimated lost productivity due to influenza pneumonia by first calculating the proportion of infections that occurred in each age group and applying these proportions to the range of estimated influenza pneumonia admissions nationwide. Because some patients return to work after hospital discharge sooner than others and data on post-pneumonia recuperation periods were not available, we developed a range that included the conservative assumption that all patients returned to work the day after hospital discharge or returned to work after a time period equivalent to half the mean hospital length of stay. We multiplied these two estimates of lost days of work by the average per capita daily income and the median national average minimum daily wage and adjusted for 2004 employment rates to estimate the total cost of lost wages due to influenza pneumonia. We assumed that children less than 15 years were not employed and days of lost school were calculated for this group. Currency conversions were calculated using the 2004 rate of 39 Thai baht to US$ 1.

3. Results

3.1. *Influenza pneumonia costs*

We enrolled 761 hospital inpatients with pneumonia from all hospitals of Sa Kaeo province and 80 (11%) were influenza positive by tissue cell culture, RT-PCR, or ≥4-fold rises in HI antibodies between acute and convalescent serum

Table 2
Definition and data source of key study variables

Variable	Definition	Rationale	Source
Influenza-associated pneumonia	Pneumonia requiring hospitalization with laboratory evidence of influenza virus infection	Study case definition. Cell culture, RT-PCR, serology positive for influenza	Population-based pneumonia surveillance in all hospitals in one province
Influenza-like illness	Acute fever >38 C with either cough or sore throat in the absence of another diagnosis	WHO Case definition	http://www.who.int/emc-documents/surveillance/whocdscsrisr992c.html
Hospital length of stay	24 h periods from admission until discharge		Population-based pneumonia surveillance
Ancillary medical costs	All pharmacy, laboratory, therapeutics services	Component of total cost	Medical records review of patients with influenza infection and Thailand MOPH
Routine service or "hotel" costs	Physical plant, staff and utilities by facility type	Component of total cost	Estimated by International Health Policy Program, using Thailand MOPH Healthcare Input Output Database
Daily wages	(1) Median national daily minimum wage (2) Average daily income from 2004 survey	Monetary value of a work day is difficult to define	(1) Thai Ministry of Labor (2) 2004 National Health and Welfare Survey. Weighted average of reported income in 15–59 and >60 age groups
Lost work days	Work days missed due to influenza infection using 23.6 work days per month	Accounts for Sundays and national holidays	Cost diary and personal interview NHWS data indicate that 79% of Thais between 15–59 and 38% of persons >60 are employed
Lost school days	School days not attended due to influenza infection	70% of children <15 are enrolled in school	Personal interview with parents of children with influenza infection
Transportation costs	Return costs to medical facility for patient, family	Public and private transport systems	Personal interview for outpatients National Health and Welfare Survey for inpatients
Recuperation period after influenza pneumonia	(1) Return to work day after hospital discharge (2) Equal to 0.5 × length of hospitals stay	True values unknown	Conservative assumption

samples (Table 3). The measured minimum annual incidence of influenza pneumonia requiring hospitalization was 18/100,000 population. After adjusting for incomplete enrollment and the proportion of patients who seek hospital outside the province, the upper limit was 111/100,000 population. Children under 5 and adults over 60 experienced the greatest burden of disease (Fig. 3). Two of 80 (2.5%) patients with laboratory confirmed influenza pneumonia died while in the hospital.

Based on the estimated incidence of between 18 and 111 per 100,000 population, we estimated that between 12,575 and 75,801 hospital admissions for laboratory confirmed influenza pneumonia occurred nationwide between September 2003 and August 2004. The mean length of stay for influenza pneumonia in Sa Kaeo was 4 days for children less than 15 years of age, 7.2 days for those over 60 years of age, and 6.6 days (range, 1–26 days) across all age groups. Direct medical costs for treatment of influenza pneumonia in Thailand were projected to be US$ 3.8 million using baseline measurements and US$ 20.7 million when adjusted for under enrollment and health-seeking behavior. Transportation costs for families of patients hospitalized for influenza pneumonia averaged US$ 9.32 per admission and were estimated to be between US$ 0.1 and US$ 0.7 million nationwide. Influenza pneumonia estimated hospitalizations resulted in a projected 118,335–941,567 days of lost work and representing between US$ 0.5 and US$ 8.7 million in lost productivity.

3.2. *Outpatient costs*

We enrolled 1092 outpatients of all ages with influenza like illness between September 2003 and August 2004 (Table 4). Of these, 192 (18%) were influenza positive using the rapid test while 205 (19%) were positive by cell culture and 252 (23%) were influenza positive by RT-PCR (Table 4). Four hundred and nineteen patients (38%) and 988 (90%) of specimens were collected within 2 and 4 days of the onset of

Table 3
Characteristics of enrolled patients

Variable	Pneumonia (number, %)	Outpatient ILI (number, %)
Enrolled	761	1092
Male	46 (58)	136 (52)
Influenza positive, any test	80 (11)	263 (24)
Rapid influenza test positive	N/A	192 (18)
Influenza positive, cell culture	16 (2.1)	205 (19)
Influenza positive, RT-PCR	56 (7.0)	252 (23)
Influenza positive, serology	38 (5.0)[a]	N/A
Age distribution of influenza cases		
<14 years	21 (26)	210 (80)
15–59 years	29 (36)	45 (17)
60+ years	30 (38)	8 (3)
Age range	0–88	0–73
Mean length of hospital stay (days)	6.6	N/A
Mean lost work days per episode	N/A	4.5

[a] Paired sera was collected from 578 of 761 (76%) of subjects. All pairs were assayed.

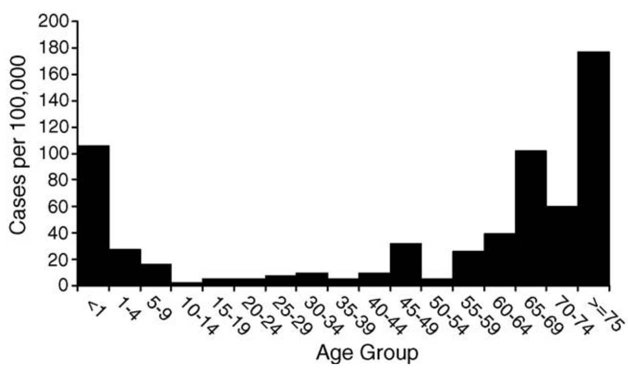

Fig. 3. Measured, age-specific incidence of influenza pneumonia ($n = 80$).

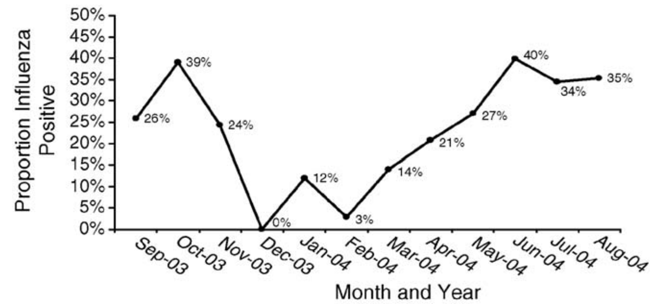

Fig. 4. Seasonal distribution of PCR positive influenza in outpatients with ILI ($n = 1092$).

symptoms, respectively. Influenza activity peaked during the months of June–October (Fig. 4). We completed cost-of-illness interviews 3 weeks after presentation on 171 of 192 (89%) of outpatients who tested influenza positive using the rapid test. Twenty-one patients were not able to be located. Adults with influenza reported missing an average of 4.5 days of work (range, 0–10) during their illness. Parents of children with influenza reported missing an average of 3.3 days of work (range, 0–10) while caring for their ill child. We estimate that laboratory confirmed influenza infection resulted in 924,478 outpatient visits nationwide for an incidence of 1420/100,000 population. Outpatient influenza infection resulted in an estimated 3,121,562 days of lost work representing between US$ 11.1 and US$ 24.9 million dollars in lost productivity. Transportation to receive outpatient medical care cost Thai families an average of US$ 1.59 per visit and US$ 1.5 million per year nationally. Children with influenza virus infection cared for in the outpatient setting missed 1,701,450 days of school. Influenza infection managed in the outpatient department cost the Thai healthcare system US$ 6.4 million in direct medical costs.

Table 4
Outpatient enrollment

Outpatient visits	Number (%)
Total observed visits (all causes)	68671
Acute visits (new illness, infection, injury)	32076(47)
Influenza-like illness (% of all visits)	1243 (1.8)
Influenza-like illness (% of acute visits)	1243 (3.9)
ILI patients enrolled in study (% of ILI enrolled)	1092 (87)

Primary influenza pneumonia hospital admissions and outpatient influenza infections resulted between US$ 23.4 and US$ 62.9 million in total losses to Thailand during September 2003 and August 2004. Considering the lower and upper boundaries of the cost estimates, lost productivity and transportation represented between 50–53% and 3–7% of total costs, respectively. Direct medical costs accounted for 43% of all costs (Table 5).

4. Discussion

Influenza has not been generally recognized as an important cause of illness in Thailand. In contrast, our findings during 2003–2004 indicate that influenza virus was a leading cause of pneumonia severe enough to require hospital admission and an important cause of febrile illness leading to outpatient clinic visits. Between 1993 and 2003, the Thailand MOPH passive surveillance system reported between 29,918 and 55,559 cases of clinically diagnosed influenza (inpatient and outpatient) annually for an incidence of 48–93 cases per 100,000. In 2004, the passive system reported 21,351 influenza cases, a rate of 33 per 100,000 [38]. Using an active, population-based surveillance system and comprehensive laboratory testing we estimate that 1420 per 100,000 influenza cases occurred among outpatients during 2004, reflecting a burden 43 times greater than recorded by the passive surveillance system. Further, our study indicated that 11% of 761 pneumonia inpatients had laboratory evidence of influenza virus infection. While there are no published studies that address influenza pneumonia in Thai adults, we found the proportion of influenza pneumonia in Thai children <5 years to be greater than that described in two earlier reports [39,40]. In both outpatient and inpatient settings, influenza is more frequently clinically diagnosed in Thai adults with the highest reported incidence in the 35–44 year old age group

Table 5
Costs of primary influenza pneumonia and outpatient influenza in Thailand, 2003–2004

Parameter	Value (range)	Percentage	
Influenza-associated pneumonia hospitalizations (cases)	12575–75801		
Outpatient influenza infection (visits)	924478		
Absenteeism (days)			
Lost school due to influenza (outpatient and inpatient)	1709207–1822335		
Lost work due to outpatient influenza	3121562		
Lost work due to influenza pneumonia	118335–941567		
		Range Low	High
Cost of influenza (US$, millions)			
Medical cost of inpatient influenza pneumonia	3.8–20.7		
Medical cost of outpatient influenza	6.4		
1. Total direct medical cost	10.2–27.1	43	43
Value of lost work due to outpatient influenza	11.1–24.9		
Value of lost work due to influenza pneumonia	0.5–8.7		
Transportation costs to families	1.6–2.2		
2. Total indirect cost	13.2–35.8	56	57
Total economic cost	23.4–62.9		

[38]. In contrast, in our study the incidence of laboratory confirmed influenza was greatest in children <15 years and in the elderly, a finding that is consistent with what has been reported in other countries.

Influenza disease burden varies from year to year as new antigenic variants emerge that may cause more frequent or more severe disease than the preceding year [41]. Scientists at the Thailand NIH report that A/Fujian/411/2002 (H3N2) and A/New Caledonia/20/99(H1N1) were the most commonly isolated strains during 2004 and that influenza activity was neither remarkably higher nor lower than the preceding 2 years [42]. In northern temperate climates, influenza also has a distinct seasonality with the majority of cases occurring between October and March [43]. While the seasonality of influenza in Thailand is not as well described, available evidence suggests that influenza peaks between June and August [26] and our findings confirm this seasonal pattern. However, to accurately characterize the seasonality of influenza in Thailand, complete data from several consecutive years of surveillance are needed.

Lost productivity due to illness accounted for the majority of costs due to influenza in Thailand, a finding that is consistent with studies in other countries [13,44,45]. While we captured the primary direct and indirect costs of influenza, our estimates are conservative for several reasons. Potentially important costs that were not included in our estimates include the cost of lost productivity due to influenza-associated mortality, the value of lost leisure time and missed school days [46,47], and costs for employers who must train new workers to perform tasks in the absence or death of their employees [48,49]. Persons with an influenza virus infection may return to work before achieving full recovery and experience decreased productivity during recuperation in the workplace. This study was not designed to estimate these costs [50,51]. Finally, our study examined only medically attended illness. Many influenza infections do not result in a visit to a medical provider but patients may still incur out of pocket costs such as self-prescribed drugs, and experience lost work or school days that our study was not designed to estimate. Complex social, cultural and economic factors influence health-seeking behavior [52]. Studies in Vietnam report that only 38–40% of patients with acute respiratory infection seek medical care while the majority preferred self-treatment [53,54]. In the past, Thai citizens with milder illness and those from poorer households also preferred self-treatment [55]. More recently however, utilization of outpatient medical clinics has increased as economic growth and health care reforms have made affordable care more accessible to a greater proportion of the population. Data from the 2004 National Health and Welfare Survey indicate that 71% of all Thais with acute upper respiratory illness seek care from a physician in either public or private clinics. Consistent with the national survey, a 2003 household survey examining health-seeking behavior in Sa Kaeo province found that 69% of ILI patients sought care from an institutional source [56].

We estimated influenza disease burden through intensive population-based surveillance and comprehensive laboratory testing, an approach that is too costly to be feasible in most other settings. In the United States for example, influenza burden estimates are developed using hospital discharge data, vital statistics registries, and sentinel clinic sites. While our methods are different, we believe the approach is robust and our results are consistent with other studies that have reported a disproportionate impact of influenza upon very young children and the elderly [10]. Our study has limitations that may influence the precision of our estimates. In this analysis we used data from a single season and a single Thai province. Influenza activity is likely to vary from year to year and influenza incidence may be different in the far northern or southern latitudes, or in densely populated cities. Data from consecutive years and different geographic regions will help to more completely describe the seasonality and burden of disease.

Accurate identification of influenza is subject to factors such as the type and quality of the specimen, time from day of illness to when specimen collection occurs, and the performance of sophisticated laboratory tests. For these reasons, morbidity due to influenza is often attributed to a secondary bacterial infection while the primary viral infection goes unrecognized [57,58]. Despite rigorous quality controls, these factors may have contributed to incomplete ascertainment of influenza in our study. In addition, influenza is associated with other complications including febrile seizures, otitis media, encephalitis, myocarditis, myositis, and secondary bacterial pneumonia that this study did not examine [58–63].

This study demonstrates that the disease and cost burden of influenza in Thailand is significantly greater than previously appreciated. Young children and the elderly were the most heavily affected age groups. Recent studies from Thailand have concluded that influenza virus is an important cause of acute exacerbations of chronic obstructive pulmonary disease and that influenza vaccine is protective in these patients [64,65], but further investigation of other risk factors for severe complications from influenza infection in Thailand is needed. In addition, an improved understanding of the proportion of non-medically attended influenza infection could provide valuable insight into the full impact of influenza infection on lost productivity and household spending in Thailand. Influenza vaccination is the primary public health tool to reduce the incidence of influenza infection and the likelihood of severe complications. A cost-benefit study of the potential impact of influenza vaccine under different target group and vaccine efficacy scenarios and consideration of the budget implications of new vaccine introduction is warranted as Thailand considers development of a national policy on influenza control.

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Who gets hospitalized for influenza pneumonia in Thailand? Implications for vaccine policy

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Abstract

Risk factor information for severe complications of interpandemic influenza is needed to inform vaccine policy in Thailand. We identified patients with lab-confirmed influenza who were hospitalized with pneumonia during September 2003 to August 2004. Among the 80 case-patients identified through a population-based pneumonia surveillance system in eastern Thailand, cases were 6.2 and 11.1 times more likely to be among persons <1 year old and >75 years old, respectively, compared with the overall population. Cases were also 7.6 times more likely to have chronic respiratory disease. In Thailand, the young, elderly, and those with chronic disease were at high risk for hospitalized pneumonia from influenza.

Keywords: Influenza; Pneumonia; Vaccination; Thailand; Risk factors

1. Introduction

Influenza is a vaccine-preventable disease responsible for extensive morbidity and mortality every year throughout the world. Large-scale influenza surveillance and immunization have mostly occurred in wealthy countries in temperate climates [1]. In 2002, the World Health Organization (WHO) adopted a global agenda on influenza surveillance and control that encouraged a number of national and international measures to reduce morbidity and mortality from annual influenza epidemics and to prepare for a potential pandemic [2].

In Southeast Asia, interest in influenza vaccination has increased in the last few years, partly due to outbreaks of avian influenza among humans and the threat of an influenza pandemic [3,4]. However, many Southeast Asian countries have limited economic resources, and the high cost of influenza vaccine relative to other vaccines and the need for annual administration continue to be an obstacle to vaccine use [4]. In Thailand in recent years, influenza vaccine has been administered to less than 1% of the population annually, mostly to people who can afford to pay for it through private

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health-care providers [1]. However, the Thailand Ministry of Public Health has expressed increased interest in adopting national guidelines for influenza vaccination. One approach to reduce the burden of severe disease associated with influenza is to target vaccination at groups at highest risk for severe complications from influenza virus infection [4–6].

In the United States, high-risk groups for influenza-related hospitalizations include people ≥65 years old, children less than 5 years of age, with higher risks among children <1 year old, and individuals with certain chronic diseases [7–10]. In a study of children in Hong Kong, which has a subtropical climate, children 5 years of age and younger were found to be at significantly higher risk for influenza-related hospitalizations compared with older children [11]. A recent study in tropical Singapore showed that rates of influenza-related mortality in that country were similar to those in Hong Kong and the U.S. [12]. However, to date, no study has evaluated risk factors for severe influenza morbidity in countries with tropical climates.

Pneumonia is one of the most common serious complications of influenza [13,14]. In this study, we describe risk factors for influenza pneumonia requiring hospitalization in Thailand, a tropical country in Southeast Asia, by examining hospitalized cases of laboratory-confirmed influenza pneumonia within a population-based surveillance system in eastern Thailand.

2. Methods

2.1. Ascertainment of influenza pneumonia cases and identification of risk factors

Since September 2001, active population-based surveillance for radiographically confirmed pneumonia has been conducted in Sa Kaeo, a rural province in eastern Thailand, through a collaboration between the Thailand Ministry of Public Health and the U.S. Centers for Disease Control and Prevention (CDC) [15]. In August 2002, a study to identify the viral causes of pneumonia among patients identified through surveillance was initiated. Eligible participants were residents of Sa Kaeo Province of any age who presented to any of the province's eight hospitals between 1 September 2003 and 31 August 2004 with evidence of acute infection (reported fever or documented temperature >38.2 °C within 24 h of admission; reported chills or documented temperature of <35.5 °C within 24 h of admission; or abnormally low or high white blood cell count or abnormal differential); signs (abnormal breath sounds on chest auscultation or tachnypnea) or symptoms (cough, sputum production, hemoptysis, chest pain or dyspnea) of respiratory tract disease; had a chest radiograph. Patients who were not residents of Sa Kaeo Province were excluded from the study. Basic demographic data were collected for all eligible participants.

Informed consent was obtained for the collection of specimens to test for evidence of influenza infection. We collected nasopharyngeal (NP) swab specimens within 48 h of admission, an acute serum sample on admission, and a convalescent serum specimen two to three weeks later, from all enrolled subjects. NP swab specimens were put into viral transport media, split into aliquots and stored at −70 °F until tested by viral culture at the Thai National Institute of Health laboratory. Tissue cell culture was performed according to established methods [17]. Another NP aliquot was sent to CDC in Atlanta, Georgia, USA, for testing of influenza virus by multiplex reverse transcriptase polymerase chain reaction (RT-PCR). Paired sera were tested at CDC by hemagglutination inhibition (HI) testing [18,19]. Either a four-fold or greater rise in HI titers, a positive RT-PCR result or a positive culture was considered evidence of influenza virus infection.

We reviewed inpatient medical records, including routine questionnaires that were administered for all hospital admissions, to assess whether subjects with evidence of influenza pneumonia had cardiovascular disease, pulmonary disease, endocrinopathy, hemoglobinopathy, renal disease, immunosuppressive disease, pregnancy, malignancy, neuromuscular disease, dementia, and/or gastrointestinal disease. Data were recorded using a standard abstraction form. Computerized inpatient and outpatient records were reviewed to determine the number of times each case-patient had been hospitalized during the year prior to the current hospitalization for influenza pneumonia.

2.2. Comparison with general population

For our comparison group we used data for the overall Thai population obtained from the 2004 Health and Welfare Survey, an annual nationwide survey conducted by the Thai National Statistical Office under the Ministry of Information and Communicational Technology [20]. The survey assesses many issues related to health care access and utilization, and results are presented by age and region. It employs a two-stage sampling design. Thailand's 75 provinces and the Bangkok metropolitan area serve as the primary strata. Household blocks and villages are the secondary sampling units for municipal and rural areas, respectively. For the 2004 survey, from 109,966 enumeration blocks and villages nationwide, 1932 were randomly selected for systematic sampling of households. More than 67,000 members from 26,520 households were interviewed by National Statistical Office staff. The results, extrapolated to the entire 2004 Thai population of 65,112,652, have been published [20].

The survey included two questions regarding chronic diseases. Survey respondents were first asked if they had a chronic disease; if they answered affirmatively, they were asked to list up to two specific diseases. Data entry coders then selected one of 17 disease categories that corresponded most closely with the specific diseases listed by respondents. These 17 categories included (the English translation was provided by the survey authors): "diseases of the respiratory system"; "diseases of the digestive system"; "diseases of urinary system"; "cardiovascular diseases"; "infectious diseases"; "diseases of the skin"; "allergic condition"; "diseases of oral cavity, ear, throat, nose, eye"; "diseases of female genital organ"; "condition related to delivery"; "diseases of endocrine system"; "metabolic diseases and nutritional status"; "diseases of the musculoskeletal system and connective tissue"; "diseases of the nervous system and mental disorder"; "ill-defined conditions"; "other"; "unknown". Survey respondents were also asked about the number of times they were hospitalized in the previous year. The survey categorized age as follows: <1 year; 1–4 years; 5-year age groups from 5 to 59; ≥60 years.

A comparison of Sa Kaeo data to national figures suggests that use of this national survey data was a valid comparison. First, survey results from the central provinces, where Sa Kaeo is included, were nearly identical to national patterns, specifically for underlying diseases [20]. Second, census figures from Sa Kaeo compared to the nation suggest a similar age and sex profile [20]. Finally, HIV prevalence rates in antenatal women in Sa Kaeo mirror those in the country as a whole [21].

2.3. Statistical analysis

The age distribution of influenza pneumonia cases was compared to that of the general population in Sa Kaeo using 2001 census data from the Sa Kaeo Provincial Health Office Census. We divided age by 5-year intervals except for infants <1 year old, children 1–4 years old, and persons ≥75 years old, who were considered as separate age groups. In our age comparison we calculated relative risks and 95% confidence intervals (CI) using EpiInfo 6 [28].

The frequencies of underlying diseases and prior hospitalization in influenza cases were compared to those reported in the 2004 Thai Health and Welfare Survey (described above). For this comparison we calculated Mantel–Haentzel risk ratios (RR) and 99% confidence intervals [29]. Because original survey information was unavailable for the population survey and, thus, could not be incorporated in the statistical comparisons between the two groups, we used a more conservative 99% CI instead of the usual 95% CI. Because of the small number of cases with chronic disease and prior hospitalizations, we defined three age groups for this analysis: ≤4, 5–59 and ≥60 years.

This study was approved by the Institutional Review Board of the Centers for Disease Control and Prevention (CDC) and the Ethical Review Committee at the Thailand Ministry of Public Health.

3. Results

Between 1 September 2003, and 31 August 2004, 3466 persons in Sa Kaeo province were hospitalized with a diagnosis of pneumonia. Of these, 2012 (58%) had a chest radiograph, of whom 762 (38% of 2012) consented to enroll in the study. Enrollment was lower in the younger age groups (see Table 1). Clinical follow-up of all eligible patients revealed that 39% of enrolled patients had severe outcomes (death, intubation, hypoxia, thoracentesis, pneumonectomy, or other surgical procedures or complications) compared with 34% of non-enrolled eligible patients.

Of the 762 consented participants, 80 (10%) tested positive for influenza (22 by culture, 56 by RT-PCR, and 38 by serology; 26 patients tested positive for influenza by more than one test). Of the 80 influenza pneumonia patients, 46 (58%) were men, compared with 62% of all study participants. One inpatient hospital chart could not be obtained for review, so that 79 subjects were available for analyses.

When compared to the age distribution of Sa Kaeo, the proportion of hospitalized influenza pneumonia cases <1 year

Table 1
Age-specific breakdown of eligible and enrolled patients in Sa Kaeo, Thailand

Age group	Total cases with clinical pneumonia	Patients with chest radiographs ordered (*N*, %)	Patients enrolled (*N*, %)
<1	354	195 (55%)	63 (32%)
1–4	907	442 (49%)	90 (20%)
5–9	257	99 (39%)	26 (26%)
10–14	114	43 (38%)	16 (37%)
15–19	70	36 (51%)	15 (42%)
20–24	84	44 (52%)	19 (43%)
25–29	109	63 (58%)	24 (38%)
30–34	107	63 (59%)	28 (44%)
35–39	132	86 (65%)	42 (49%)
40–44	103	70 (68%)	44 (63%)
45–49	171	113 (66%)	42 (37%)
50–54	100	70 (70%)	39 (56%)
55–59	135	86 (64%)	32 (37%)
60–64	142	88 (62%)	44 (50%)
65–69	201	155 (77%)	76 (49%)
70–74	180	124 (69%)	59 (48%)
≥75	300	235 (78%)	103 (44%)
Total	3466	2012 (58%)	762 (38%)

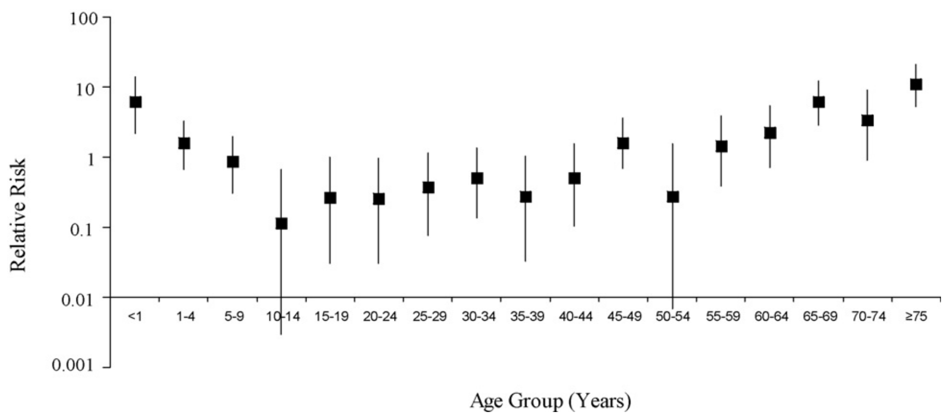

Fig. 1. Relative risk of hospitalized influenza pneumonia cases by age group compared to the general population of Sa Kaeo Province.

old or ≥65 years was significantly higher than expected. The proportion of influenza pneumonia patients ≤1 year old was 6.2 times higher than expected, while the proportion of influenza pneumonia patients ≥75 years old was 11.1 higher than expected (Fig. 1). Both differences were statistically significant. Thirty-eight percent of all hospitalized influenza pneumonia cases occurred in people over 60.

Underlying cardiopulmonary disease was associated with an increased risk for influenza pneumonia (Table 2). Underlying respiratory disease was a statistically significant risk factor among influenza pneumonia patients aged 5–59 years (RR 16.5) and those ≥60 years old (RR 8.1). A higher percentage of influenza pneumonia patients aged 5–59 years had underlying cardiovascular disease (RR 4.0) compared to the general Thai population, a difference which approached statistical significance. There were no influenza pneumonia patients <5 years old who had respiratory disease or cardiovascular disease; as a result relative risks for this age group could not be calculated. Among influenza pneumonia patients, 26.4% of 5–59 year olds and 29.0% of people 60 and older had underlying respiratory disease. Additionally, influenza pneumonia patients were more likely to have endocrine disease, although the difference was not statistically significant (7.6% versus 2.8%, RR 1.4, 99% CI 0.5–3.7).

Influenza pneumonia patients were more likely to have any underlying chronic disease (33.0% versus 16.6%, RR 1.6, 99% CI 1.2–2.1) compared with the general population. The risk among influenza pneumonia patients with underlying chronic disease was especially pronounced among 5–59 year olds (50.0% versus 13.3%, RR 3.2, 99% CI 2.1–4.7).

Two of the 79 influenza pneumonia patients had a history of gastrointestinal disease, two had a history of renal disease, two had a history of anemia and two were infected with human immunodeficiency virus. None of the influenza pneumonia cases had any history of cancer, neuromuscular disease or dementia. There was no information regarding influenza vaccination status for any of the patients.

Influenza pneumonia cases were significantly more likely to have been hospitalized in the preceding year compared with the general Thai population. Thirty-four percent of cases had been hospitalized in the previous year compared with 6.9% of the national population (RR 3.7) (Table 3). This difference was further magnified in children <5 years old; 57.1% of influenza pneumonia patients <5 years old had been hospitalized in the previous year compared with 8.0% of children of the same age in the national population (RR 8.3).

Table 2
Age-adjusted prevalence of chronic diseases among influenza pneumonia cases compared with the general population of Thailand

AGE	Influenza pneumonia cases, *N* (%)	Population with cardiovascular disease, *N* (%)	Risk ratio (99% confidence Interval)
Cardiovascular disease			
0–4	0/14 (0)	18,617/5,111,697 (0.4)	Undefined
5–59	5/34 (14.7)	1,420,611/53,599,551 (2.7)	4.0 (1.6–10.1)
>60	9/31 (29.0)	1,387,158/6,401,404 (21.7)	1.3 (0.7–2.8)
Total	14/79 (17.7)	2,826,387/65,112,652 (4.3)	1.7 (1.0–3.1)
Respiratory disease			
0–4	0/14 (0)	162,651/5,111,697 (3.2)	Undefined
5–59	9/34 (26.5)	777,469/53,599,551 (1.4)	16.5 (7.9–34.2)
>60	9/31 (29.0)	308,850/6,401,404 (4.8)	6.0 (2.9–12.4)
Total	18/79 (22.7)	1,248,969/65,112,652 (2.2)	7.6 (4.5–12.9)

Age group 0–4, 5–59 and total are adjusted for age; reported odds ratio is Mantel–Hansel.

Table 3
Number and proportion of pneumonia influenza cases that were hospitalized within the previous year compared to the general population

Age	Influenza pneumonia cases that were hospitalized in the previous year, *N* (%)	Total population that was hospitalized in the previous year, *N* (%)	Risk ratio (99% confidence intervals)
0–4	8/14 (57.1)	410,544/5,111,697 (8.0)	8.3 (4.5–15.6)
5–59	8/34 (23.5)	3,230,374/53,599,551 (6.0)	3.8 (1.7–8.5)
>60	11/31 (35.5)	859,263/6,401,404 (13.4)	2.6 (1.4–4.9)
Total	27/79 (34.1)	4,500,181/65,112,652 (6.9)	3.7 (2.5–5.6)

Age group 0–4, 5–59 and total are adjusted for age; reported odds ratio is Mantel–Hansel.

4. Discussion

Although previous studies have identified risk factors for severe influenza in developed countries in temperate and subtropical climates, to our knowledge this is the first study that has identified risk factors for hospitalized influenza pneumonia in a country with a tropical climate. Studies from the United States have demonstrated an increased risk of influenza-related hospitalizations among young children [9,10], and among people of all ages with high-risk conditions such as respiratory and cardiac disease [9,10,22,23]. A recent study in Hong Kong identified disproportionately high rates of influenza-associated hospitalizations among children <2 years old [11]. A study from Holland and a study from Canada showed previous hospitalization to be an independent prognostic factor for influenza-associated hospitalization [24,25]. Like these studies, we found that in Thailand, the elderly, young children and people with chronic cardiac and respiratory disease were more likely to be hospitalized for influenza pneumonia. We also found that people who had been hospitalized in the previous year were more likely to be hospitalized with influenza pneumonia.

In our study, the high percentage (23.8%) of our patients with hospitalized influenza pneumonia who had underlying respiratory disease is consistent with previous studies in Thailand that described a high incidence of influenza in unvaccinated patients with chronic obstructive pulmonary disease [5,26].

The findings presented here document groups at increased risk for severe disease associated with influenza infection in Thailand. Based on data from studies that were conducted predominantly in the United States, the U.S. Advisory Committee on Immunization Practices (ACIP) has recommended influenza vaccine for persons aged ≥50 years, adults and children who have chronic disorders of the pulmonary and cardiovascular systems, adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic disease, and children aged 6–59 months [27]. Our findings suggest that vaccination policies in Thailand targeting some of the same high-risk groups – young children, the elderly, and individuals with chronic disease – may be an effective strategy to reduce influenza-related hospitalizations.

Since patients in our study who had been hospitalized during the previous year were at increased risk for developing influenza pneumonia, vaccinating inpatients against influenza before discharge from the hospital should also be considered. In the United States, the ACIP recommends influenza vaccination for persons of all ages with high-risk conditions and persons aged ≥50 years who are hospitalized during September–March [27]. In Thailand, seasonal differences in influenza would necessitate a May through October vaccination strategy [6].

Our study has a number of limitations that may have affected the estimated differences between the influenza pneumonia cases and the general population. First, overall enrollment was 38% and only 32% in infants. We do not know how the enrollment rates may have biased our results. However, the high-risk groups we found in our study are consistent with those identified in other countries. Low enrollment in the younger age groups however, limited our analyses. In addition, because our study included only 79 patients, our ability to do subgroup analysis was limited. For example, although older patients with cardiovascular disease have been shown to be at especially high-risk for influenza [22] and were at an elevated risk in our study, we did not identify a statistically significant increase in influenza-associated pneumonia among case-patients >60 years old with underlying cardiovascular disease compared to the Thai population.

Second, information for hospitalized influenza pneumonia cases and survey participants was obtained in different ways. While survey respondents were administered questionnaires, we obtained information about cases from hospital charts and computerized records. While in many cases the information from hospital charts was taken from questionnaires the admitted patients had filled out, we also looked at doctors' notes. This thorough review of medical records may have been more likely to identify underlying medical problems in the influenza cases and thus overestimated differences between the two groups.

In addition, definitions of chronic diseases varied between the influenza cases and the survey population. The survey used a broad interpretation of chronic disease compared to the stricter definition of chronic disease we used for our influenza cases. For example, respondents who listed "cough," "sore throat" or "tonsillitis" as chronic diseases were coded as having "diseases of the respiratory system." This potential misclassification of acute diseases as chronic diseases in the survey population may have resulted in an underestimation of the true differences between underlying disease profiles in severe influenza cases compared with the general population. However, our results are consistent with other analyses of risk factors except where power was limited. Additionally, because we did not have access to individual survey data, we were not able to perform multivariate analysis to evaluate the potential confounding effect of different chronic diseases.

Finally, we conducted our study in a rural province in eastern Thailand during one calendar year. We compared the age distribution of the case-patients to the age distribution in Sa Kaeo according to the latest census figures, but we compared chronic disease profiles and hospitalization rates of case-patients with national survey data. National survey data was broken down by region but not by province. Although survey data showed that the chronic disease profile and the hospitalization rates in the central region, where Sa Kaeo is located, mirrored national patterns, we do not have these data for Sa Kaeo province itself. If Sa Kaeo province varies substantially from the central region and the nation as a whole, our results would be less generalizable. While the age distribution, ethnic makeup and chronic disease profile of the provincial population parallel those of the nation as a whole, it is possible the behavior of influenza may differ in other parts of the country.

The impact of influenza varies annually [8,11,12]. Thus, evaluation of surveillance data from other provinces and additional years is ongoing and should help attain a more complete picture of risk factors for hospitalized influenza pneumonia in Thailand.

Despite these limitations, our findings are consistent with existing medical literature, mostly from developed countries in temperate climates, that has identified young and advanced age, and underlying chronic disease, especially cardiopulmonary disease, and previous hospitalization within the last year as risk factors for severe complications from influenza infection. Prospective studies looking at risk factors for influenza morbidity and mortality in tropical countries could be conducted to further characterize high-risk groups. In the meantime, the risk factors for influenza pneumonia in Sa Kaeo, Thailand identified in this study provide an initial foundation for the development of national guidelines for influenza vaccination in Thailand and perhaps other countries in Southeast Asia.

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Conflict of interest statement: No conflicts declared.

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A HOUSEHOLD SURVEY TO ASSESS THE BURDEN OF INFLUENZA IN RURAL THAILAND

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Abstract. Little is known about the disease burden of influenza in middle-income tropical countries like Thailand. The recent outbreak of avian influenza (H5N1) and studies on influenza from neighboring countries highlight the need for data on incidence, access to care, and health care cost. In May/ June 2003, we conducted a province-wide household survey using two-stage cluster sampling to determine the burden of influenza-like illness in Sa Kaeo Province. We used the total number of reported influenza that occurred in May 2003 and a prospective study of outpatient influenza in clinic patients to develop an estimate of the annualized incidence of influenza. Of 718 subjects, 16 (2.2%) suffered an episode of influenza-like illness in the preceding month; 14 sought care, of whom 7 went to a hospital facility. Fifty percent reported missing on average 3 days of work or school. The total individual cost per illness episode was 663 baht (US$15.78). The proportion of outpatients with influenza-like illness caused by an influenza virus in May was 16% and the annualized influenza incidence was estimated to be 5,941/100,000 in Sa Kaeo Province. This survey adds to information indicating that in rural Thailand, the burden of influenza is substantial and costs associated with an illness episode are up to 20% of an average monthly income.

INTRODUCTION

In tropical countries, and Southeast Asia in particular, influenza has traditionally been viewed as a mild disease occurring at low levels year round with one to two seasonal peaks (Fitzner *et al*, 1999; Ng *et al*, 2002; Thawatsupha *et al*, 2003; Simmerman *et al*, 2004). However several recent studies in Hong Kong and Singapore have confirmed a substantial disease burden associated with influenza (Chew *et al*, 1998; Fitzner *et al*, 1999; Ng *et al*, 2002). In Thailand, the outbreaks of highly pathogenic influenza A (H5N1) virus in poultry and humans have increased awareness of influenza in general and interest in better data on the burden from usual influenza viruses (CDC, 2004).

The Thai Ministry of Public Health conducts passive surveillance for clinically diagnosed influenza; laboratory confirmation of these cases is not available. Between 1997 and 2004, the average annual reported incidence for influenza was 66 cases per 100,000 persons (Anonymous, 1997-2001). The Thai National Institute of Health conducts sentinel site laboratory surveillance for influenza through its WHO-designated National Influenza Center (Thawatsupha *et al*, 2003). While these data are useful to monitor national patterns and circulating strains, they are limited in their ability to accurately estimate burden or cost of disease. We conducted a household survey to assess health care seeking behavior and expenditures for influenza-like illness in a rural Thai community and used this information

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n combination with ongoing virological studies n the province to refine estimates of the incidence of influenza in the community.

MATERIALS AND METHODS

Study population

Sa Kaeo Province, population 438,557, is located approximately 3 hours east of Bangkok and borders Cambodia. The average individual monthly wage in 2001 was 3,712 baht (US $95) Alpha Research Co, 2004 #25). Since 2002, Sa Kaeo has been the site of surveillance and research activities by the International Emerging nfections Program (IEIP), a collaboration between and the Thai Ministry of Public Health and the US Centers for Disease Control and Prevention (CDC) (Dowell *et al*, 2004). In addition to the pneumonia surveillance which captures severe, hospitalized chest-radiograph confirmed pneumonia caused by influenza and other pathogens, there is outpatient surveillance for influenza-like illness with systematic laboratory testing and virologic confirmation. To better ascertain access to health care and influenza-like illness that may not present to health care, we conducted a household survey in May 2003. This study was approved by the Institutional Review Board of US CDC and the Ethics Committee of the Thai Ministry of Public Health.

Study design

We used a two-stage cluster sampling design that has proved valuable in assessing disease incidence and evaluating utilization of health services (Henderson and Sundaresan, 1982; Galazka and Stroh, 1986; Turner *et al*, 1996). From the complete list of villages in the province, forty villages (clusters) were selected using probabilities proportional to the size of the village. Within each village, 5 households were then randomly selected from complete lists of village households. A trained interviewer from the province and a village volunteer familiar with the families visited each household. After obtaining informed consent of each participant, a questionnaire was administered in Thai that included questions on household composition and socio-economic status. Each household member was asked, "Have you had new fever with sore throat and/or cough during the last four weeks?" (WHO, 1999). If the answer was 'Yes', a detailed second questionnaire about symptoms, length of illness, missed work or school days, type of health care facility visited, reasons for not seeking care, cost of care and means of payment followed. People were considered members of the household if they had slept and eaten in the house for ≥6 months during the past 12 months. For children ≤15 years old and members of the household not present, the primary caretaker was interviewed as a proxy.

Sample size

Published data on the expected rate of influenza-like illness in Southeast Asia are very limited. Using data from one Singapore study, we estimated that each Thai might suffer from up to 1 episode of influenza-like illness per year (Ng *et al*, 2002). Since the period covered by the survey was one month, the expected frequency of influenza-like illness was up to 8.3% per month. We used EpiInfo (Epi Info6; CDC, US, January 2001) to calculate the sample size for a simple random sample using either 5.6% or 11% as the worst acceptable value, the two end points of our sample confidence interval. At the 95% confidence level the upper sample size estimate needed was 401. This sample was further inflated by 1.5 to account for the design effect of case clustering and 1.2 to account for an estimated 20% non-response (Ng *et al*, 2002) yielding a total sample size of 722 persons (190 households). To reach 200 households, we interviewed 5 households in each of the 40 villages. We estimated that up to 63 people would report having had an influenza-like illness during the preceding month.

Estimating the annual incidence of influenza in Sa Kaeo

To estimate the incidence of influenza in Sa Kaeo we used 2 different surveillance systems, the National Passive Surveillance System (Bureau of Epidemiology, Thai Ministry of Public Health) and an ongoing, prospective study on the etiology of influenza-like illness in outpatients. The ongoing, prospective study on the etiology of influenza-like illness aims to identify respiratory pathogens responsible for influenza-like illness in patients visiting 5 hospital outpatient departments in Sa Kaeo Province. Influenza-like illness is defined as acute fever >38°C and cough or sore throat in the absence of other diagnoses (WHO, 1999). Patients are invited to participate in the study if they have these symptoms and documented fever >38°C. Research nurses administer a brief questionnaire, collect a nasal swab and immediately test for influenza A and B using the QuickVue® rapid antigen test kit (Quidel Co). Swab samples are later tested and confirmed by viral culture at the Thai National Institute of Health and by reverse transcriptase polymerase chain reaction at US CDC. For the month of May 2004, we expanded enrollment to include persons with cough or sore throat and subjective fever to match the case definition in the household survey.

To calculate an incidence for influenza, we used 2003 data from the National Passive Surveillance System to estimate the proportion of clinically diagnosed influenza that occurs in May. No influenza cases were reported in Sa Kaeo Province during the month of May in 2003, therefore we used nationwide numbers. The total number of influenza cases in Thailand reported in 2003 was 29,918, with 1,840 cases occurring in May (6%). The incidence in the household survey was divided by this proportion to calculate an annual incidence and then multiplied by the proportion of influenza-like illness caused by influenza during May as determined in the prospective outpatient study to estimate influenza incidence.

Cost calculation

In the survey, questions related to costs were answered in categories, ranging from 1-100, 101 to 200, 201-300, 301-500, 501-750, 751-1,000, and 1,001-1,500 to greater than 1,500 baht. For the analysis, we took the mean value of each category, 50.5 baht, 150.5 baht, etc. The average number for the May 2003 exchange rate was used to convert Thai baht into US Dollar (42 baht=US$1). The total expenditure per episode of influenza-like illness and influenza was divided into direct costs, which include medical and transportation fees, and indirect costs, such as lost wages. Average daily wages were calculated using the average monthly individual wage in Sa Kaeo Province in 2001 (3,712 baht), and dividing it by 23.6, the number of work days per month (Alpha Research Co, 2004).

Statistical analyses

Data were analyzed using SPSS 12.0 (SPSS Inc, Chicago, Illinois) and EpiInfo 6 (CDC, US, January 2001). We used frequencies for the descriptive statistics and chi-square to compare proportions. A p-value of <0.05 was considered significant.

RESULTS

Between May 28 and June 30, 2003, 200 households were visited and 718 people were interviewed. Sixteen (2%) persons reported an episode of influenza-like illness during the previous month. There were no households reporting more than one case. Thirteen (81%) cases were female and the mean age was 37 years (range 1 to 79). Two cases were in children below the age of 5, and 4 cases were in persons over age 50. Persons were ill for a median of 5 days (range 2-30) and 8 (50%) cases reported having missed work or school. All 16 reported having experienced at least 3 symptoms and 13 out of 16 reported experiencing at least 5 symptoms. Clinical signs and symptoms are illustrated in Table 1.

Table 1
Clinical signs and symptoms of 16 persons with influenza-like illness in the household survey, May 2003, Sa Kaeo Province, Thailand.

Sign or symptom	N (%)
Fever[a]	16 (100)
Cough/sore throat[a]	16 (100)
Headache	14 (88)
Decreased activity	13 (81)
Runny nose	11 (69)
Muscle aches	10 (63)
Chills	7 (44)
Difficult or fast breathing	6 (38)
Nausea or vomiting	6 (38)
Wheezing	3 (19)
≥ 3 symptoms	16 (100)
≥ 5 symptoms	13 (81)

[a]Part of case definition

Fourteen (88%) persons sought health care. Of the 2 persons who did not seek care one stated that the hospital was too far away and the other preferred self-care. Eleven out of sixteen people (69%) sought care at a health center, private clinic or hospital outpatient department. Among places where initial care was sought, health centers were most commonly visited (6/14, 43%), followed by hospital outpatient departments (3/14, 21%) and pharmacies and drug sellers (people who sell medications in stores not designated as pharmacies) (3/14, 21%). Health centers are small clinics which are staffed with a public health trainee or a registered nurse and are popular for initial check-ups. One case each reported seeing a private physician and a traditional healer. Eight cases (50%) reported seeking health care at more than one place. Seven (44%) persons sought care at a hospital facility at some point during their illness. One six year old girl was hospitalized. There were no deaths.

Out of the 16 persons reporting an influenza-like illness, nine (56%) had completed the survey themselves and seven were completed by proxy. Fifteen households had a caretaker whose education was at primary school level or less. Ten out of 16 case households (63%) reported having a combined household income less than 5,000 baht ($119) per month and on average 3 people lived in one household. The mean cost per doctor's visit was 147 baht ($3.50) and 151 baht ($3.60) per traditional healer visit. Expenses at the pharmacy or drug seller averaged 16 baht ($0.38). Almost half of the affected households (44%) reported having to get a personal loan to help pay for their medical expenses, and costs for only one person were entirely covered by welfare. For the 16 influenza-like illness case households, the total direct cost per illness episode was calculated using the average of individual costs associated with doctor's visits, traditional healer's visits and pharmacy visits added to the mean transportation cost. Lost income was defined as indirect cost. The total individual costs per episode of influenza-like illness are illustrated in Table 2.

The incidence for influenza-like illness for the month of May 2003 among our household survey population in Sa Kaeo Province was 2,228/100,000 [(16/718) 100,000]. Applying this rate to the population of Sa Kaeo, we estimate there were 9,771 influenza-like illness cases in Sa Kaeo Province during May. The total number of cases reported by the national passive surveillance system for the month of May in 2003 was 1,840, which accounts for 6% of the annual number of cases. Therefore, the total number of influenza-like illness cases in Sa Kaeo in 2003 was approximately 162,850. We multiplied this number by 16, the proportion of influenza-like illness in outpatients that was actually caused by influenza viruses in May 2004 to estimate the number of these cases that were caused by influenza. The estimated total number of influenza cases in Sa Kaeo in 2003 was calculated to be 26,056 (6% of the provincial population) yielding an annual incidence of 5,941/100,000.

Table 2
Average household costs in Thai baht (US dollars) per episode of influenza-like illness, May 2003, Sa Kaeo Province, Thailand.

Type of cost	Cost in baht (US $)
Out of pocket	
Medical	98 ($2.33)
Transportation	94 ($2.24)
Productivity	
Lost income[a]	471[b] ($11.21)
Total	663 ($15.78)

[a]Calculated using 157 baht (US$3.74) as average wage per day
[b]Average missed days of work/school for 8 out of 16 cases = 3 days 157 baht

DISCUSSION

Our small survey adds to other recent influenza studies and provides an initial estimate of the burden of influenza in the Thai community setting (Dowell *et al*, 2004). Approximately 6% of the Sa Kaeo population suffered from an influenza infection in 2003, which caused substantial costs related to health care, transportation and work absenteeism. The annual incidence of influenza in rural Thailand may be 1000-times greater than reported through the national passive surveillance system. Individual costs associated with an episode of influenza may be less in Thailand than in other wealthier countries because health care coverage is more comprehensive in Thailand given the national health care system which provides coverage for people without private or government insurance. This system was implemented in 2001 and requires patients to pay a fee of 30 baht (US$0.71) for each health care visit.

Our study suggests that even in a rural province, accessibility to healthcare services is good. Only one out of 16 cases in the household survey stated that care was not sought because of the distance to the nearest hospital. Health centers, which are staffed with nurses, were the most popular choice among the study population for initial health care visit, since they provide comparatively inexpensive care. Health centers in Thailand provide routine preventative care, such as immunizations, to a defined population and could function as an appropriate venue for influenza vaccination should that be considered in the future.

Our study had several limitations. Although our sample size was relatively large, the number of persons who reported having an influenza-like illness was small, limiting our ability to further characterize these cases. When we calculated our sample size, we searched for similar studies in tropical countries, however there are very few. We based our calculations on results from a study in Singapore that detected at least one episode of influenza-like illness per person/year (Ng *et al*, 2002). It is possible that these other studies were conducted during a time of high prevalence of viruses responsible for influenza-like illness, or that May 2003 had an atypically low prevalence of influenza-like illness in Sa Kaeo Province. However, despite obtaining only a small number of cases with influenza-like illness the methodology of the survey was robust and the findings are consistent with other studies in Sa Kaeo Province (Dowell *et al*, 2004).

The survey covered illness events over a period of one month in parts of May and June, yet we now know that influenza in Thailand has a distinct seasonality peaking between June and October (Thawatsupha *et al*, 2003; Simmerman *et al*, 2004). Given the limitations in the national surveillance data, our ability to extrapolate the incidence to an annual rate using these data is restricted. We believe surveys such as this should be repeated at other times during the year. We may have also had some overrepresentation of females in our survey possibly because they were most likely to be home and answer the questionnaire. Despite these limitations, our survey provides needed initial insight into the rural community incidence of a disease of growing importance in the region.

The burden of influenza in rural Thailand, with more than 26,000 cases in 2003 in Sa Kaeo Province alone, is substantial and costs to the individual are high. Although the total direct costs per episode of only US$5 appear small in comparison to industrialized countries, costs per influenza-like illness episode including lost wages can make up as much as 20% of the average monthly income. Nearly half of the sick residents needed a personal loan to pay for their illness related expenses.

Given the large disease burden and cost from influenza illness, as well as the recent outbreaks of influenza A (H5N1), Thailand may need to focus on ways to better survey and control influenza, and such a strategy might include use of a vaccine. Continued research to isolate and identify influenza strains circulating in Thailand will be critical in the decision making process of introducing influenza vaccination in the future. With information guiding vaccine selection, Thailand will be in a unique position to consider a vaccination demonstration project using the preexisting immunization program that has been shown to be effective as a model for influenza.

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Influenza in Thailand: a case study for middle income countries

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Abstract

Recent studies in Hong Kong and Singapore suggest that the annual impact of influenza in these wealthy tropical cities may be substantial, but little is known about the burden in middle-income tropical countries. We reviewed the status of influenza surveillance, vaccination, research, and policy in Thailand as of January 2004. From 1993 to 2002, 64–91 cases of clinically diagnosed influenza were reported per 100,000 persons per year. Influenza viruses were isolated in 34% of 4305 specimens submitted to the national influenza laboratory. Vaccine distribution figures suggest that less than 1% of the population is immunized against influenza each year. In January 2004, Thailand reported its first documented outbreak of influenza A H5N1 infection in poultry and the country's first human cases of avian influenza. Thailand's growing economy, well-developed public health infrastructure, and effective national immunization program could enable the country to take more active steps towards influenza control.
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Keywords: Influenza; Influenza surveillance; Thailand

1. Introduction

Worldwide, annual outbreaks of influenza result in widespread illness, causing deaths in the elderly and young, social disruption, and a substantial economic burden to society and the individual [1,2]. Large-scale influenza surveillance and vaccination has been mostly limited to wealthy countries in temperate climates. In contrast, in the world's poorest nations influenza surveillance and control may be unrealistic given the acute shortage of human and financial resources and competing health problems. However, there are an increasing number of middle-income countries in tropical climates that may be in a position to better define the burden of disease and take more active steps towards influenza control.

Although effective vaccines have been available for many years, influenza vaccination coverage has often been suboptimal even in high-income countries in North America and Europe [3,4]. The requirements for annual vaccination and the high cost of the influenza vaccine when compared to other vaccines recommended by WHO are likely to be significant obstacles to vaccine introduction in less wealthy countries. In the United States, vaccination with inactivated influenza vaccines has been shown to be cost-effective in elderly persons and in working adults in higher-income countries where influenza-related costs from lost productivity and health care utilization are high [5–9]. Comparatively little is known about the burden of influenza in most middle-income countries and

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few studies have attempted to assess the cost-effectiveness of the vaccine in these countries [10]. However, the available data suggest that influenza may represent a significant burden of disease in Southeast Asia.

2. Thailand as a middle-income country

Thailand is located in tropical Southeast Asia between 6 and 22° North latitude. The population in 2000 was 62,350,000. The overall life expectancy is 68 years and infant mortality is 29.5 per 1000 live births [11]. Thailand's US$ 2160 per capita GNP in 1998 places the country in the middle-income category. It is considerably wealthier than neighboring Southeast Asian countries where data are available such as Laos, Cambodia, and Vietnam whose per capita GNP in 1998 was US$ 320, 260, and 350, respectively [12]. The Thai economy is making a strong recovery from its 1997 economic crisis, which may allow the country more opportunities to implement additional preventive health measures such as influenza vaccine.

Thailand has a well-developed public health infrastructure and is undergoing a health care reform program that emphasizes preventive care delivered locally [13]. Thailand's national immunization program has a record of success in maintaining immunization programs and implementing new vaccines. In 2002 Thailand was recognized in a joint United Nations and World Health Organization (WHO) report for maintaining one of the highest performing routine immunization programs in Southeast Asia [14]. Thailand was also among the first countries in the region to introduce universal Hepatitis B vaccination, and reported a 96% coverage in 1998 [15].

3. Influenza in Southeast Asia

Published data on influenza in much of Southeast Asia are limited, especially when compared to recognized tropical diseases such as malaria or dengue. In the 10 years since 1993, a Pubmed search using the terms "Thailand" and "influenza" found nine papers on influenza in Thailand compared to 120 on dengue, and 419 on malaria. This is despite the fact that malaria in Thailand is now only endemic in certain border regions.

Recent papers from Singapore and Hong Kong provide additional insight on influenza in the region. In Singapore, the burden of influenza-like illness (ILI) and influenza infection in adults were estimated from routine official and published sources, community sample surveys, national virological surveillance, hospitalization and mortality data. In a population of 3 million people, 630,000 cases of influenza virus infection, resulting in 520,000 sick visits and 315,000 lost days of work were estimated to occur each year [16].

Influenza-like illness surveillance in Hong Kong has been conducted by means of a sentinel physician program. Influenza-like illness was found to occur throughout the year and accounted for 15% of all outpatient doctor visits over a 2-year period. The annual incidence of ILI was 117 per 1000 patients and was highest among children 1–4 years of age [17]. A second Hong Kong study determined that influenza resulted in 7055 excess hospital bed-days annually in a population of 6.9 million persons, amounting to US$ 3.6 million in hospital costs alone [18]. In 2002 Chiu and colleagues published a retrospective study analyzing more than 90% of all hospital admissions in Hong Kong combined with virologic data from a sentinel hospital over a 3-year period. Influenza was found to be an important cause of hospitalization among children less than 15 years of age with rates exceeding those reported in temperate climates [19]. While these data suggest that influenza may be an important disease in certain large cities in tropical Southeast Asia, there is little information on the burden of influenza in rural areas and in less wealthy countries of the region.

4. Human influenza surveillance in Thailand

Virological surveillance is conducted at the Thailand National Institute of Health (NIH). The NIH participates in the WHO influenza laboratory network as a national influenza center by conducting laboratory surveillance, subtyping viruses responsible for disease outbreaks, and contributing strain surveillance data. Clinical samples are submitted by four provincial government hospitals and from two hospitals and Public Health Center #17 in Bangkok that participate in its Emerging Infectious Disease (EID) program. Approximately 70–80% of samples come from Public Health Center #17 and 60% of these samples are from children. In 2001, the Thai NIH tested oropharyngeal specimens by culture in Madin Darby Canine Kidney (MDCK) cells and a commercially available indirect fluorescent antibody screening kit (Chemicon International Inc., USA). Of the 711 specimens tested, 338 (48%) were positive for influenza virus and all but 11 viruses were typed and subtyped. The results showed that 155, 70, and 102 influenza isolates were A(H1), A(H3N2), and B viruses, respectively. Influenza virus is identified throughout the year in Thailand with a peak in the proportion of positive isolates typically occurring between June and October [20] (Fig. 1).

The Bureau of Epidemiology at the Thai MOPH conducts passive surveillance on reported cases of influenza in Thailand. Because testing for influenza infection is not routinely available, very few reported cases are ever confirmed in the laboratory. A recent review of the passive reporting system for pneumonia in SaKaeo province in eastern Thailand suggested that surveillance case definitions are not uniformly applied [21]. As with many passive surveillance systems, underreporting is also a concern. Alternatively, because the majority of ILI cases are not caused by influenza, the lack of laboratory confirmation could also result in over-estimates of influenza infections.

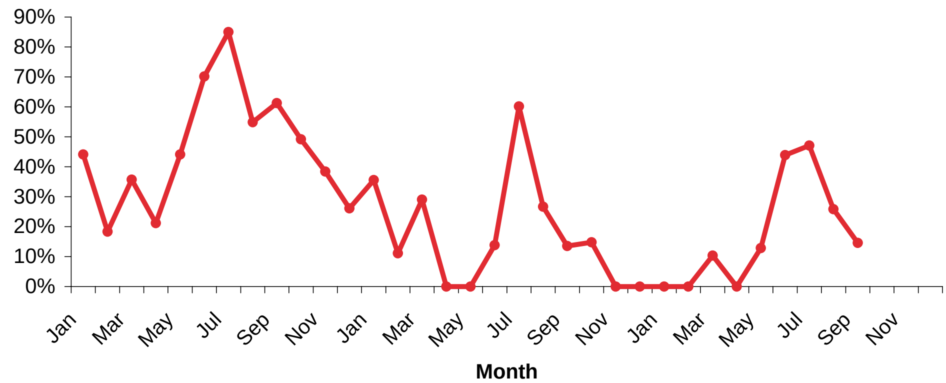

Fig. 1. Proportion of specimens positive for influenza virus by month in Thailand: January 2001–September 2003. Source: Thailand National Institute of Health.

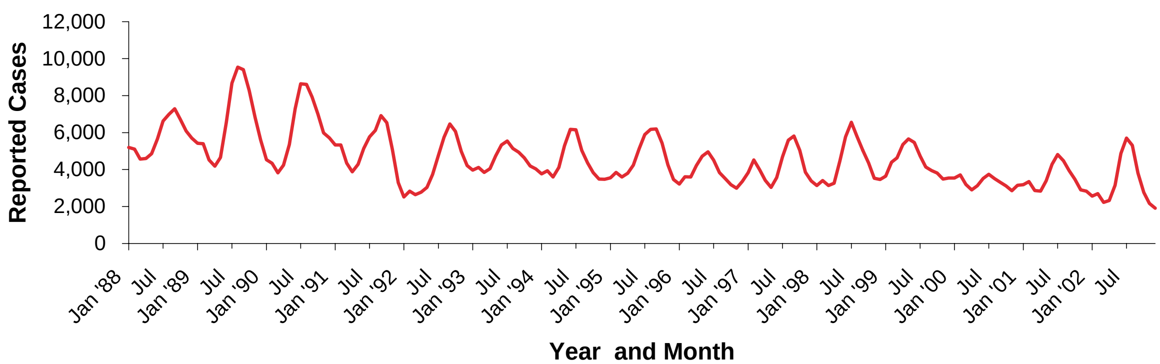

Fig. 2. Seasonal distribution of reported influenza 1988–2002. Source: Bureau of Epidemiology, Thailand Ministry of Public Health.

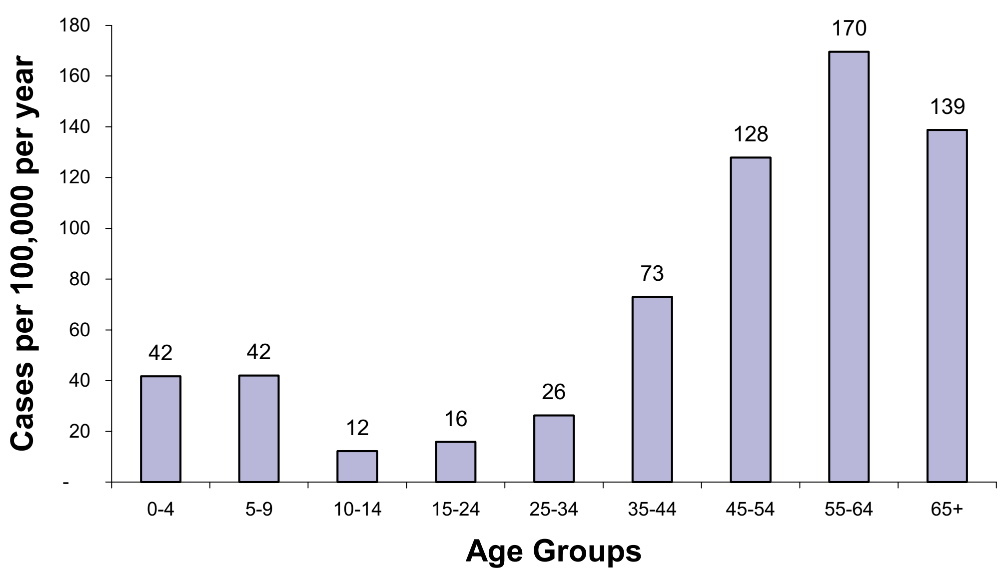

Fig. 3. Age Distribution of reported influenza in Thailand 1999–2002. Source: Bureau of Epidemiology, Thailand Ministry of Public Health.

Thailand reported between 64 and 91 cases of influenza per 100,000 persons per year across all age groups during the years 1993–2002 [22,23]. Sharp peaks in reported influenza cases are observed during the months of June through September with smaller increases in reported cases sometimes being seen in January and February (Fig. 2). In 1999, 11,869 hospitalizations due to influenza were reported in Thailand, a rate of 21 per 100,000 population per year [23]. These data imply that there are three to four ((21/64)–(21/91)) community influenza cases per influenza-associated hospitalization. This high ratio in Thailand could be the result of an increased likelihood of reporting more severe, hospitalized cases or a lower threshold for hospital admission, or perhaps most likely, the result of underreporting of milder cases in the community. The age distribution of reported cases of influenza infection in Thailand during 1999–2002 indicates that influenza may be more likely to be diagnosed in older age groups (Fig. 3).

5. Avian H5N1 influenza in Thailand

The Thailand Department of Livestock Development (DLD) conducts passive and active surveillance for influenza virus in birds and swine. According to the Thai Broiler Processing Exporters Association, approximately 800 million chickens are produced every year in Thailand with more than 400,000 people employed in this industry[24]. Recent studies suggest an increased risk for avian influenza infection from occupational exposure to poultry [25,26]. Moreover, given the size of the poultry industry, the identification of highly pathogenic avian influenza (HPAI) might have significant health and economic implications. Highly pathogenic avian influenza had not been reported in Thailand prior to January 2004 [27].

By early January 2004, farms in southern, central and northern Thailand provinces were experiencing large-scale poultry deaths. At the same time, Vietnam reported its first human deaths caused by avian H5N1 infection as well as widespread, large-scale poultry infections. In response, the Thailand DLD strengthened active surveillance in all kinds of poultry. On 23 January 2004, the Ministry of Agriculture announced that H5N1 influenza had been identified as the cause of poultry die-offs in Thailand and reported the isolation of HPAI to the International Organization for Animal Health (OIE). Efforts to cull poultry from affected provinces began. By 6 February, the DLD had identified H5N1 infection in 156 specimens collected from across Thailand in several bird species including chickens, ducks, geese, peacocks, and ostriches. Thailand has no AIV vaccination policy at present. It is thought that migratory waterfowl and perhaps passerine species may act as an asymptomatic reservoir for a wide range of avian influenza subtypes and strains, including H5N1 [28]. To better describe the role of waterfowl and other wild birds in influenza ecology in Thailand, surveillance for AIV infection in wild birds was initiated in 2004. In addition to safeguarding the health of livestock, this type of surveillance is important because avian and swine influenza viruses may be precursors to human pandemic influenza viruses [28–30].

6. Status of influenza vaccination in Thailand

Influenza vaccine is not widely used in Thailand and is mostly limited to persons who can afford to pay private health care providers for the immunization [31]. Three companies currently distribute inactivated influenza vaccine in Thailand at an average retail cost of approximately 300 Thai baht (US$ 7) per dose. According to vaccine company representatives, the majority of influenza vaccine distributed in recent years has gone to the public sector, mainly to university hospitals and to the Thai MOPH. In the private sector, influenza vaccines were sold mainly to hotels and airline companies interested in protecting their employees from exposure to influenza during travel or contact with tourists (Table 1). Since 2000, Thailand has provided influenza vaccine without charge for approximately 30,000 Thai Muslims each year who travel to Mecca for the Hajj [32].

Thailand's immunization program has proven to be highly effective in delivering Expanded Program of Immunization (EPI) vaccines to the country's 7.2 million children less than 5 years of age. Most Thai children receive their immunizations through community health centers and hospital immunization clinics. Introducing inactivated influenza vaccine to high-risk children per WHO recommendations would represent a special challenge to the national immunization program given the need to provide two immunizations to children who have never received the influenza vaccine and to annually revaccinate [33]. Recent vaccine distribution data indicate that fewer than 80,000 doses of influenza vaccine have been administered annually in Thailand in recent years (Table 1). When this figure is applied to Thailand's population of 62,350,000 persons, this suggests that less than 1% of the general population may be currently vaccinated for influenza. Vaccine coverage may be higher among subgroups such as Thai Muslims, healthcare workers, or those with high-risk conditions such as obstructive pulmonary disease. However, no systematic assessment of influenza vaccine coverage has been conducted in Thailand.

7. Influenza research in Thailand

Published influenza literature from Thailand is limited but suggests that influenza may be more important than commonly appreciated. Since 1990 several papers have been published describing antigenic typing of influenza viruses isolated in Thailand [34–36]. Other published papers discussed an influenza outbreak in a mountain village [37], influenza infection in nursing assistants [38], and an outbreak of fever of unknown origin (FUO) that was attributed to a mix of dengue and influenza infection [39]. In a study of 117 patients with

Table 1
Number of influenza vaccine doses sold in Thailand by year and sector

Company	2000		2001		2002		2003	
	Public	Private	Public	Private	Public	Private	Public	Private
A	60, 240	11, 862	46,760	4,189	31,632	8,368	15,557	38,632
B	0	0	0	2,676	0	2,165	0	7,507
C	Not available	Not available	5,915	2,535	2,790	3,410	16,557	4,090
Annual total		72, 102		62, 075		48, 365		82, 343

fever at community hospitals in northeastern Thailand during May–November 2000, 14 (12%) were positive for influenza by hemagglutination inhibition testing [40]. Finally, Wongsurakiat and colleagues conducted a placebo-controlled, double-blinded efficacy and cost-effectiveness study of influenza vaccine in 125 chronic obstructive pulmonary disease patients. The vaccine was found to have reduced acute respiratory infection caused by influenza virus by 76% when compared to placebo. The vaccine was determined to be cost-effective, primarily by reducing the frequency of hospital admission and the need for mechanical ventilation [41].

In August 2003, the Thai MOPH and the US Centers for Disease Control and Prevention's International Emerging Infections Program (IEIP) began a 2-year study to determine the incidence of influenza in hospitalized patients with radiographic confirmation of pneumonia and in outpatients with influenza-like illness in SaKaeo province in eastern Thailand. Nasopharyngeal (NP) specimens from enrolled patients are tested for influenza and other respiratory viruses and cost of illness data are collected from patients who test positive for influenza.

8. Thai MOPH influenza policy

Recent interest by the WHO in establishing the burden of influenza in less-developed, tropical countries and the WHO's recommendation that national health authorities develop pandemic preparedness plans has led to increased interest in influenza among Thai public health decision-makers. Although available in the private market, influenza vaccine uptake in the general population has been poor due to low awareness and the relatively high cost of the vaccine. In addition to providing influenza vaccine to Thai pilgrims who attend the Hajj, the Thai MOPH is considering providing influenza vaccines to institutionalized elderly persons. As of February 2004, no formal action had been taken on this proposal. Neither the Thai MOPH nor the Thai Medical Association has published guidelines for influenza vaccine use in Thailand.

9. Summary

Thailand is a middle-income country with a capable public health system that has maintained high coverage rates for EPI vaccines. Although more study is needed, the available literature suggests that influenza may be a surprisingly important cause of illness in Southeast Asia. Influenza surveillance in Thailand needs improvement, but the available data suggest a disease burden that is greater than generally appreciated. Influenza vaccines are available in Thailand but uptake is very low. Importantly, the Thai MOPH is open to policy changes with regard to influenza surveillance and control, suggesting that the findings of influenza research in Thailand could influence influenza control policy in the near term. The scale of the 2004 regional outbreak of influenza A H5N1 infection in poultry combined with the first report of human H5N1 deaths in Thailand may influence the debate on the importance of influenza surveillance and control.

Future research should include further examination of the seasonality and health and economic burden of influenza in Thailand and other respiratory infections such as respiratory syncytial virus. Studies on the ecology of avian influenza in Thailand may help predict the emergence of avian influenza viruses with the potential to cause the next influenza pandemic [42,43]. Data on the epidemiology and economic impact of influenza infection and the cost-effectiveness of the influenza vaccination are also needed to guide possible decisions about vaccine usage. For example, studies in healthy working adults, the elderly and other high-risk groups demonstrating the usefulness of the vaccine in reducing serious adverse health outcomes and economic losses due to influenza would be valuable. Further strengthening of influenza surveillance in Thailand, perhaps involving rapid antigen testing and expanding virological surveillance would greatly facilitate efforts to estimate the burden of disease.

Middle-income countries such as South Africa, South Korea, Brazil, and others may be in a similar position as Thailand. Coordinated research efforts using standardized case definitions and laboratory methods could result in important advances for influenza control in these countries. Such an endeavor will require the collaboration of diverse partners including ministries of public health, the WHO, and the vaccine and biologics industry.

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