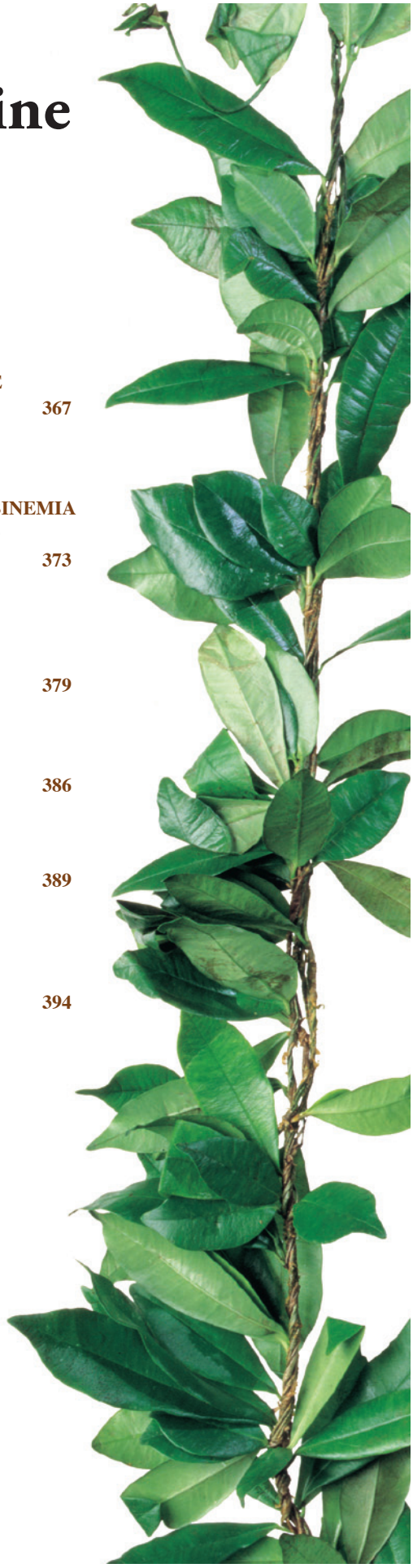
Hawai‘i Journal of Medicine & Public Health

A Journal of Asia Pacific Medicine & Public Health

December 2016, Volume 75, No. 12, ISSN 2165-8218



Hawai‘i Journal of Medicine & Public Health

A Journal of Pacific Medicine & Public Health

ISSN 2165-8218 (Print), ISSN 2165-8242 (Online)

The Journal’s aim is to provide new scientific information in a scholarly manner, with a focus on the unique, multicultural, and environmental aspects of the Hawaiian Islands and Pacific Rim region.

Published by University Clinical, Education & Research Associates (UCERA)

Hawai‘i Journal of Medicine & Public Health
677 Ala Moana Blvd., Suite 1016B
Honolulu, Hawai‘i 96813
http://www.hjmph.org; Email: info@hjmph.org

The Hawai‘i Journal of Medicine & Public Health was formerly two separate journals: The Hawai‘i Medical Journal and the Hawai‘i Journal of Public Health. The Hawai‘i Medical Journal was founded in 1941 by the Hawai‘i Medical Association (HMA), which was incorporated in 1856 under the Hawaiian monarchy. In 2009 the journal was transferred by HMA to University Clinical, Education & Research Associates (UCERA). The Hawai‘i Journal of Public Health was a collaborative effort between the Hawai‘i State Department of Health and the Office of Public Health Studies at the John A. Burns School of Medicine established in 2008.

D. Varez

Discrepancy Between Identification of Early-Term Elective Deliveries by Manual Chart Review and Data Vendor

Kelly Yamasato MD; Pai-Jong Stacy Tsai MD, MPH; Marguerite Bartholomew MD; Marsha Durbin; Chieko Kimata PhD; and Bliss Kaneshiro MD, MPH

Abstract

Elective delivery from 37 to 39 weeks gestation (early-term deliveries) is a Joint Commission National Quality Measure, and hospitals report on early-term elective delivery rates through Outcome Research Yields Excellence (ORYX) vendors. The objective of this study was to compare early-term elective deliveries, identified through ORYX vendors with those identified through manual chart review, the traditional method of medical record review. We reviewed early-term labor inductions and cesarean deliveries at a single hospital from June 1, 2010 to May 31, 2012. Rates of early-term elective deliveries identified by the data vendor were compared to physician chart review. Overall, the rate of elective deliveries by ORYX was 3% compared to 2% by physician chart review (RR 1.51 [95% CI 1.12-2.03], P < *.001). Of the 116 elective early-term deliveries identified by vendor and/or chart review, vendors classified significantly more inductions and cesareans as elective (*P < *.001) and missed nine elective deliveries. Of the 107 deliveries identified as elective by ORYX, 62 (57.9%) were verified by chart review, including 69.0% of cesareans and 36.1% of inductions. Findings from this study suggest substantial discrepancy between identification of early-term elective deliveries by data vendors and physician chart review, and indicate that vendor-derived data may overestimate the number of electively delivered patients.*

Keywords

Labor, induced; Cesarean Section; Joint Commission on Accreditation of Healthcare Organizations; elective surgical procedures; delivery, obstetric

Introduction

While elective delivery has come under increasing scrutiny and restriction nationwide, elective inductions in Hawai'i continue to occur in 4 to 5 percent of term deliveries.[1] Elective deliveries prior to 39 weeks gestational age, including induction of labor and cesarean delivery, are associated with an increased risk of neonatal intensive care admission.[2,3] Interestingly, several studies have not supported these findings.[4-6] Despite the availability of guidelines on the timing of delivery,[7] inconsistent means of classifying deliveries as elective or obstetrically indicated may contribute to these discrepancies.[4] Previous studies reporting rates and outcomes of elective deliveries have identified elective labor inductions based on manual chart review,[3,8] maternal hospital discharge data,[4] and maternal admission diagnosis codes.[9] Multiple diagnostic criteria have also been used to classify deliveries as elective or medically indicated, including criteria created by the American College of Obstetrics and Gynecology,[8,10] the Joint Commission (JC),[4] or other hybrid criteria.[3]

Elective delivery from 37 to 39 weeks gestation (early-term deliveries) is a JC National Quality Measure.[11] To participate in Medicare and Medicaid incentives in 2015 and beyond[12] and to receive JC accreditation,[13] hospitals must report on early-term elective delivery rates through Outcome Research Yields Excellence (ORYX) vendors, also known as performance measurement systems. ORYX vendors extract and process data to identify elective deliveries as dictated by an algorithm specified by the JC (available at https://manual.jointcommission.org/releases/TJC2013A/MIF0166.html),[14] though the exact methodology may not always be readily available to clinicians.

Automated identification of elective deliveries through such systems may fulfill national mandates and bypass costly and time-consuming chart review, yet few studies have compared ORYX vendors with manual chart review, the traditional method of medical record review, in identifying elective early-term deliveries. Using automated electronic processes to derive data on early-term elective deliveries can impact hospital finances, policy, and ultimately, medical care. The objective of this study was to compare elective deliveries, both labor inductions and cesarean deliveries, between 37 to 39 weeks gestation identified through our ORYX vendors with those identified through manual chart review.

Materials and Methods

Subject Identification and Selection

We performed a retrospective study of deliveries from June 1, 2010 to May 31, 2012 at Kapi'olani Medical Center for Women and Children (Honolulu, Hawai'i), a tertiary care maternity hospital that performs approximately 6500 deliveries annually. An initial list of patients who delivered from 37 weeks and 0 days to 38 weeks and 6 days gestation, was generated through data extraction from the electronic health record. Labor inductions were identified by International Classification Diagnosis-9 (ICD-9) codes. Patients with diagnoses of hypertension and/or diabetes by ICD-9 codes and patients who underwent cesarean delivery with cervical dilation of ≥5 centimeters were further excluded. A single board-certified obstetrician study investigator then performed manual chart review for all of the remaining patients who underwent labor induction or cesarean delivery (Figure 1).

Data Collection

To determine if a patient underwent elective delivery, discharge ICD-9 codes, admitting history and physical examinations, progress notes, operative reports, cervical exam records at the time of admission, and medications were reviewed. Labor inductions, as identified by ICD-9 codes (73.1, 73.01, 73.4), were classified elective if they did not contain a diagnosis included in the Joint Commission National Quality Measures

ICD-9-CM Code Table 11.07: Conditions Possibly Justifying Elective Delivery Prior to 39 Weeks Gestation.[11] In addition, if the patient made cervical change in the absence of induction agents she was deemed to be in labor and therefore not an induction. Cesarean deliveries were elective if the preceding criteria were met, cervical dilation was less than 5 centimeters, and there was no documentation of contractions and abdominal pain or a diagnosis of labor. Contractions with abdominal pain, even in the absence of cervical change, was considered a medical reason for delivery when cesarean was indicated as the concern for uterine rupture or other risks of labor is medical justification to avoid delaying delivery. The JC algorithm used by ORYX vendors identifies deliveries between 37 and 39 weeks in women without prior uterine surgery and not in a medical trial. Within this cohort, elective deliveries are then defined as those without an ICD-9 code justifying early-term delivery as specified by the JC (Appendix A). Deliveries missing information required by the algorithm are excluded.[14] We were unable to review the procedures used by ORYX vendors for data collection and screening.

Elective labor inductions and cesarean deliveries identified by manual chart review were compared to those identified by the ORYX vendor. In October 2011, 16 months into the 24-month study period, the hospital changed commercial data carriers, referred to in this study as ORYX vendor 1 and ORYX vendor 2. Therefore, elective deliveries were also stratified by the two vendors employed during the study interval. The investigator who initially reviewed records was blinded to the results of the ORYX vendor until the review was complete. In instances where disagreement between manual chart review and the computer program was noted, a second investigator reviewed cases to determine the final designation.

Statistical Analysis

The proportion of elective deliveries identified through manual chart review versus the ORYX vendor was compared using McNemar's test. The kappa statistic, a measure of the difference between observed and expected inter-observer agreement, was calculated for each comparison as well. The kappa statistic was interpreted based on a commonly cited scale defining degree of agreement as kappa of 0.01-0.20 (slight), 0.21-0.40 (fair), 0.41-0.60 (moderate), 0.61-0.80 (substantial), 0.81-0.99 (almost perfect).[15] A P value of < .05 was considered statistically significant. All analyses were performed through the Statistical Program for Social Sciences (SPSS 20.0 for Mac; SPSS Inc. Chicago, IL). This study was granted exemption by the Hawai'i Pacific Health Research Institute.

Results

A total of 3595 deliveries between 37 and 39 weeks occurred during the study period (Table 1). Of these, 71 (2%) deliveries were identified as elective (including labor inductions and cesareans) by chart review, compared with 107 (3%) by ORYX vendors (RR 0.79 [95%CI 0.66-0.95], P < .001). A total of 116 deliveries were identified as elective by ORYX vendors and/or manual chart review; 62 by both vendor and chart review, 45 by vendor only, and 9 by chart review only (Table 2a). Therefore, 62/107 (57.9% [95% CI 44.8-73.8%]) of elective deliveries identified by ORYX vendor were verified by chart review. Conversely, 9/71 (12.7%, [95%CI 6.2-23.4%]) of elective deliveries identified by chart review were not detected by the ORYX vendor. Significant and substantial agreement was noted between elective deliveries identified by chart review and those identified by the ORYX vendors (kappa = 0.689, P < .001).

This agreement was moderate to substantial when deliveries were stratified by labor induction versus planned cesarean delivery and by ORYX vendors (kappa = 0.517-0.761). Among cesarean deliveries, 49/71 (69.0%) deliveries deemed elective by ORYX vendor were also identified as elective by manual review, and 8/57 (14.0%) of elective cesareans identified by manual chart review were not identified by ORYX vendor. For labor inductions, 13/36 (36.1%) of elective inductions identified by ORYX vendor were verified by chart review, and 1/14 (7.1%) elective induction identified by chart review was missed by the ORYX vendor (Table 2b and 2c). When stratified by vendor, ORYX vendor 1 was in agreement with manual chart reviews in 56/102 (54.9%) of cases identified as elective by vendor and/or chart review, while ORYX vendor 2 was in agreement in 6/14 (42.9%).

Delivery indications in cases of discrepancy between the ORYX vendor and the manual chart review are described in Tables 3a and 3b. The most common delivery indication among discrepancies classified as elective by ORYX vendor and medically indicated by chart review was labor. For inductions, the presence of labor indicated that the case was misclassified. For cases requiring cesarean, labor generally necessitates delivery. Eight of the nine deliveries identified as elective by chart review but not by ORYX vendor were planned cesarean deliveries. In addition, eight of these nine deliveries were excluded by the JC algorithm due to missing information, while one was classified as obstetrically indicated.

Table 1. Elective Deliveries 37 to 39 Weeks Gestation Identified Through Manual Chart Review versus ORYX Vendors

All Deliveries N=3595	Manual Chart Review* n (%)	ORYX Vendors n (%)	*P* Value
All Elective Deliveries	71 (2.0)	107 (3.0)	< .001
Elective Inductions	14 (0.4)	36 (1.0)	< .001
Elective Cesarean Deliveries	57 (1.6)	71 (2.0)	< .001

*Labor inductions and cesarean deliveries were manually reviewed. Inductions and cesareans with ICD-9 codes of hypertension and/or diabetes or cesarean deliveries with cervical dilation of >5 centimeters were classified as nonelective without manual chart review.

Table 2a. Discrepancies in Elective Deliveries 37 to 39 Weeks Gestation as Identified by Manual Chart Review versus ORYX Vendors (All Elective Deliveries)

		Manual Chart Review*	
		Not Elective** (n=3,524)	Elective (n=71)
ORYX Vendors (all deliveries, N=3,595)	Not Elective or Excluded (n=3,488)	3,479	9
	Elective (n=107)	45	62

kappa = 0.689 (95% confidence interval, 0.611-0.767; *P*<.001)

Table 2b. Discrepancies in Elective Deliveries 37 to 39 Weeks Gestation as Identified by Manual Chart Review versus ORYX Vendors (Elective Cesareans Among All Deliveries)

		Manual Chart Review*	
		Not an Elective Cesarean Delivery** (n=3,538)	Elective Cesarean Delivery (n=57)
ORYX Vendors (N=3,595)	Not an Elective Cesarean Delivery or Excluded (n=3,524)	3,516	8
	Elective Cesarean Delivery (n=71)	22	49

kappa = 0.761 (95% confidence interval, 0.679-0.843; *P*<.001)

Table 2c. Discrepancies in Elective Deliveries 37 to 39 Weeks Gestation as Identified by Manual Chart Review versus ORYX Vendors (Elective Labor Inductions Among All Deliveries)

		Manual Chart Review*	
		Not an Elective Labor Induction** (n=3,581)	Elective Labor Induction (n=14)
ORYX Vendors (N=3,595)	Not an Elective Labor Induction or Excluded (n=3,559)	3558	1
	Elective Labor Induction (n=36)	23	13

kappa = 0.517 (95% confidence interval, 0.348-0.686; *P*<.001)

*Labor inductions and cesarean deliveries were manually reviewed. Inductions and cesareans with ICD-9 codes of hypertension and/or diabetes or cesarean deliveries with cervical dilation of >5 centimeters were classified as nonelective without manual chart review.

**Includes all deliveries that were deemed not elective by meeting at least 1 of the following criteria: no ICD-9 code for labor induction or cesarean, an ICD-9 code for hypertension or diabetes, cervical dilation > 5 cm with and indication for cesarean delivery, contractions and abdominal pain with and indication for cesarean delivery, rupture of membranes, an ICD-9 code from the JC Code Table 11.07, or a diagnosis from the JC Code Table 11.07 gathered on manual chart review.

Table 3a. Indications for Delivery in Discrepancies Between ORYX vendors and Manual Chart Review (Cases identified as elective by ORYX vendors and medically indicated by manual chart review)

n	Indication for Delivery Identified by Manual Chart Review
22	Labor or contractions with abdominal pain
6	Cholestasis of pregnancy
5	Fetal heart rate decelerations (n=4), fetal arrhythmia (n=1)
4	Fetal polycystic kidneys/pyelectasis (n=1), fetal anemia (n=1), gastroschisis (n=1), fetal pelvic cyst (n=1)
2	Gestational hypertension
1	Premature spontaneous rupture of membranes
1	Patient on enoxaparin during pregnancy for history of pulmonary embolus
1	Symptomatic episodic tachycardia worsening through pregnancy
1	Pregestational diabetes
1	Vasa previa
1	HIV positive, nonadherent to antiviral medication

Table 3b. Indications for Delivery in Discrepancies Between ORYX vendors and Manual Chart Review (Cases identified as elective by manual chart review and medically indicated or excluded by ORYX vendor)

n	Indication for Delivery Identified by Manual Chart Review
3	Scheduled primary cesarean section for breech, not in labor
3	Scheduled repeat cesarean section
2	Scheduled cesarean section. Polyhydramnios present antepartum, but resolved prior to delivery
1	Labor induction for asthma exacerbation

Discussion

Our study is one of few to compare automated computer programs used by ORYX vendors and manual chart review in the identification of early-term elective deliveries. Substantial agreement was demonstrated between cases identified by the ORYX vendor and manual chart review. However, ORYX vendors overestimated the number of patients electively delivered compared to physician review. Overall, the rate of elective deliveries identified by ORYX vendor was 3% versus 2% by manual chart review, a statistically significant difference. While the absolute difference is modest it also represents a 50% increase, which may deserve further consideration in institutions with higher rates of elective deliveries. Disagreement between ORYX vendor and manual chart review was present for both cesarean deliveries and labor inductions, even when the same diagnostic criteria were used.

Though statistically moderate to substantial agreement between manual chart review and ORYX vendor was present, the overestimation of elective deliveries by ORYX vendors raises questions regarding the validity of automated computer program data for determining hospital accolades, reimbursements, and

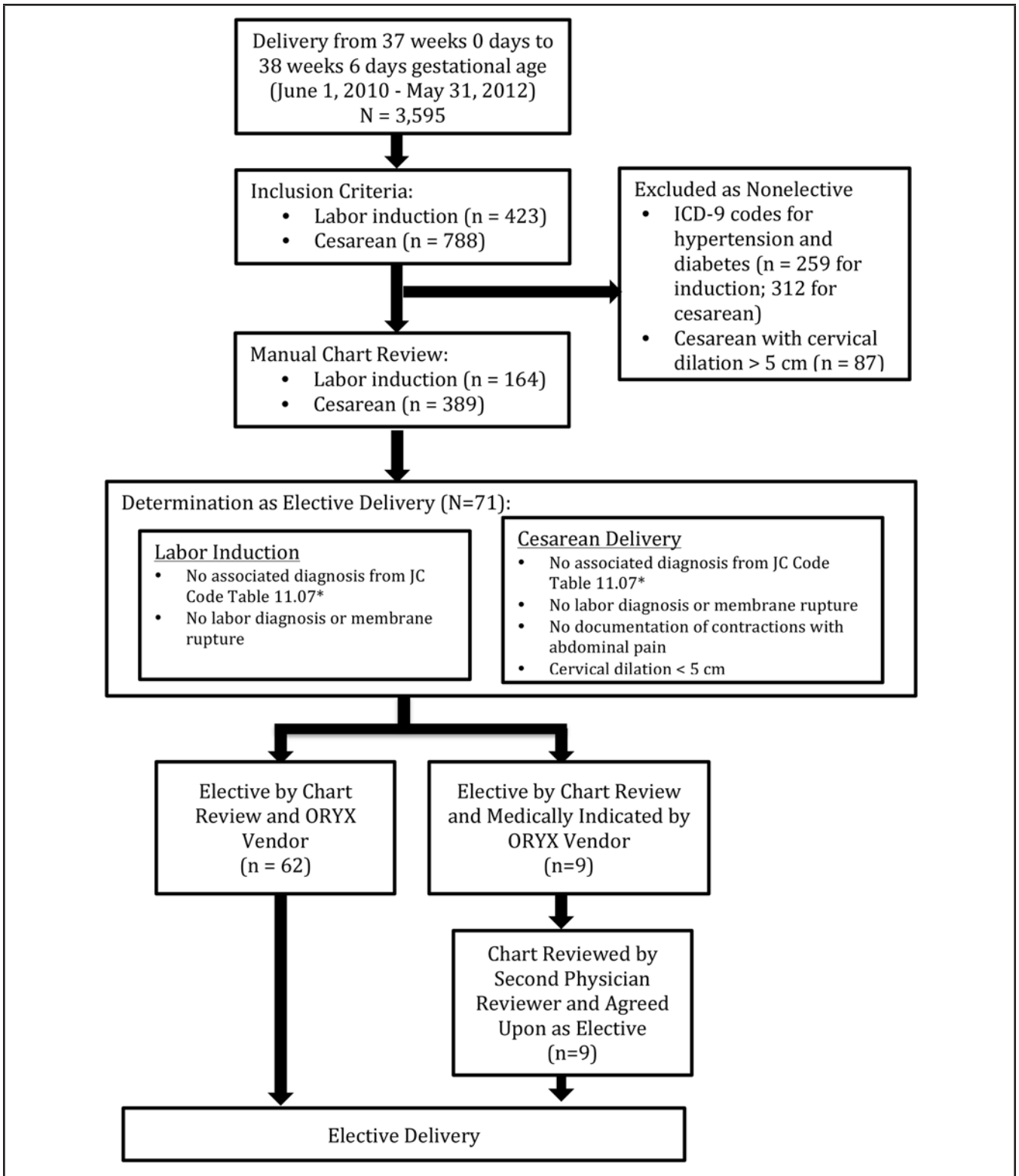


Figure 1. Subject Selection and Determination of Elective Delivery by Manual Chart Review

*JC Code Table 11.07: Joint Commission National Quality Measures ICD-9-CM Code Table 11.07: Conditions Possibly Justifying Elective Delivery Prior to 39 Weeks Gestation

policies. Two independent ORYX vendors were examined in this study, both of which overestimated elective deliveries, though there were only 14 total elective deliveries identified while ORYX vendor 2 was used. The small number of elective deliveries for ORYX vendor 2 and institutional changes in the elective induction rate over the course of the study limit comparisons between the two vendors themselves.

Advantages of automated data collection include relative ease of collection, standardization, and nationwide comparability between institutions. However, we found the most common discrepancy was a delivery classified as elective by the ORYX vendor and medically indicated by manual chart review, resulting in the vendor identifying significantly more elective deliveries compared to manual chart review. ORYX vendors may miss legitimate reasons for delivery if the correct diagnosis codes or data fields are not completed. Examination of progress notes by a qualified health professional may identify indications for delivery that are missed by the program. We describe the most common diagnoses involved in these discrepancies as potential targets for improvement of the JC algorithm. The identification of labor as an indication for a planned cesarean delivery was the most common discrepancy in this study. While the JC provides a definition of active labor[16] these discrepancies reflect a possible disconnect between the JC definition and clinical judgment used to diagnose labor. However, objective delivery indications such as hypertension, diabetes, and vasa previa were also missed by vendor-abstracted data.

While manual chart review may be more sensitive in identifying legitimate indications for delivery, potential disadvantages of this methodology include prohibitive time requirements, human error, reviewer variability, and reviewer bias. Inadequate documentation can affect manual chart review as well as automated review. Joint Commission criteria are used by ORYX vendors to comply with national mandatory hospital reporting requirements. In this study, JC criteria were used for the manual chart review as well for consistency with the ORYX vendors. However, an estimated 10% of ORYX vendor-identified elective deliveries involve legitimate delivery indications not included in the JC criteria.[17] The validity of these criteria warrant continued evaluation to best identify truly elective deliveries within the current medical standard of care.

Rates of agreement between elective deliveries identified by ORYX vendors and manual chart review in this study are largely consistent with previous studies. Persell, et al, compared automated measurement with a review of free-text data to assess compliance with national quality measures in coronary artery disease. They found that 15% to 81% of failures identified by automated methods were reclassified following chart review.[18] Clark, et al, employed a two-physician chart review to examine 205 early-term deliveries classified as elective by ORYX vendors. The physician reviewers disagreed with the classification of an early-term delivery in 45% of cases. Seventy-eight percent of the discrepancies were attributed to errors in data abstraction, coding, or documentation and the remaining discrepancies to medically valid indications for delivery not included in the JC criteria.[17] The study by Clark et al did not explore whether some early-term elective deliveries were missed by an automated computer system. In this study only one delivery classified as medically indicated by the ORYX vendor was identified as elective by manual chart review. The majority of elective deliveries (8 of 9) missed by the ORYX vendor were excluded by the algorithm due to missing information. We are also the first to stratify elective deliveries into cesarean deliveries and labor inductions. At our institution we found the rate of discrepancies to be greatest for labor inductions, indicating a potential target for improvement in the identification of elective deliveries.

A limitation of this study includes the involvement of a single physician reviewer for most charts, though a second physician reviewed all discrepancies between the ORYX vendor and the manual review. In addition, our institution demonstrated low baseline rates of elective deliveries between 37 and 39 weeks gestation during the study period. Caution should be exercised when extrapolating the results of this study to institutions with higher rates of elective deliveries. Due to the large volume of deliveries during the study interval, labor inductions for potential manual chart review were identified through ICD-9 codes. Thus, it is possible that inductions were missed by both manual chart review and ORYX vendor. While this is relevant to the sensitivity of manual chart review to identify elective inductions, it does not affect our assessment of agreement between the two methods. Finally, this study was performed with incomplete knowledge of the ORYX vendor methodology, though access to these protocols may improve the interpretation of our results

In the technological age, healthcare oversight is increasingly reliant on automated data and medical informatics. Our findings imply that such data analysis in its present form may require additional review to best identify elective deliveries. Larger and ongoing studies of this nature may provide information that helps to align clinician and ORYX vendor perspectives within current medical practice.

Conflict of Interest

None of the authors identify any conflict of interest.

Authors' Affiliations:
- Department of Obstetrics Gynecology, and Women's Health, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (KY, P-JST, MB, BK)
- Hawai'i Pacific Health, Patient Safety and Quality Services, Honolulu, HI (MD, CK)

Correspondence to:
Kelly Yamasato MD; 1319 Punahou Street, #824, Honolulu, HI 96826;
Email: kyamasat@hawaii.edu

References

1. Yamasato K, Bartholomew M, Durbin M, Kimata C, Kaneshiro B. Induction rates and delivery outcomes after a policy limiting elective inductions. *Matern Child Health J.* 2015;19:1115-1120.
2. Sengupta S, Carrion V, Shelton J, et al. Adverse neonatal outcomes associated with early-term birth. *JAMA Pediatr.* 2013;167:1053-9.
3. Hoffmire C, Chess PR, Saad TB, et al. Elective delivery before 39 weeks: The risk of infant admission to the neonatal intensive care unit. *Matern Child Health J.* 2012;16:1053-62.
4. Darney B, Snowden JM, Chen YW, et al. Elective induction of labor at term compared with expectant management. *Obstet Gynecol.* 2013;122:761-9.
5. Stock S, Ferguson E, Duffy A, et al. Outcomes of elective induction of labour compared with expectant management: population based study. *BMJ.* 2012;344:e2838.
6. Glavind J, Kindberg SF, Uldbjerg N, et al. Elective caesarean section at 38 weeks versus 39 weeks: neonatal and maternal outcomes in a randomised controlled trial. *BJOG.* 2013;120:1123-32.
7. Spong C, Mercer BM, D'Alton M, et al. Timing of indicated late-preterm and early-term birth. *Obstet Gynecol.* 2011;118:323-33.
8. Fisch J, English D, Pedaline S, et al. Labor induction process improvement. *Obstet Gynecol.* 2009;113:797-803.
9. Oshiro B, Henry E, Wilson J, et al; Women and Newborn Clinical Integration Program. Decreasing elective deliveries before 39 weeks of gestation in an integrated health care system. *Obstet Gynecol.* 2009;113:804-11.
10. Ehrenthal D, Hoffman MK, Jiang X, et al. Neonatal outcomes after implementation of guidelines limiting elective delivery before 39 weeks of gestation. *Obstet Gynecol.* 2011;118:1047-55.
11. The Joint Commission. AppendixATJC- Manual-Performance Measurement Network. 2012 [cited January 31, 2014]. Available from: https://manual.jointcommission.org/releases/TJC2013A/AppendixATJC.html#Table_Number_11_07_Conditions_Po.
12. Centers for Medicare and Medicaid Services. Electronic Specifications for Clinical Quality Measures - Centers for Medicare and Medicaid Services. 2014 [cited January 31, 2014]. Available from: http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/Electronic_Reporting_Spec.html.
13. The Joint Commission. Facts about ORYX Vendors. 2014 [cited January 31, 2014] Available from: http://www.jointcommission.org/assets/1/6/ORYX_vendors.pdf.
14. The Joint Commission. Specifications Manual for Joint Commission National Quality Measures (v2013A1). 2012 [cited January 31, 2014]. Available from: https://manual.jointcommission.org/releases/TJC2013A/MIF0166.html.
15. Viera AJ, Garrett JM. Understanding interobserver agreement: The kappa statistic. *Fam Med.* 2005;37:360-3.
16. The Joint Commission. Specifications Manual for Joint Commission National Quality Measures (v2012B). 2012 [cited April 26, 2014]. Available from: https://manual.jointcommission.org/releases/TJC2012B/DataElem0263.html.
17. Clark SL, Meyers JA, Milton CG, et al. Validation of The Joint Commission exclusion criteria for elective early-term delivery. *Obstet Gynecol.* 2014;123:29-33.
18. Persell S, Wright JM, Thompson JA, et al. Assessing the validity of national quality measures for coronary artery disease using and electronic health record. *Arch Intern Med.* 2006;166:2272-7.

Obstetric Obesity is Associated with Neonatal Hyperbilirubinemia with High Prevalence in Native Hawaiians and Pacific Island Women

Luc R.A. Rougée PhD; Shogo J. Miyagi PhD, PharmD; and Abby C. Collier PhD

Abstract

Obesity and pregnancy both place the liver under metabolic stress, but interactions between obstetric obesity and bilirubin metabolism have not been studied. We determined associations between obesity, maternal/neonatal bilirubin levels, and uridine 5'diphosphate-glucuronosyltransferase 1A1 (UGT1A1) enzyme that eliminates bilirubin. Adult livers were analyzed for UGT1A1 expression, activity, and bilirubin clearance by pharmacokinetic modeling. Then, matched maternal and neonatal sera (N = 450) were assayed for total and unconjugated bilirubin. Associations between obesity, UGT1A1, maternal and neonatal hyperbilirubinemia were determined statistically through correlation analysis (Pearson's test) as well as binned categories (one-way ANOVA). Morbid obesity decreased hepatic UGT1A1 protein levels, activity, and bilirubin clearance (P < .001). Increasing obesity corresponded to elevated maternal unconjugated bilirubin (P < .05). Maternal obesity was also significantly positively correlated with elevated neonatal bilirubin levels (P < .01, N = 450) and this was strongest in Native Hawaiians and Pacific Islander (NHPI) women (P < .01, n = 150). Obstetric obesity is associated with maternal and neonatal hyperbilirubinemia, likely through inhibition of hepatic UGT1A1. The NHPI cohort was the most obese and had the highest levels of maternal and neonatal unconjugated bilirubin. Neonates from obese mothers may be more susceptible to jaundice and side effects from parenteral nutrition.

Keywords

bilirubin, developmental pharmacology, glucuronidation, jaundice

Introduction

Obesity is the most common high-risk obstetric syndrome and is associated with increased incidence of pregnancy- and neonatal-complications.[1] The impact of obesity on pregnancy complications, independent of culture and ethnicity, includes stress effects of pregnancy on liver functions (eg, gestational diabetes). However, obesity-mediated inhibition of bilirubin metabolism in the mother and developing child has not previously been studied. The uridine 5'diphosphate-glucuronosyltransferase (UGT) enzymes are a superfamily of proteins that are responsible for the clearance of endogenous and exogenous substrates through direct conjugation of the large water-soluble sugar moiety, glucuronic acid.[2] These enzymes are found in tissues throughout the body, with the highest expressions located in the liver, kidney, and small intestine.[3] The UGT1A1 enzyme is the sole clearance pathway for bilirubin metabolism and is not active in the fetal liver or at birth, resulting in increased levels of unconjugated bilirubin (hyperbilirubinemia) in the mother and neonate.[4]

Because UGT1A1 is largely nonfunctional in fetal livers,[5-7] bilirubin detoxification in pregnancy is performed by the maternal liver and placenta.[8-10] Therefore, inhibition of maternal UGT1A1 during pregnancy could be dangerous. Moreover, even in normal, uncomplicated pregnancies, immature development of UGT1A1 coupled with breakdown of red blood cells at birth commonly causes high systemic free bilirubin and neonatal jaundice.[11] Left untreated, this can lead to kernicterus and impaired neurological development.[12] Although the prevalence of kernicterus is 2.7 per 100,000 live births in North America and Europe, prevalence is one hundred times higher, at 2.7 per 1,000 births in developing countries.[13] Concern also arises about the effects of hyperbilirubinemia in preterm neonates, which are more subtle than in term infants, but potentially just as deleterious.[14]

Over 30% of US adults are obese, and up to 70% of Native Hawaiians and Pacific Islander (NHPI) women are obese.[15,16] This is extremely troubling since these same minority women, independent of obesity, have worse obstetric outcomes including low birth weight, prematurity, and adverse neonatal events.[17,18] Moreover, published studies indicate that NHPI women have less access to obstetric care early in their pregnancies and are more likely to prefer alternatives to hospital births due to cultural and economic considerations.[19,20] While no studies in adults exist, rodent studies have found UGT1A1 to be reduced ~30%-60% in mice fed a high fat diet.[21,22] Because pregnant NHPI women have higher prevalence of obesity, are more likely to have non-hospital births, and are more likely to be in remote and/or resource-poor settings,[1-7] we set out to determine whether obesity alone was associated with hyperbilirubinemia, as a result of compromised UGT1A1 liver function, and whether this might vary with ethnicity. Ethnicity is important as a co-variable due to the differential rates of genetic polymorphisms as well as obesity in different ethnic populations. Here we investigate the association of obesity in pregnancy with incidence of maternal as well as neonatal hyperbilirubinemia in three ethnic populations: Caucasian, Asian, and NHPI women. These populations were chosen for their reported UGT1A1 polymorphism incidence (Asian = 3%-5%; Caucasian = 2%-10%; NHPI = 0-5%) which result in decreased UGT1A1 activity.[23,24] Due to the increase in obesity and negative pregnancy outcomes frequently observed in NHPI, it is hypothesized that a higher incidence of hyperbilirubinemia will be detected in this population.

Abbreviations
BMI: body mass index
K_m: Michaelis-Menten constant
NHPI: Native Hawaiians and Pacific Islanders
UGT: uridine 5'diphosphate-glucuronosyltransferase

Subjects and Methods

Interactions between Obesity and Serum Bilirubin Levels

A retrospective analysis of sera from 450 pregnant women with singleton live births was undertaken. The samples were obtained from the Hawai'i Biorepository and comprised three distinct ethnic groups: Caucasian, NHPI, and Asian. The NHPI group consisted of Native Hawaiian, Samoan, and Tongan ethnicities and the Asian group consisted of Japanese, Korean, and Filipino ethnicities. Ethnicity was self-reported to grandparents' generation, with inclusion criteria being ≥ 50% for Native Hawaiian and 100% for other groups. Although self-report can be problematic, DNA markers of ethnicity (also called "Ancestral Informative Markers") do not exist for Pacific Islanders; hence, self-report was used. The Hawai'i Specimen Biorepository collects data by direct download of Electronic Medical Record. Data relating to obesity and other demographics were abstracted directly by Biorepository staff from the ~350 existing categories in each record using ICD9/ICD10 codes. The study authors do not have access to these codes since they are third party users of the existing database and this study is anonymized. The Biorepository staff only supply the demographics requested. There are no data elsewhere as to the representativeness of the data to the Hawai'i population except to say that all samples are taken from Kapi'olani Women's and Children's hospital, the largest and most comprehensive obstetric hospital in Hawai'i. Samples were obtained randomly across the collection period of the Biorepository (2006 – 2012).

Obesity was defined by body mass index (BMI) as follows: Underweight = < 18.5; Normal weight = 18.5 – 24.9; Overweight = 25 – 29.9; Obese = 30 – 39.9; and morbidly obese ≥ 40 kg/m^2. Elevated unconjugated serum bilirubin was defined as total bilirubin ≥ 0.5 mg/dL, direct bilirubin < 20% of total, and indirect bilirubin ≥ 0.4 mg/dL.[25]

Maternal sera (collected at birth) were assayed for total and unconjugated bilirubin by Clinical Laboratories of Hawai'i LLC (Aiea, Hawai'i, USA), and the matching neonatal serum bilirubin levels were extracted directly from electronic medical records by Hawai'i Biorepository staff. Additionally, information on pregnancy, labor and neonatal complications including gestational diabetes mellitus type 1 and 2, type 1 and 2 diabetes mellitus, intrauterine growth restriction, premature rupture of membranes, premature birth, pre-term labor, gestational hypertension, preeclampsia, eclampsia, hemolysis, elevated liver enzymes, low platelet count syndrome, pancreatitis, cholecystitis, neonatal malformation, small for gestational age, neonatal hyperbilirubinemia, and apnea-bradycardia were extracted from the electronic medical records and compared to bilirubin and obesity levels.

This study was approved by The University of Hawai'i Institutional Review Board for Human Subjects with expedited approval using anonymized, de-identified donors from an existing archive. This study was approved under US federal statutes CFR 46.110 and 21 CFR 56.110 Category (5).

Activity and Expression of UGT1A1 in Hepatic Microsomes

Pools of human liver microsomes were used to test the hypothesis that human UGT1A1 protein and activity varied with obesity in the human liver. Liver tissues were not available from the original sample set of 450 women and their children so a separate source of liver microsomes (that are made by centrifuging the liver at 10,000 xg to extract and concentrate the UGT1A1 proteins) were acquired. Pools of normal weight (n = 10), overweight (n = 10), obese (n = 10), and morbidly obese (n = 5) adults were purchased from BD Biosciences (East Rutherford, NJ, USA). Pools contained equal numbers of adult males and females, except morbidly obese where the sample contained microsomes from 3 females and 2 males.

The presence of UGT1A1 proteins in microsomes was determined by western blot, as previously described using a 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis with semi-dry transfer to polyvinylidene difluoride.[7] Briefly, detection of specific UGT1A1 was with a primary antibody from Santa Cruz Biotechnology (Santa Cruz, CA, USA sc-27415) at 1:1000 dilution, secondary donkey-anti-goat-biotin antibody (1:4000 dilution, Jackson Immunoresearch, West Grove, PA, USA) and detection with streptavidin-biotin-horse radish peroxidase (1:3000 dilution, GE Healthcare, Piscataway, NJ, USA) and chemiluminescent reagent. Area-density analysis of the subsequent films was performed using Image J software (National Institute of Health, Bethesda, Maryland, USA), using a consistently sized box, manually moved along the blot and applying background subtraction.

The biochemical activity of UGT1A1 towards the substrate bilirubin using the reagent ethyl anthranilate was performed spectrophotometrically as previously reported.[26]

Modeled Hepatic Clearance of Bilirubin

Scaled metabolism of bilirubin was investigated to understand if microsomal activity normalized to weight would be impacted by obesity irrespective of ethnicity. The experimentally determined enzyme activities for each pool were scaled for hepatic clearance using a pharmacokinetic model as previously reported by our group, except that the 3/4 power scaling factor for children was omitted.[7] Michaelis-Menten kinetics was assumed. Standard pharmacokinetic parameters were used with liver size of 1500 g, hepatic flow rate of 1.5 L/min and microsomal protein per gram of liver 45 mg/g.[27] Published values for bilirubin of $K_m = 5.0$ μM and unbound fraction 0.001 were used.[28,29] Finally, hepatic clearances were standardized by weight assuming 70 kg for normal weight, 86 kg for overweight, 101 kg for obese and 132 kg for morbidly obese. The weights were calculated using an average height of 177 cm, where each weight corresponded to the median BMI of normal (18.5-24.9), overweight (25-29.9), obese (30-39.9), and morbidly obese (40+) BMI.

Statistical Analyses

All statistical analyses were performed using Prism 5.0 (Graph Pad, San Diego, CA, USA) with $\alpha = 0.05$. The D'Agostino-Pearson Omnibus test for normality was used and since these data satisfied the conditions for normality, parametric statistics were performed. For continuous data (BMI and bilirubin levels) correlations were determined using Pearson's test. For binned categorical data, one-way ANOVA with Bonferroni's post hoc analysis was used to assign significance with categories compared to normal weight.

Results

Population Characteristics

Details regarding the study population (N = 450) are listed in Table 1. The incidence of elevated unconjugated maternal serum bilirubin was 10% in the cohort, translating to 7.7% in Caucasians, 10.3% in Asians, and 12.1% in NHPI (Table 1). The obesity rate for the entire population was 21.4%, comprising 5.7% in Asians, 11.5% in Caucasians, and 53.2% in NHPI, which is reflective of reported population averages (Table 1).[15,16]

Effects of Obesity and Associations with Clinical Outcomes

There were no apnea-bradycardia, cholecystitis, complicated labor, neonatal malformation, premature rupture of membranes, premature birth, or pre-term labor cases reported in the cohort.

Neither obesity nor bilirubin levels were associated with gestational diabetes mellitus, types 1 and 2 diabetes mellitus, intrauterine growth restriction, preeclampsia, eclampsia, hemolysis elevated liver enzymes low platelet count (HELLP) syndrome, pancreatitis, or small for gestational age (data not shown). However, there were small numbers for all of these (< 20 each) so statistical power to detect interactions with these syndromes and diseases was compromised.

Maternal obesity did not significantly correlate with maternal unconjugated bilirubin for the total population ($P = .249$, r = -0.067) or for any of the sub-populations (Caucasian: $P = .848$, r = -0.02017; Asian: $P = .147$, r = -0.139; NHPI: $P = .288$, r = -0.112). However, increasing maternal obesity was significantly associated with elevated neonatal unconjugated bilirubin for the cohort (Figure 1A, $P = .003$) with a moderate correlation (r = 0.21). These effects were strongest in women of NHPI descent (Figure 1B, $P = .007$) and the correlation strengthened (r = 0.32). NHPI women were also the most obese and had the highest rates of elevated unconjugated bilirubin. No significant relationship was observed for neonatal unconjugated bilirubin in the sub-populations of Asians and Caucasians ($P = .689$, r = -0.046 and $P = .624$, r = 0.068 respectively), analyzed individually.

UGT1A1 Expression, Activity, and Modeled Hepatic Clearance of Bilirubin

Obesity in adult livers (comprising both male and female adult samples) was associated with lower hepatic UGT1A1 protein expression in overweight ($P < .05$), obese, and morbidly obese individuals ($P < .001$, both, Figure 2). Similarly, enzyme activities of hepatic UGT1A1 towards bilirubin were significantly lower ($P < .001$) in morbidly obese individuals, and a significant decrease in the liver's overall ability to eliminate bilirubin was observed in morbidly obese individuals ($P < .001$, Figure 2).

Table 1. Study Population Characteristics

	Total Cohort	Caucasian	Asian	NHPI
BMI Range	16.2 – 50.3	16.7 – 49.6	16.3 – 36.7	16.2 – 50.3
BMI Median	23.8	22.5	21.3	30.4
BMI Mean	26.0 ± 7.1	23.7 ± 4.8	22.3 ± 4.0	31.6 ± 7.8
% Obesity[a]	21.4%	11.5%	5.7%	53.2%
% Unconjugated Maternal Serum Bilirubin	10%	7.7%	10.3%	12.1%

[a]Including obese and morbidly obese individuals.

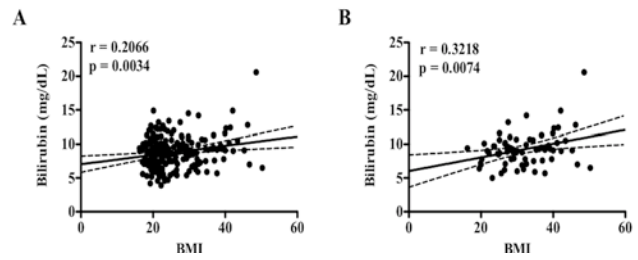
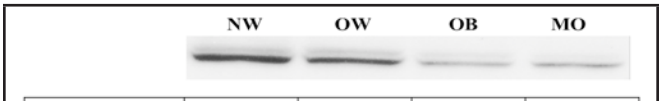


Figure 1. Maternal obesity affects neonatal serum bilirubin. A) Maternal obesity compared to neonatal serum unconjugated bilirubin for all ethnicities; B) Maternal obesity compared to neonatal serum unconjugated bilirubin for NHPI women. population. Solid line represents linear regression. Dashed line represents 95% confidence interval for correlation. Pearson's correlation coefficient (r) and significance values (*P*) of the correlation are presented. BMI = body mass index.



UGT1A1	NW (n = 10)	OW (n = 10)	OB (n = 10)	MO (n = 5)
Protein Expression (area:density)	5.3	3.7*	1.4***	1.5***
Activity (nmol/min/mg protein)	1.21 ± 0.06	1.22 ± 0.07	1.33 ± 0.07	0.08 ± 0.02***
Hepatic Clearance (mL/hr/kg)	15.2 ± 0.07	14.4 ± 0.08	15.0 ± 0.08	8.4 ± 0.03***

Figure 2. Impact of obesity on hepatic UGT1A1 protein expression, bilirubin metabolism, and clearance. Western blot, activity, and clearance for UGT1A1 protein in pooled liver samples from normal weight (NW), overweight (OW), obese (OB), and morbidly obese (MO) adult donors. * = P < .05, *** = P < .001.

Discussion and Conclusions

The critical finding of this study was that obesity during pregnancy, when the liver is already under metabolic stress, is associated with elevated maternal and neonatal unconjugated bilirubin. This finding was strongest in the NHPI population, who were the most obese but have the smallest reported frequency of UGT1A1 low-activity polymorphisms.[30] The incidence of elevated unconjugated maternal serum bilirubin observed in this study are as high (Caucasian) or higher (Asians and NHPI) than the rate of UGT1A1 functional polymorphisms in the respective populations.[23,24] We further provided preliminary mechanistic evidence for the elevated unconjugated bilirubin by showing that obesity is associated with lower amounts of UGT1A1 proteins, and in the morbidly obese is associated with decreased hepatic elimination of bilirubin.

This study introduces an interesting concept regarding gene-environment interactions in glucuronidation. Although the precise signaling pathways are not elucidated here, the molecular and biochemical evidence presented suggests that obesity-related down regulation of UGT1A1 proteins is at least partly responsible for the changes in unconjugated bilirubin levels. Interestingly, while UGT1A1 protein levels decreased significantly in overweight, obese, and morbidly obese individuals, this only translated to significantly lower bilirubin clearance in the morbidly obese. As a person becomes more obese, the liver enlarges, and the compensatory increase in liver volume appears to balance the lower levels of UGT1A1 protein per hepatocyte, up to a threshold. This threshold appears to occur at morbid obesity (BMI ^{3} 40). Whether this is due to overwhelming UGT1A1 depletion (per hepatocyte), other associated failures in liver function, or a combination of the two was not determined. Regardless, the mechanism applies to the population in general because both male and female livers were included in pooled samples. Sex differences with regards to the changes in the UGT1A1 enzyme and obesity should be further investigated.

Elevated bilirubin in pregnancy (above non-pregnant values) is uncommon and is almost always diagnostic of liver disease or dysfunction.[31] In terms of obesity, Nelson and colleagues have recently shown that acute fatty liver in pregnancy causes hemostatic dysfunction, which primarily triggers problems with coagulation, but has also been associated with hemolysis and elevated bilirubin in the mother.[32] This may account for the higher rates of maternal unconjugated bilirubin observed here in our obese and morbidly obese women. However, although unconjugated and conjugated bilirubin are extruded from the fetal compartment into the maternal circulation by placental proteins of the ATP-binding cassette family,[33,34] bilirubin is not transported across the placenta into the fetal compartment. Thus, amniotic bilirubin is reflective of fetal blood bilirubin in pregnancy and not maternal factors.[35] Therefore, increased maternal bilirubin, even if due to fatty liver dysfunction, is not directly causing the higher neonatal bilirubin. Additionally, it has been demonstrated that high levels of fetal and neonatal total bilirubin can be caused by polymorphisms in placental ATP-binding cassette proteins that confer low activity and prevent detoxification of the fetal compartment.[33] Because these polymorphisms are rare, it is unlikely that the neonatal outcomes observed were due to placental transporter dysfunction. Finally, certain pregnancy complications, such as increased length of second-stage labor are associated with higher neonatal bilirubin levels.[1] Retrospective analyses of these data were performed to consider complicated labor, pre-term labor, and fetal malformations. There were none in our population. Hence labor and delivery outcomes that independently cause higher bilirubin levels were not a confounding factor for this study.

One plausible explanation for the higher levels of unconjugated bilirubin could be increased plasma free fatty acids that can directly uncouple glucuronide from bilirubin.[36,37] This occurs in pre-term neonates given IV lipids – the standard of nutritional care for premature infants – where high serum free fatty acids directly de-conjugate bilirubin glucuronides and overwhelm the infant's limited capacity to eliminate the compound.[36,37] The direct de-conjugation of glucuronides causing jaundice is an area of much concern in preterm infants requiring parenteral nutrition. There is also evidence that free fatty acids are potent direct inhibitors of some UGT enzymes at the protein level.[38,39] Using *in vitro* assays, addition of bovine serum albumin (which sequesters fatty acids) alters UGT1A1 activity, thereby implying some effects of fat on UGT1A1 catalysis.[40]

Free fatty acids in the neonatal blood may be derived from the mother because maternal circulating free fatty acids are directly transported across the placenta.[41] Hence, when the mother is obese, high levels of circulating maternal fats from the diet and/or liver dysfunction may drive more fat into the fetal compartment. Combined with the known lack of fetal and neonatal UGT1A1 activity this may predispose neonates of obese mothers to higher levels of unconjugated bilirubin, a hypothesis supported by our findings. [5,6,42]

It could be suggested that these results are primarily due to polymorphisms in the UGT1A1 gene because low-activity UGT1A1 polymorphisms in the population is common. A previous report has indicated that Pacific Islanders have a prevalence of 0 – 5% for the most common low-activity polymorphism of UGT1A1 UGT1A1*28;[24] however this depends on how "Pacific Islander" is defined. The referenced study contained Papua New Guineans, Fijians, and Tongans. Papua New Guinea and Fiji belong to Melanesia, while Tonga belongs to Polynesia. These two separate regions have a migratory heritage and founder effects that would be expected to give rise to differing genetic patterns.[43] Since our NHPI cohort was made up exclusively of Native Hawaiians, Tongans, and Samoans, the genetic basis for low-activity UGT1A1 is more correctly identified using the Tongan sub-sample of the report, where prevalence of UGT1A1*28 homozygous individuals was 2%. With such a low frequency (in all Pacific Islanders as well as specifically NHPI), and a sample size of 150, it is highly unlikely that the effects reported in the NHPI cohort are primarily due to polymorphisms. The finding of 12% maternal unconjugated hyperbilirubinemia in pregnant NHPI women and a significant positive correlation between

neonatal elevated unconjugated bilirubin and obesity indicates that a factor other than genetics is responsible. We contend that direct depletion of hepatic UGT1A1 proteins caused by obesity is one mechanism for this.

In Asians, the UGT1A1*28 allele is less common than in other ethnicities and different polymorphisms in the coding region (notably UGT1A1*6) occur with significant minor frequencies. The rate of UGT1A1*28 in Asians ranges 2%-3% and UGT1A1*6 around 3%, with both occurring together in less than 3% and having no linkage in their expression. Hence low rates of obesity in Asians, combined with low rates of genetic polymorphism are consistent with our findings of low levels of maternal and neonatal unconjugated hyperbilirubinemia.[23,30] Because the prevailing genetic theory is that NHPI are of Asian origin[43] and studies have shown similar prevalence of polymorphisms between the two ethnic groups,[24] it would be expected that they would show similar rates of hyperbilirubinemia if polymorphisms were responsible. However, this is the opposite of what was observed, with one critical physical difference between the Asian and NHPI cohorts being levels of obesity.

Cultural and socioeconomic characteristics of ethnic populations are also important. For example, lower educational attainment has been linked to increased BMI and waist circumference in NHPI.[44] Additionally, several environmental exposures including drugs, chemicals, and nutritional compounds have been demonstrated to inhibit UGT1A1.[45] While the current study cannot determine the effects of socio-economic, cultural, or environmental differences on the outcomes reported, all of these pregnant women and neonates came from the same isolated geographic location with a mixed, integrated population (Honolulu, Hawai'i, USA). This includes shared experiences such as commonalities in food, environmental exposures, access to healthcare and so on. Thus, these participants represent a more homogeneous sample than would be expected if they were from disparate geographic populations.

Conclusions

Obesity is a pan-global epidemic, and there is a need to better understand the downstream health consequences and mechanisms behind these in order to mitigate them. This study has demonstrated an association between obesity and elevated maternal and neonatal unconjugated bilirubin. Our findings are supported by a recent study where acute fatty liver in pregnancy was associated with elevated maternal unconjugated bilirubin.[32] We have also presented molecular and biochemical data that indicate that the relationship between morbid obesity and hyperbilirubinemia is mediated through a depletion of UGT1A1 proteins. However, further investigation is warranted to illuminate the significance of these findings. As a pilot study with a limited number of individuals (only 150 individuals per ethnicity), this project provides promising avenues for further investigation, including the inclusion of laboratory tests for the type of hyperbilirubinemia in both the mother and the neonate. Power analyses have revealed that a future study with sample size of 3000 individuals (1000 for each ethnicity) and inclusive of both serum bilirubin, liver enzyme and tests for the diseases (such as UGT1A1 polymorphisms or ABCC2 transporter levels) combined with multivariate analyses will elucidate these findings in greater detail.

These findings are particularly relevant to the developed world with respect to midwifery and non-hospital obstetric care. For example in rural and remote settings in North America, as well as in Europe, Australia and New Zealand, midwives are increasingly responsible for primary obstetric care and for decisions regarding neonatal hospital transfer.[46,47] Additionally, for premature infants requiring parenteral nutrition, jaundice is a real concern. In the developing world, up to 3% of neonatal hospital admissions are caused by bilirubin encephalopathy, in large part due to resource-poor settings.[48] Increased vigilance and preparedness at delivery for jaundiced neonates of obese, pregnant mothers can hasten decisions regarding medical treatment, including transfer of neonates to hospital from non-hospital births. Targeting and optimizing healthcare resources in an ever more obese population is critical to promote optimal obstetric care and neonatal outcomes.

Conflict of Interest

None of the authors identify any conflict of interest.

Disclosure Statement

These studies were funded in part by NIH GM024206 and G12 MD007601 (to Abby Collier) and a U54 MD007584 Pilot Grant to Luc Rougée. Granting bodies provided funding for research only and did not influence design, experiments, data interpretation or publishing.

Authors' Affiliations:
- Department of Tropical Medicine, Medical Microbiology and Pharmacology; John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (LRAR, SJM, ACC)
- Faculty of Pharmaceutical Sciences, University of British Columbia, 6609-2405 Wesbrook Mall, Vancouver, BC V6T1Z3, CANADA (ACC)

Correspondence to:
Abby C. Collier PhD; UBC Pharmaceutical Sciences, 2405 Wesbrook Mall, Vancouver, BC V6T 1Z3, Canada; Email: abby.collier@ubc.ca

References

1. Galtier-Dereure F, Boegner C, Bringer J. Obesity and pregnancy: complications and cost. *Am J Clin Nutr.* May 2000;71(5 Suppl):1242S-1248S.
2. Riches ZC, AC. Posttranscriptional regulation of uridine diphosphate glucuronosyltransferases. *Exp Opin Drug Metab Toxicol.* 2015;11(6):949-965.
3. Ohno SN, S. Determination of mRNA expression of human UDP-glucuronosyltransferases and application for localization in various human tissues by real-time reverse transcriptase-polymerase chain reaction. *Drug Metab Dispos.* 2009;37(1):32-40.
4. Guillemette C. Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. *Pharmacogenomics J.* 2003;3(3):136-158.
5. Burchell B, Coughtrie M, Jackson M, et al. Development of human liver UDP-glucuronosyltransferases. *Dev Pharmacol Ther.* 1989;13(2-4):70-77.
6. Kawade N, Onishi S. The prenatal and postnatal development of UDP-glucuronyltransferase activity towards bilirubin and the effect of premature birth on this activity in the human liver. *Biochem. J.* Apr 15, 1981 1981;196(1):257-260.
7. Miyagi SJ, Collier AC. The development of UDP-glucuronosyltransferases 1A1 and 1A6 in the pediatric liver. *Drug Metab Dispos.* May 2011;39(5):912-919.
8. Collier A, Ganley N, Tingle M, et al. UDP-glucuronosyltransferase activity, expression and cellular localization in human placenta at term. *Biochem Pharmacol.* 2002;63(3):409-419.
9. Collier A, Tingle M, Paxton J, Mitchell M, Keelan J. Metabolizing enzyme localization and activities in the first trimester human placenta: the effect of maternal and gestational age, smoking and alcohol consumption. *Hum Reprod.* 2002;17(10):2564-2572.
10. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Glucuronidation in humans. Pharmacogenetic and developmental aspects. *Clin Pharmacokinet.* 1999;36(6):439-452.
11. Tiribelli C, Ostrow JD. The molecular basis of bilirubin encephalopathy and toxicity: report of an EASL Single Topic Conference, Trieste, Italy, 1-2 October, 2004. *J Hepatol.* 2005;43(1):156-166.
12. Maimburg RD, Bech BH, Vaeth M, Moller-Madsen B, Olsen J. Neonatal jaundice, autism, and other disorders of psychological development. *Pediatrics.* 2010;126(5):872-878.
13. Watchko JF, Tiribelli C. Bilirubin-induced neurologic damage--mechanisms and management approaches. *N Engl J Med.* 2013;369(21):2021-2030.
14. Hegde D, Jasani B, Mutha S. Bilirubin-induced neurologic damage. *N Engl J Med.* 2014;370(10):978-979.
15. Hughes RG, Lawrence MA. Globalization, food and health in Pacific Island countries. *Asia Pac J Clin Nutr.* 2005;14(4):298-306.
16. McEligot AJ, McMullin J, Pang K, et al. Diet, psychosocial factors related to diet and exercise, and cardiometabolic conditions in Southern Californian Native Hawaiians. *Hawaii Med J.* 2010;69(5 Suppl 2):16-20.
17. Bryant AS, Worjoloh A, Caughey AB, Washington AE. Racial/ethnic disparities in obstetric outcomes and care: prevalence and determinants. *Am J Obstet Gynecol.* 2010;202(4):335-343.
18. Rao AK, Daniels K, El-Sayed YY, Moshesh MK, Caughey AB. Perinatal outcomes among Asian American and Pacific Islander women. *Am J Obstet Gynecol.* 2006;195(3):834-838.
19. Dixon L, Andrews A, Eddy A, Guilliland K, Hendry C, J. H. Changing trends in pregnancy registration for New Zealand women. *J Prim Health Care.* 2014;6(4):279-285.
20. Makowharemahihi C, Lawton BA, Cram F, Ngata T, Brown S, B R. Initiation of maternity care for young Maori women under 20 years of age. *NZ Med J.* 2014;127(1393):52-61.
21. Ghose RO, O.; Gandhi, A.; Shah, P.; Strohacker, K.; Carpenter, KC.; McFarlin, B.; Guo, T. Role of high-fat diet in regulation of gene expression of drug metabolizing enzymes and transporters. *Life Sci.* 2011;89(1-2):57-64.
22. Shah PG, A.; Romi, Ghose. Altered irinotecan pharmacokinetics in diet-induced obesity (1052.6). *FASEB J.* 2014;28(1 Supplement):1052.1056.
23. Kurose K, Sugiyama E, Saito Y. Population differences in major functional polymorphisms of pharmacokinetics/pharmacodynamics-related genes in Eastern Asians and Europeans: implications in the clinical trials for novel drug development. *Drug Metab Pharmacokinet.* 2012;27(1):9-54.
24. Premawardhena A, Fisher CA, Liu YT, et al. The global distribution of length polymorphisms of the promoters of the glucuronosyltransferase 1 gene (UGT1A1): hematologic and evolutionary implications. *Blood Cells Mol Dis.* 2003;31(1):98-101.
25. Abel G, Palmor-Toy D. Heme synthesis and catabolism. In: McClatchey KD, ed. *Clinical Laboratory Medicine*. 2 ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:407-417.
26. Heirwegh KVdV, M.; Fevery, J. Assay and properties of dititonin-activated bilirubin uridine diphosphate glucuronyltransferase from rat liver. *Biochem J.* 1972;129:605–618.
27. Houston J. Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance. *Biochem Pharmacol.* 1994;47(1469–1479).
28. Ostrow J, Pascolo L, Shapiro S, C CT. New concepts in bilirubin encephalopathy. *Eu J Clin Invest.* 2003;33(988–997).
29. Ciotti M, Cho J, George J, Owens I. Required buried alpha-helical structure in the bilirubin UDP-glucuronosyltransferase, UGT1A1, contains a nonreplaceable phenylalanine. *Biochemistry.* 1998;37(11018–11025).
30. Fukui T, Mitsufuji H, Kubota M, et al. Prevalence of topoisomerase I genetic mutations and UGT1A1 polymorphisms associated with irinotecan in individuals of Asian descent. *Oncol Lett.* 2011;2(5):923-928.
31. Than N, Neuberger J. Liver abnormalities in pregnancy. *Best Pract Res Clin Gastroenterol.* 2013;27(4):565-575.
32. Nelson D, Yost N, Cunningham F. Hemostatic dysfunction with acute fatty liver of pregnancy. *Obstet Gynecol.* 2014;124(1):40-46.
33. Jedlitschky G, Hoffmann U, Kroemer H. Structure and function of the MRP2 (ABCC2) protein and its role in drug disposition. *Expert Opin Drug Metab Toxicol.* 2006;2(3):351-366.
34. Pascolo L, Fernetti C, Garcia-Mediavilla M, Ostrow J, Tiribelli C. Mechanisms for the transport of unconjugated bilirubin in human trophoblastic BeWo cells. *FEBS Lett.* 2001;495(1-2):94-99.
35. Sikkel E, Pasman S, Oepkes D, Kanhai H, Vandenbussche F. On the origin of amniotic fluid bilirubin. *Placenta.* 2004;25(5):463-468.
36. Hegyi T, Kathiravan S, Stahl GE, Huber AH, Kleinfeld A. Unbound free fatty acids from preterm infants treated with intralipid decouples unbound from total bilirubin potentially making phototherapy ineffective. *Neonatology.* 2013;104(3):184-187.
37. Kerner JA, Jr., Poole RL. The use of IV fat in neonates. *Nutr Clin Pract.* Aug 2006;21(4):374-380.
38. Tsoutsikos P, Miners J, Stapleton A, Thomas A, Sallustio B, Knights K. Evidence that unsaturated fatty acids are potent inhibitors of renal UDP-glucuronosyltransferases (UGT): kinetic studies using human kidney cortical microsomes and recombinant UGT1A9 and UGT2B7. *Biochem Pharmacol.* 2004;67(1):191-199.
39. Wattanachai N, Tassaneeyakul W, Rowland A, et al. Effect of albumin on human liver microsomal and recombinant CYP1A2 activities: impact on in vitro-in vivo extrapolation of drug clearance. *Drug Metab Dispos.* 2012;40(5):982-989.
40. Rowland A, Knights K, Mackenzie P, Miners J. The "albumin effect" and drug glucuronidation: bovine serum albumin and fatty acid-free human serum albumin enhance the glucuronidation of UDP-glucuronosyltransferase (UGT) 1A9 substrates but not UGT1A1 and UGT1A6 activities. *Drug Metab Dispos.* 2008;36(6):1056-1062.
41. Herrera E. Implications of dietary fatty acids during pregnancy on placental, fetal and postnatal development--a review. *Placenta.* 2002;23(Suppl A):S9-19.
42. Coughtrie M, Burchell B, Leakey J, Hume R. The inadequacy of perinatal glucuronidation: immunoblot analysis of the developmental expression of individual UDP-glucuronosyltransferase isoenzymes in rat and human liver microsomes. *Mol Pharmacol* 1988;34(6):729-735.
43. Kayser M, Brauer S, Weiss G, et al. Melanesian origin of Polynesian Y chromosomes. . *Current Biology.* 2000;10(20):1237–1246.
44. Brown DE, Hampson SE, Dubanoski JP, Murai AS, Hillier TA. Effects of ethnicity and socioeconomic status on body composition in an admixed, multiethnic population in Hawaii. *Am J Hum Biol.* 2009;21(3):383-388.
45. Chang J, Plise E, Cheong J, Ho Q, Lin M. Evaluating the in vitro inhibition of UGT1A1, OATP1B1, OATP1B3, MRP2, and BSEP in predicting drug-induced hyperbilirubinemia. *Mol Pharmaceut.* 2013;10(8):3067-3075.
46. de Jonge A, de Vries R, Lagro-Janssen AL, et al. The importance of evaluating primary midwifery care for improving the health of women and infants. *Front Med (Lausanne).* 2015;2:17.
47. Patterson J, Skinner J, Foreur M. Midwives' decision making about transfers for 'slow' labour in rural New Zealand. *Midwifery.* 2015; 31(6):606-12.
48. Ogunlesi TA, Dedeke IO, Adekanmbi AF, Fetuga MB, Ogunfowora OB. The incidence and outcome of bilirubin encephalopathy in Nigeria: a bi-centre study. *Niger J Med.* 2007;16(4):354-359.

Impact of Helmet Use on Injury and Financial Burden of Motorcycle and Moped Crashes in Hawai'i: Analysis of a Linked Statewide Database

Daniel J. Galanis PhD; Nikki A. Castel BS; Linda L. Wong MD; and Susan Steinemann MD

Abstract

Helmet use reduces injury severity, disability, hospital length of stay, and hospital charges in motorcycle riders. The public absorbs billions of dollars annually in hospital charges for unhelmeted, uninsured motorcycle riders. We sought to quantify, on a statewide level, the healthcare burden of unhelmeted motorcycle and moped riders. We examined 1,965 emergency medical service (EMS) reports from motorcycle and moped crashes in Hawai'i between 2007-2009. EMS records were linked to hospital medical records to assess associations between vehicle type, helmet use, medical charges, diagnoses, and final disposition. Unhelmeted riders of either type of vehicle suffered more head injuries, especially skull fractures (adjusted odds ratio (OR) of 4.48, P < .001, compared to helmeted riders). Motorcyclists without helmets were nearly three times more likely to die (adjusted OR 2.85, P = .001). Average medical charges were almost 50% higher for unhelmeted motorcycle and moped riders, with a significant (P = .006) difference between helmeted ($27,176) and unhelmeted ($40,217) motorcycle riders. Unhelmeted riders were twice as likely to self-pay (19.3%, versus 9.8% of helmeted riders), and more likely to have Medicaid or a similar income-qualifying insurance plan (13.5% versus 5.0%, respectively). Protective associations with helmet use are stronger among motorcyclists than moped riders, suggesting the protective effect is augmented in higher speed crashes. The public financial burden is higher from unhelmeted riders who sustain more severe injuries and are less likely to be insured.

Keywords

Helmet, Motorcycle, Moped, Hospital charges, Insurance

Introduction

Helmet use is an important factor in mitigating the severity of injuries from motorcycle crashes. Unhelmeted riders are more likely to have head injuries and are 3-4 times more likely to die.[1-9] In addition, unhelmeted motorcycle riders sustain more severe injuries, suffer greater disability, require longer hospital stays, and incur higher hospital charges.[2,3] Nineteen states have adopted universal motorcycle helmet laws, saving an average of $6,000 in health care costs per motorcyclist.[4] The state of Hawai'i requires helmet use only in motorcycle and moped operators and passengers under the age of 18 and prohibits passengers under the age of 7.[10]

Data specific to moped crashes and injuries are scarce and are often combined with motorcycle data. However, there are known differences in demographics and injury patterns for moped crashes. Moped riders have a higher incidence of alcohol use.[11,12] Moped crashes occur at lower speeds,[13] and riders are therefore less susceptible to serious extremity injury.[14] States have variable requirements for registration, operation, insurance, and helmet use for moped drivers. However, given the paucity of studies focused on moped riders, it is not clear if the regulations governing moped operation are well aligned with the risks of injury and liability.

This report examines moped and motorcycle riders in Hawai'i requiring medical attention at a hospital for an injury. This subset of a larger previously published sample[1] allows for a more detailed description of hospital diagnoses, charges, and principal source of payment for helmeted versus unhelmeted riders and emphasizes the public health implications of helmet usage. Diverse statewide datasets that link inpatient information with pre-hospital parameters allow us to uniquely quantify the protective effects of helmet use across the spectrum of motorcycle and moped crashes.

Methods

Emergency Medical Service Reports

This study is based on patient care reports (PCRs) from Hawai'i emergency medical service (EMS) providers from 2007 to 2009. All Hawai'i EMS providers complete PCRs electronically with standardized input screens. Discrete fields describe vehicle type (motorcycle or moped), helmet use, demographic variables, patient disposition, and a free-text space to record a narrative of the incident. All 2,923 EMS records for injured motorcyclists or moped riders over the 3-year period were reviewed. A total of 287 records were excluded from further analysis because they were related to off-road or non-traffic crashes (n = 150), riders of all-terrain vehicles (n = 77), or documented a patient transfer to another EMS unit (n = 60). Another 83 records were excluded due to unknown helmet status, resulting in records from 2,553 riders, 75% of whom (1,913) were transported to hospitals by EMS for further medical attention.

Linkage to Hospital Records

The Hawai'i Health Information Corporation (HHIC) linked EMS records to hospital records for both emergency department (ED) visits and hospitalizations. HHIC is a non-profit organization which maintains a repository of billing data abstracts for the medical records of all acute care hospitals in the state, with the exception of the ED records of one facility on the island of O'ahu.[15] Linkage of EMS records to HHIC records was accomplished deterministically, using patient name, date of birth, date of crash, and location of crash. Since HHIC maintains a master patient identifier, the definitive patient disposition and cumulative medical charges were available for patients who were transferred between hospitals in the state. Charges include those for room and board, pharmacy, laboratory, X-ray and hospital-based physician charges. Some analyses utilize a threshold of $25,000 in medical charges, to indicate treatments resulting in relatively high medical charges; $25,000

represented the 77th percentile of the distribution of medical charges. The principal source of payment was categorized into groups of interest. Payment from automobile insurance plans was considered "private insurance."

Hospital records were linked to 1,783 (93.2%) of the 1,913 transported by EMS to hospitals, leaving 130 records that could not be linked to HHIC data. These 130 patients were significantly younger than the 1,783 linked to HHIC data (33.3 versus 36.2 years, respectively, $P = .026$), and there was a higher prevalence of helmet use among motorcyclists (67.4% versus 50.0%, respectively, $P = .002$. Pre-hospital condition, as characterized by EMS personnel, was generally better among the 130 unlinked riders. Only 1.5% were in "critical" condition (indicating unstable vital signs and level of consciousness), compared to 7.8% of the other riders ($P = .01$). Patient condition was more likely to be "serious" (stable vital signs but impending deterioration) among the latter (60.9%), compared to the 130 unlinked riders (41.5%, $P < .001$). Data from these 130 riders were excluded from further analyses. Hospital records were available for another 182 riders who refused transport by EMS, but made their own way to hospitals, resulting in a final study sample size of 1,965 records.

HHIC data was used to define injury categories, using the principal diagnosis by ICD9-CM code: fractures (ICD9-CM code series 800-829), skull fractures (800-804), dislocations (830-839), sprains and strains (840-848), internal injuries (850-869), intracranial injury without skull fracture (850-854), open wounds (870-897), contusions and superficial injuries (910-924), as well as other injuries and non-injuries (ICD9-CM code less than 800). Traumatic brain injury (TBI) and spinal cord injuries were identified using the code series recommended by the CDC.[16] A category of "head injury" was also constructed, using the Barell Matrix.[17] HHIC data identified 62 patients who eventually died from their injuries, and all deaths were confirmed through linkage with the Hawai'i Department of Health's death certificate database.

Statistical Analysis

All statistical analyses for this report were performed using JMP software, version 5.[18] Differences in the distributions of categorical variables were tested using differences in proportions, while differences in the means of continuous variables were assessed by 2-tailed t-tests. Differences described as "significant" had an associated P value of less than .05. For multivariate logistic regression analyses, rider age was categorized into 4 groups: those 25 years and younger (referent group), 26 to 35 years, 36 to 54 years, and 55 years and older. Helmet status was dichotomized, with helmeted riders as the referent group. Our previous study[1] showed the associations between helmet use and injury outcomes varied considerably between motorcycle and moped riders, so all of the analyses included stratification by vehicle type. Study procedures were approved by the Hawai'i Department of Health's Institutional Review Board.

Results

Demographics

The mean age of the 1,965 patients was 35.9 years (SD 14.3 years) (Table 1). Helmeted motorcyclists were younger than unhelmeted motorcyclists on average (34.8 vs 39.0 years, $P < .001$), while helmeted moped riders were older than unhelmeted moped riders (average 37.9 vs 34.2 years, $P = .017$).

Motorcycle riders were more likely to be male (87.2%) compared to moped riders (70.0%, $P < .001$). Overall, helmet use was significantly less common among female riders (25.6%) compared to male riders (34.6%, $P = .001$). However, this association differed across vehicle types. In moped riders, helmet usage in females was significantly higher than in males (15.2% vs 9.8%, $P = .027$), but was comparable among motorcyclists (45.3% for females vs. 50.7% for males). About two-thirds of all riders were not wearing a helmet at the time of the crash. This proportion was significantly higher among moped riders (88.6%) than motorcyclists (50%, $P < .001$).

Motorcyclists were more likely to be Hawai'i residents (89.6%) compared to moped riders (77.8%, $P < .001$). Hawai'i residents were more likely to wear helmets (33.8%) compared to non-residents (27.4%, $P = .027$).

Insurance

Overall, the most common principal payer was private insurance (60.8% of patients), followed by self-pay (16.2%), income-qualifying insurance (such as Medicaid, QUEST) (10.7%), and Department of Defense (8.0%). The proportion of riders who did not utilize an insurance payer (ie, self-pay) was nearly double among unhelmeted riders (19.3%), compared to helmeted riders (9.8%, $P < .001$). The latter were also significantly less likely to have income qualifying insurance as their principle source of payment (5.0%), compared to unhelmeted riders (13.5%, $P < .001$), and more likely to have policies under the Department of Defense (17.7% versus 3.35%, respectively, $P < .001$). These differences in payer mix between helmeted and unhelmeted riders were also evident within the strata of motorcycle and moped riders.

Disposition and Pattern of Injury

Moped riders were more likely to be discharged from the ED, whereas motorcyclists were significantly more likely to be hospitalized (40.7% vs 28.4%, $P < .001$) or die (4.7% vs 1.3%, $P < .001$). There were no significant differences in the distribution of final medical disposition between helmeted and unhelmeted moped riders (Table 2). Among motorcyclists, however, unhelmeted riders were significantly more likely to be admitted to the hospital (44.1%), compared to helmeted motorcyclists (37.3%, $P = .02$), or to ultimately die (7.0% versus 2.4%, respectively, $P = .001$).

When principal diagnoses were reviewed, the incidence of fractures was statistically comparable between helmeted and unhelmeted riders of both vehicle types. However, the incidence of skull fractures was nearly 3 times greater for unhelmeted moped riders, and more than 6 times greater for unhelmeted motorcyclists.

Table 1. Demographic characteristics of motorcycle/moped riders injured in traffic crashes in Hawai'i, by helmet usage, 2007-2009			
	Helmeted	**Unhelmeted**	**Total**
All riders, n (%)	644 (32.8%)	1,321 (67.2%)	1,965
Age, mean (SD), y	35.3 (14.2)	36.2 (14.3)	35.9 (14.3)
Sex, n (%)			
Male	541 (84.0%)	1,022 (77.4%)*	1,563 (79.5%)
Female	103 (16.0%)	299 (22.6%)*	402 (20.5%)
Residence status, n (%)			
Hawai'i resident	559 (86.8%)	1,095 (82.9%)*	1,654 (84.3%)
Non-resident	84 (13.0%)	223 (16.9%)*	307 (15.6%)
Unknown	1 (0.2%)	3 (0.2%)	4 (0.2%)
Principal payer, n (%)			
Dept. of Defense	114 (17.7%)	44 (3.3%)*	158 (8.0%)
Private insurance	404 (62.7%)	791 (59.9%)	1,195 (60.8%)
Income-qualifying/Medicaid	32 (5.0%)	178 (13.5%)*	210 (10.7%)
Self-pay	63 (9.8%)	255 (19.3%)*	318 (16.2%)
Other	31 (4.8%)	53 (4.0%)	84 (4.3%)
Motorcycle riders, n (%)	544	544	1,088
Age, mean (SD), y	34.8 (13.7)	39.0 (13.8)*	36.9 (13.9)
Sex, n (%)			
Male	481 (88.4%)	468 (86.0%)	949 (87.2%)
Female	63 (11.6%)	76 (14.0%)	139 (12.8%)
Residence status, n (%)			
Hawai'i resident	475 (87.3%)	499 (91.7%)*	974 (89.6%)
Non-resident	68 (12.5%)	45 (8.3%)*	113 (10.4%)
Unknown	1 (0.2%)	0	1 (0.1%)
Principal payer, n (%)			
Dept. of Defense	108 (19.9%)	26 (4.8%)*	134 (12.3%)
Private insurance	339 (62.3%)	341 (62.7%)	680 (62.5%)
Income-qualifying/Medicaid	27 (5.0%)	71 (13.1%)*	98 (9.0%)
Self-pay	46 (8.5%)	86 (15.8%)*	132 (12.1%)
Other	24 (4.4%)	20 (3.7%)	44 (4.0%)
Moped riders, n (%)	100	777	877
Age, mean (SD), y	37.9 (16.7)	34.2 (14.3)	34.6 (14.6)
Sex, n (%)			
Male	60 (60%)	554 (71.3%)*	614 (70.0%)
Female	40 (40%)	223 (27.7%)*	263 (30.0%)
Residence status, n (%)			
Hawai'i resident	84 (84%)	596 (76.7%)	680 (77.8%)
Non-resident	16 (16%)	178 (22.9%)	194 (22.1%)
Unknown	0	3 (0.4%)	3 (0.3%)
Principal payer, n (%)			
Dept. of Defense	6 (6.0%)	18 (2.3%)*	24 (2.7%)
Private insurance	65 (65.0%)	450 (57.9%)	515 (58.7%)
Income-qualifying/Medicaid	5 (5.0%)	107 (13.8%)*	112 (12.8%)
Self-pay	17 (17.0%)	169 (21.8%)	186 (21.2%)
Other	7 (7.0%)	33 (4.3%)	40 (4.6%)

*Indicates statistically significant difference ($P < .05$), compared to helmeted riders.

Table 2. Disposition and injury-related diagnoses of motorcycle and moped riders in Hawai'i, by vehicle type and helmet usage, 2007-2009				
	Moped riders		Motorcyclists	
	Helmeted (n=100)	Unhelmeted (n=777)	Helmeted (n=544)	Unhelmeted (n=544)
Disposition				
discharged from ED	75 (75.0%)	542 (69.8%)	328 (60.3%)	266 (48.9%)*
admitted to hospital	24 (24.0%)	225 (29.0%)	203 (37.3%)	240 (44.1%)*
died	1 (1.0%)	10 (1.3%)	13 (2.4%)	38 (7.0%)*
Principal diagnosis				
fractures	23 (23.0%)	250 (32.2%)	193 (35.5%)	217 (39.9%)
fracture of skull	3 (3.0%)	69 (8.9%)*	10 (1.8%)	64 (11.8%)*
dislocations	1 (1.0%)	15 (1.9%)	12 (2.2%)	9 (1.7%)
sprains and strains	8 (8.0%)	41 (5.3%)	40 (7.4%)	17 (3.1%)*
internal	14 (14.0%)	110 (14.2%)	86 (15.8%)	81 (14.9%)
intracranial (no skull fracture)	14 (14.0%)	95 (12.2%)	48 (8.8%)	68 (12.5%)*
open wound	16 (16.0%)	140 (18.0%)	42 (7.7%)	63 (11.6%)*
contusion/superficial	29 (29.0%)	157 (20.2%)*	122 (22.4%)	91 (16.7%)*
other/unspecified injury	5 (5.0%)	42 (5.4%)	34 (6.3%)	34 (6.3%)
non-injury	4 (4.0%)	22 (2.8%)	14 (2.6%)	28 (5.2%)*
Any diagnosis				
any head injury	35 (35.0%)	392 (50.5%)*	127 (23.4%)	291 (53.5%)*
fracture of skull	7 (7.0%)	103 (13.3%)	19 (3.5%)	92 (16.9%)*
intracranial (no skull fracture)	18 (18.0%)	161 (20.7%)	81 (14.9%)	126 (23.2%)*
concussion	12 (12.0%)	121 (15.6%)	69 (12.7%)	85 (15.6%)
open wound	17 (17.0%)	225 (29.0%)*	30 (5.5%)	169 (31.0%)*
contusion/superficial	1 (1.0%)	9 (1.2%)	1 (0.2%)	10 (1.8%)*
traumatic brain injury	22 (22.0%)	273 (35.1%)*	115 (21.1%)	225 (41.4%)*
spinal cord injury	1 (1.0%)	3 (0.4%)	5 (0.9%)	6 (1.1%)

*Indicates statistically significant ($P < .05$) difference in proportion, compared to helmeted riders, within each vehicle type.

When all diagnoses were considered, the risk for any type of head injury was significantly higher for unhelmeted riders of either type of vehicle. Approximately half of the unhelmeted motorcycle (53.5%) or moped riders (50.5%) sustained a head injury, compared to 35.0% of the helmeted moped riders and 23.4% of the helmeted motorcycle riders. The incidence of traumatic brain injury (TBI), which includes the spectrum from concussion to intracranial hemorrhage, was also significantly higher among unhelmeted riders of either type of vehicle. For moped riders, the incidence of TBI among unhelmeted riders was 60% higher (35.1% versus 22.0% for helmeted riders, $P = .009$). For motorcyclists, the incidence was nearly double (41.4% versus 21.1% for helmeted riders, $P < .001$).

Charges

Average medical charges were approximately 50% higher for unhelmeted riders of both vehicle types (Table 3). More than one-third (35.1%) of medical charges to unhelmeted motorcyclists were paid by income-qualifying plans or self-pay, compared to only 13.7% of the charges to helmeted motorcyclists. Medical charges among unhelmeted moped riders were also more likely to be paid by income-qualifying plans or self-pay, compared to helmeted riders (37.9% vs 15.2%, respectively).

Approximately one-quarter (23.3%) of the 1,965 riders had medical charges of $25,000 or more, although this proportion was significantly higher among motorcyclists (28.5%) than moped riders (16.9%, $P < .001$). Unhelmeted motorcyclists were almost 50%, and unhelmeted moped riders almost 40%, more likely to incur $25,000 or more in total charges compared to helmeted riders (Table 3). Unhelmeted riders were about 3 times as likely to have an income-qualifying plan as the principal source of payment for these higher charge totals. They were also more likely to self-pay. As a result, unhelmeted riders in both motorcycles and mopeds had more than double the incidence of accruing $25,000 or more in total charges, combined with an income-qualifying payer plan or self-pay status.

Adjusted Outcomes

After controlling for age and gender by multivariate logistic regression, unhelmeted motorcycle riders had significantly higher odds of hospital admission (1.54, $P = .001$), and nearly three times the odds of a fatal injury (2.85, $P = .001$), compared

Table 3. Total charges for injured motorcycle and moped riders in Hawai'i, by vehicle type and helmet usage, 2007-2009				
	Moped riders		Motorcyclists	
	helmeted (n=100)	unhelmeted (n=777)	helmeted (n=544)	unhelmeted (n=544)
Total charges	$1,411,877	$16,382,380	$14,783,792	$21,878,109
Average charges	$14,119	$21,084	$27,176	$40,217*
Percent of charges, by principal payer category (average amount[a])				
Private insurance	76.1% ($10,747)	52.9% ($11,150)	62.2% ($16,896)	57.6% ($23,149)
Dept. of Defense	3.6% ($506)	1.7% ($351)	20.3% ($5,508)	3.1% ($1,254)
Medicaid/QUEST	1.2% ($167)	20.6% ($4,333)	6.8% ($1,841)	18.1% ($7,264)
Self-Pay	14.0% ($1,978)	17.3% ($3,652)	6.9% ($1,869)	17.0% ($6,829)
Other**	5.1% ($721)	7.6% ($1,597)	3.9% ($1,062)	4.3% ($1,720)
Charges of $25,000 or more	12 (12.0%)	136 (17.5%)	132 (24.3%)	178 (32.7%)*
Medicaid/QUEST	0	17 (2.2%)	13 (2.4%)	28 (5.2%)*
Self-Pay	3 (3.0%)	32 (4.1%)	12 (2.2%)	29 (5.3%)*
Medicaid/QUEST or Self-Pay	3 (3.0%)	49 (6.3%)	25 (4.6%)	57 (10.5%)*

[a]Calculated by multiplying the average charge by the proportion associated with each payer category. Example for helmeted moped riders with private insurance: $14,119 multiplied by 76.1% equals $10,747. *Indicates statistically significant ($P < .05$) difference in proportion, compared to helmeted riders, within each vehicle type. **Other includes Medicare or similar, and person's with worker's compensation.

Table 4. Adjusted* odds ratios for adverse medical and financial outcomes among unhelmeted motorcycle and moped riders in Hawai'i, by vehicle type, 2007-2009 (95% confidence interval given in parenthesis)			
Adverse outcome	**Moped riders**	**Motorcyclists**	**Total**
Final disposition			
Hospital admission or death	1.3 (0.8-2.1)	1.5 (1.2-2.0)	1.5 (1.2-1.9)
Death	1.0 (0.2-18.4)	2.9 (1.5-5.7)	2.8 (1.6-5.4)
Injury-related diagnoses			
TBI, any diagnosis	1.8 (1.1-3.1)	2.8 (2.1-3.6)	2.5 (2.0-3.2)
Skull fracture, any diagnosis	1.9 (0.9-4.7)	5.7 (3.5-9.8)	4.5 (2.9-7.1)
Head injury, any diagnosis	1.9 (1.2-2.9)	3.9 (3.0-5.1)	3.2 (2.5-4.0)
Total charges and principal source of payment			
Charges of $25,000 or more	1.6 (0.9-3.1)	1.5 (1.1-2.0)	1.5 (1.2-1.9)
Charges of $25,000 or more, and income qualifying or self-pay	2.1 (0.7-8.6)	2.4 (1.5-4.0)	2.4 (1.5-3.8)
Income qualifying payer	3.0 (1.3-8.6)	3.1 (2.0-5.1)	3.0 (2.0-4.6)
Self-pay	1.3 (0.8-2.3)	2.1 (1.5-3.1)	1.9 (1.4-2.6)
Income qualifying or self-pay	1.9 (1.2-3.1)	2.8 (2.1-3.9)	2.5 (1.9-3.3)

*All models adjusted for rider age and gender. Models for the total sample additionally adjusted for rider type (motorcyclist or moped rider). Helmeted riders served as the reference group with an odds ratio set to 1.0.

to helmeted riders (Table 4). There were no significant differences in either hospital admission or risk of fatal injury among moped riders.

Unhelmeted riders had significantly higher odds of TBI (2.49, $P < .001$), skull fracture (4.48, $P < .001$), or any head injury (3.18, $P < .001$), compared to helmeted riders, independent of age or gender. The disparity in outcomes was greater among motorcyclists, although unhelmeted moped riders also had significantly higher odds of TBI or head injury, compared to helmeted moped riders. Similar associations were found if only the principal diagnosis was considered.

The odds of incurring $25,000 or more in total charges were nearly 50% higher among unhelmeted motorcyclists, compared to helmeted riders. The former were also about 3 times as likely to have an income-qualifying plan as principal source of payment and twice as likely to self-pay. As a result, unhelmeted motorcyclists had more than twice the odds (2.82, $P < .001$) of accruing $25,000 or more in total charges, combined with an income-qualifying plan or self-pay as the principal source of payment.

Discussion

Multiple prior studies have characterized motorcycle and moped crashes, but few have compared and contrasted outcomes by vehicle type. Patient outcomes might be predicted to be different, as other investigators have reported differences between the populations of moped versus motorcycle riders. Matzch, et al, noted older age and a higher proportion of females in moped compared to motorcycle accidents.[19] Similarly, our study showed a higher percentage of females in moped crashes (30% versus 13% of motorcyclists) but no difference in age between the two groups. Others have identified operator factors associated with lethal moped crashes. Alcohol use is prevalent, with rider blood levels above the legal limit at the time of injury in up to 49% of lethal crashes.[11,12,20]

This study confirms the deleterious associations between non-use of helmets and adverse medical dispositions of injured riders. McSwain, et al, studied motorcycle riders from twelve states and five countries to show that the fatality rate was almost four times higher in unhelmeted compared to helmeted riders.[9] Braddock, et al, in 2,361 hospital discharges and 112 deaths from motorcycle accidents, revealed that non-helmeted motorcycle riders were 3.4 times more likely to die than helmeted riders.[21] While many studies report the injuries and fatality of motorcycle riders, no known study compares the impact of helmet use in motorcycle vs moped riders. Similar to motorcyclists, our data demonstrates that helmets have a significant protective effect for moped riders, with nearly a two-fold lower risk of overall head injury and TBI, and a three-fold lower risk of skull fractures.

An increase in skull fractures and head injuries in unhelmeted riders ultimately results in longer hospitalizations, greater disability, and increased cost. This has been well documented for motorcyclists, with acute care hospital charges for unhelmeted riders up to three times higher than helmeted riders.[3] Orsay, et al, in a study of 1,231 motorcycle riders, demonstrated that unhelmeted motorcycle riders were more likely to sustain serious head-related injuries, which resulted in longer ICU stay and a three-fold increase in hospital charges.[22] Max, et al, studied 11,163 motorcycle injuries and found patients with head injuries averaged $18,527 in hospital costs, compared to $10,350 in patients without head injuries.[23] Belavadi, et al, studied 1,900 motorcycle accidents. Acute care costs for unhelmeted motorcycle riders was three times that of a helmeted rider.[24] Our study confirmed that average hospital charges for unhelmeted riders (both moped and motorcycle) were approximately 50% higher than for helmeted riders. Importantly, these increased charges were seen to the same extent in unhelmeted moped as well as motorcycle riders.

The economic and social impact of the increased rate of TBI in unhelmeted riders (35% of moped and 41% of motorcyclists) may be underestimated if we consider only direct acute care medical charges. Compared to thoraco-abdominal and extremity injuries, TBI may have prolonged disability, incomplete recovery, and diminished performance status or ability to return to work. The disability and loss of productivity may go unrecognized and undocumented, particularly in a patient population that is underinsured and does not seek regular medical care.

The direct cost of crashes involving unhelmeted riders is borne disproportionately by the taxpaying public. Nationwide, state governments absorb nearly $5 billion in hospitalization for unhelmeted riders without medical insurance.[9] Riders in Hawai‘i had a similarly unfavorable distribution of principal insurance policies: one-third used income qualifying plans or self-pay, compared to only 15% of helmeted riders. These outcomes have important implications when considering the public burden in caring for injured unhelmeted riders. For example, unhelmeted motorcyclists accounted for 79% of the $3.2 million average annual medical charges associated with income qualifying insurance plans or self-payment, although they made up only 50% of injured motorcyclists in Hawai‘i.

Conclusions

In summary, motorcycle riders are almost 50% more likely than moped riders to be hospitalized, and over 3 times more likely to suffer from a fatal injury. The mortality rate for helmeted motorcyclists is reduced by nearly 3-fold, but there is no significant impact of helmet use on mortality in moped riders, suggesting that the protective effect of helmets is augmented in higher speed crashes.[1]

A protective association with helmet use is evident for both motorcyclists and moped riders, with a reduced rate of skull fracture (nearly 6-fold and 2-fold, respectively) and TBI. These higher rates of injury are reflected in hospital charges, which are doubled for unhelmeted moped and motorcycle riders. The public burden of these charges is augmented by the unfavorable payer status of unhelmeted riders, with over 35% having income-qualifying (government-assisted) coverage or self-pay. The odds ratio for high cost (>$25,000) and underinsured hospital stays are more than doubled for unhelmeted versus helmeted riders. This data provides direct economic incentive for universal helmet laws covering mopeds as well as motorcycles.

Limitations

Limitations of this study are the inclusion of only injured riders who were attended to by EMS personnel, and the limited sample size of moped riders. Hospital records could not be located for approximately 7% of the injured riders who were transported to hospitals by EMS. However, the exclusion of these riders probably did not bias the results of multivariate logistic regression models, since these riders were more likely to have worn helmets and had a more favorable distribution of pre-hospital injury severity. Another limitation is the availability of only acute care charges in the initial hospitalization. Therefore, medical charges we report may underestimate the true financial burden of long-term injuries. It should be noted that we only had access to medical charges, and not the actual medical costs that were ultimately paid after insurance adjustments. Finally, diagnostic data may be less accurate than the original medical records because HHIC data systems is generated for billing reimbursement.[1]

Strengths

This study includes statewide data collection which was possible through uniform data collection for all EMS providers in Hawai'i, and the existence of HHIC, a central repository of billing data from hospital medical records in the state. The capability of HHIC to track individuals transferred across medical facilities improved the ascertainment of final medical dispositions and reduced loss to follow-up. Finally, this study had a comprehensive comparison of demographics, injury, mortality, cost, and insurance information in four different groups: motorcycle riders with and without helmets, and moped riders with and without helmets. This is the first study with detailed analysis of helmet use between the two vehicle types.

Future Impact

Our study shows that unhelmeted riders are much more likely to suffer serious injury or death and to incur higher hospital charges. Furthermore, these higher hospital charges are more likely to be absorbed by public funds or the hospitals that provide them medical treatment. This is true for both motorcycle and moped riders, a distinction that was previously unstudied. These are important findings for those advocating for legislative policies requiring helmet use. Our study supports that implementing mandatory helmet laws for both motorcycle and moped riders would decrease severity of injury, medical charges, and cost to society.

Conflict of Interest

None of the authors identify any conflict of interest.

Acknowledgments

The data linkage activities were supported by a Highway Safety grant from the Hawai'i Department of Transportation.

Authors' Affiliations:
- EMS & Injury Prevention System Branch, Hawai'i Department of Health, Honolulu, HI (DJG)
- Department of Surgery, John A Burns School of Medicine, University of Hawai'i, Honolulu, HI (NAC, LLW, SS)

Correspondence to:
Daniel Galanis PhD; Injury Prevention Program, EMS & Injury Prevention System Branch, Hawai'i Department of Health, Leahi Hospital, Trotter Annex, 3675 Kilauea Ave., Honolulu, HI 96816; Email: daniel.galanis@doh.hawaii.gov

References

1. Galanis DJ, Ly CL, Wong LL, Steinemann S, and Rosen L. Helmet Use Among Motorcycle and Moped Riders Injured in Hawaii: Final Medical Dispositions from a Linked Database. *J Trauma*. 2014;77(5):743-8.
2. Brown CV, Hejl K, Bui E, Tips G, and Coopwood B. Risk Factors for Riding and Crashing a Motorcycle Unhelmeted. *J Emerg Med*. 2011;41(4):441-6.
3. Heldt KA, Renner CH, Boarini DJ, and Swegle JR. Costs Associated with Helmet Use in Motorcycle Crashes: The Cost of Not Wearing a Helmet. *Traffic Inj Prev*. 2012;13(2):144-9.
4. Brandt MM, Ahrns KS, Corpron CA, Franklin GA, and Wahl WL. Hospital Cost Is Reduced by Motorcycle Helmet Use. *J Trauma*. 2002;53(3):469-71.
5. O'Keefe T, Dearwater SR, Gentilello LM, Cohen TM, Wilkinson JD, McKenney MM. Increased fatalities after motorcycle helmet law repeal: is it all because of lack of helmets? *J Trauma*. 2007;63:1006-1009.
6. Croce MA, Zarzaur BL, Magnotti LJ, Fabian TC. Impact of motorcycle helmets and state laws on a society's burden: a national study. *Ann Sur*g. 2009;250:390-394.
7. Abbas AK, Hefny AF, Abu-Zidan FM. Does wearing helmets reduce motorcycle-related death? A global evaluation. *Accid Anal Prev*. 2012;49:249-252.
8. MacLeod JB, DiGiacomo CJ, Tinkoff G. An evidence-based review: helmet efficacy to reduce head injury and mortality in motorcycle crashes: EAST practice management guidelines. *J Trauma*. 2010;69:1101-1111.
9. McSwain NE Jr., and Belles A. Motocycle Helmets- Medical Costs and the Law. *J Trauma*. 1990;30(10):1197-9.
10. State of Hawaii, Department of Health. Injury Prevention and Control Section: Motorcycle and Moped Safety. Available at: http://health.hawaii.gov/injuryprevention/home/traffic-safety/motorcycle-and-moped-safety/. Accessed June 7, 2015.
11. Christmas AB, Brintzenhoff RA, Schmeizer TM, Head KE, and Sing RF. MOPEDS- Motorized Objects Propelling Ethanol Drinking Subjects. *Am Surg*. 2011;77(3):304-6.
12. Brintzenhoff RA, Christmas AB, Braxton VG, Janulis KE, Huynh TT, and Sing, RF. Mopeds: The Legal Loophole for Repeat Driving While Intoxicated Offenders. *Am Surg*. 2011; 202(6):697-700.
13. Blackman RA, and Haworth NL. Comparison of Moped, Scooter, and Motorcycle Crash Risk and Crash Severity. *Accid Anal Prev*. 2013;57:1-9.
14. Matzsch T. Injuries in Moped and Motorcycle Accidents, a Five-Year Series. *Laekartidningen*. 1983;80(24):2514-7.
15. Hawaii Health Information Corporation (HHIC). About. Available at: http://hhic.org/. Accessed March 9, 2015.
16. Centers for Disease Control and Prevention (CDC). State Injury Indicators Report. Instructions for Preparing 2010 Data. Available at: http://www.cdc.gov/injury/pdfs/2010_State_Injury_Indicator_Instructions-a.pdf. Accessed January 20, 2014.
17. Centers for Disease Control and Prevention (CDC). The Barell Injury Diagnosis Matrix, Classification by Body Region and Nature of the Injury. Available at: http://www.cdc.gov/nchs/data/ice/final_matrix_post_ice.pdf. Accessed January 20, 2014.
18. JMP. Software. Available at: http://www.jmp.com/en_us/software.html. Accessed March 9, 2015.
19. Matzsch T, and Karlsson B. Moped and Motorcycle Accidents-Similarities and Discrepancies. *J Trauma*. 1986;26(6):538-43.
20. Miggins M, Lottenberg L, Liu H, Moldawer L, Efron P, and Ang D. Mopeds and Scooters: Crash Outcomes in a High Traffic State. *J Trauma*. 2011;71(1):217-22.
21. Braddock M, Schwartz R, Lapidus G, Banco L, and Jacobs L; A Population-Based Study of Motorcycle Injury and Costs; *Annals of Emergency Medicine*. 1992;21(3):273-8.
22. Orsaw E, Holden JA, Williams J, and Lumpkin JR. Motorcycle Trauma in the State of Illinois: Analysis of the Illinois Department of Public Health Trauma Registry. *Ann Emerg Med*. 1995;26(4):455-60.
23. Max W, Stark B, and Root S. Putting a Lid on Injury Costs: The Economic Impact of the California Motorcycle Helmet Law. *J Trauma*. 1998;45(3):550-6.
24. Shankar BS, Ramzy AI, Soderstrom CA, Dischinger, PC, and Clark CC. Helmet Use, Patterns of Injury, Medical Outcome, and Costs Among Motorcycle Drivers in Maryland. *Accident Analysis & Prevention*. 1992;24(4):385-96.

MEDICAL SCHOOL HOTLINE

The Role of Mini-Medical Schools in Education

Kathleen Kihmm Connolly PhD and Virginia S. Hinshaw PhD

The Medical School Hotline is a monthly column from the John A. Burns School of Medicine and is edited by Satoru Izutsu PhD and Kathleen Kihmm Connolly PhD; HJMPH Contributing Editors. Dr. Izutsu is the vice-dean of the University of Hawai'i John A. Burns School of Medicine and has been the Medical School Hotline editor since 1993.

Introduction

The explosion of information on the World Wide Web (WWW) makes it vital that consumers and students are properly informed on health information and know how to distinguish and decipher that information. In this fast moving information age, many sources of data may not be based on science or may be skewed based on the intentions of the provider. Mini-Medical Schools (MMSs) can provide a dependable forum for health information, such that participants can become conscientious health consumers and are able to make informed health-related decisions. In addition, MMSs can specialize in particular areas of medicine and medical education for in-depth knowledge.

Most MMSs have similar goals of empowering the student to take ownership of their health, introducing medical school faculty and medical education, demystifying medicine, and showcasing medical schools and/or teaching hospitals.[1] Speakers in MMSs are typically faculty of medical schools or local professionals with expertise in specific topics. Their services are usually voluntary and are provided as a community service. The concept of MMSs was first developed at the University of Colorado School of Medicine in 1990 by J. John Cohen MD, PhD. Dr. Cohen's initial community outreach effort was designed to engage and empower people to communicate effectively with their health care providers. Free series of talks were given on understanding the basic science underlying medical practice. Course content was outlined as to what medical students learned in their first two years of education.[2]

Over the years, MMSs, typically developed by medical schools or community hospitals, have increased in popularity. They are now available in 34 states and 3 countries with a wide variety of programs.[3] A few examples of programs offered by different MMSs are further discussed in this article. Included are educational courses to motivate youth to pursue health careers, to increase medical librarians' knowledge, and to equip adults to age in a healthy way. The latter is the focus of the Dr. Rosita Leong Mini-Medical School on Healthy Aging at the John A. Burns School of Medicine (JABSOM).

Mini-Medical School for Primary and Secondary School Students

Given the growing world-wide physician shortage, several MMSs focus on education for primary and secondary school students to promote careers in health care. Several programs have conducted studies that demonstrate the potential of MMSs in this area. For example, the Mini-Medical School (MMS) of Drexel University College of Medicine focused on encouraging high school students to consider medical school. A survey conducted showed that their MMS significantly impacted students' decisions to pursue a pre-med course of study or to apply to medical school. Most participants indicated that their questions about the field of medicine were answered and that they would recommend the program to friends.[4]

Another example geared towards youth is the MMS developed at the West Virginia School of Osteopathic Medicine's Clinical Education Center. Evaluation of their course indicated that a daylong MMS geared toward high school students improved their knowledge on the structure of medical schools and life as a physician. Survey results after the program demonstrated a statistically significant increase both in the students' understanding of medical school and their desire to pursue a career in medicine.[5]

MMSs are especially important in reaching under-served communities where barriers for higher education exist. Studies have shown that students who are from under-served and rural areas are more likely to train and practice medicine in those areas.[6] In Canada, the University of Calgary's Cumming School of Medicine's MMS developed a program targeting low-income and minority students. The goal was to address the underrepresentation of First Nations people (various groups of Aboriginal people from Canada) in the field of medicine. The MMS included courses for both junior high and high school students from First Nations communities. Study results showed that the program was successful in increasing students' interest in medicine and in pursuing medical education. The MMS was especially influential for students at the junior high school level in developing a road map to medical school. In addition, the MMS was a vehicle for community engagement and a means for students to establish opportunities with partnering organizations, such as social services, local businesses and educational networks.[7]

Ireland is experiencing a physician shortage that is impacted by the low production of indigenous physicians and high rates of emigration. The Royal College of Surgeons in Ireland developed a four-day MMS focusing on local students to address

the shortages in the medical workforce. The course included lecture-based presentations, hands-on session and interactive question-and-answer discussions directed towards students residing in rural areas. This program focused on four areas: (1) structure of medical education, (2) medical terminology, (3) techniques for medical examinations and diagnosis, and (4) specialties in medicine. The program had success in guiding students towards health care professions and instilling a systematic approach to career choices.[8]

Mini-Medical Schools for Librarians

Librarians for medical schools need to understand medicine, medical education, and the basis for medical practice to better serve students and community patron members. Librarianship is improved by increased knowledge of the specific information needs of medical libraries. In 2002, the New York-New Jersey Chapter of the Medical Library Association (MLA) held its first "Mini-Medical School for Librarians." This program received the 2003 Majors/MLA Chapter Project of the Year Award. In an effort to expand the program, the MLA chapter conducted a study to evaluate the outcomes of the MMS. Results revealed statistically significant increases in self-assessed confidence immediately after the completion of the program and longitudinally six months later, thus enforcing the concept that a MMS can increase understanding of medicine and meet medical education needs for librarians.[9]

A librarian's job includes helping patrons search, question, and evaluate information on the WWW. The abundance of health information available on the WWW makes it critically important for consumers to know how to distinguish reliable, versus questionable or inaccurate, medical information. The Stony Brook's University Health Sciences Center Library partnered with Stony Brook's School of Medicine to educate the community on how to refine searches effectively and to question and evaluate website health information. The MMS taught students to ascertain the credibility of websites focusing on MLA's Content Evaluation Guidelines. Key areas of focus were sponsorship, currency, factual information, and audience. The course also emphasized and provided the following examples: the abundance of misleading information, the technology behind search engines, and examples of sponsored versus non-sponsored websites.[10]

The Dr. Rosita Leong Mini-Medical School for Healthy Aging at JABSOM

JABSOM's Mini-Medical School on Healthy Aging was developed by Chancellor Emeritus Virginia Hinshaw with the overall goal of improving the health and well-being of Hawai'i's citizens, particularly those entering the second half of their lives. The concept was to provide accurate, current and scientifically based information for participants, similar to what medical students learn but in terms appropriate for the lay public. The four focus areas included being physically active, socially connected, nutritionally balanced, and mentally engaged with the theme "Seniors Rock." The MMS started in 2014 with the intention of offering it once a year; however, due to demand, two sessions of the MMS with the same topics are offered annually (in the spring and in the fall). New topics and speakers are developed for the following year.

In each MMS, the participants attend 2.5 hours sessions (two lectures, question and answer periods, and a social time) for six consecutive Saturday mornings. Attendance is taken. The MMS is presented in a lecture format and speakers continue to volunteer. Classes offered cover a wide range of topics of particular relevance to healthy aging (list available at http://jabsom.hawaii.edu/minimedschool/course-program.html). Examples of lectures include the following:

Geriatric Pharmacology – Shari Kogan MD
Physiologic changes associated with normal aging in relation to drug absorption, distribution, metabolism, and excretion.

No One Has to Die Alone – Lani Leary PhD
How to help a loved one at end of life through communication, comfort, and care.

Resistance Training is Good For You! – Brian Copeland CPT
Overview on what is resistance training, reasons to resistance train, major considerations and benefits of resistance training.

Skin: Your Largest Organ – Carla Nip-Sakamoto MD
Discussion on intrinsic and extrinsic aging influences on the skin and preventative measures of extrinsic aging.

Having a Sense of Humor Can Help You Be More Resilient! – Virginia Hinshaw PhD
Having a sense of humor, the trait of appreciating the humorous, can help with the ability to overcome challenges of all kinds. This includes trauma, tragedy, personal crises, and plain 'ole' life problems.

Using Medications the Right Way – Kamal Masaki MD
Discussion on key issues in geriatric pharmacology: the effects, risks, and drug interactions on the aging body.

The MMS is open to UH donors, UH alumni and community members. The target audience is anyone interested in healthy aging. To date, the majority of participants have been between 55-75 years of age. Young people and caregivers are encouraged to attend. Recently more young adults have attended with their parents. The MMS is well attended with all 165 available seats reserved via electronic registration, indicating a strong interest and need for such information. Typically there is a waiting list for the next course.[11] There is no charge to attend JABSOM's MMS. This is possible because participants have been generous in donating to the MMS, including a significant endowment gift. Such a program requires organizational support and cooperation. Since its inception, the University of Hawai'i Foundation (UHF) partnered with JABSOM to support the MMS — a factor of major importance. Examples of the UHF support include the

administering of the MMS enrollment, providing volunteers at each session, and processing the donations from participants. Both entities provide personnel, facilities and other resources needed to support the MMS. In addition, the UH Cancer Center, the venue for the sessions, also provides personnel and facilities support.

Evaluations of every MMS by participants indicate that 90%-100% would recommend the course to others and 85%-90% rate the course as excellent. Most importantly, the participants list the many changes they have made in response to the information provided, such as getting vaccinated, increasing exercise, engaging in more learning activities, reviewing their drugs and lab tests with healthcare providers, becoming more positive about growing older. Such actions are the desired outcome because those activities will enable the participants to improve their health and well-being.

To share the information broadly, each lecture is videotaped and accessible on JABSOM's MMS website http://jabsom.hawaii.edu/minimedschool/; this effort was supported by grants from the Hawai'i Medical Service Association Foundation. Videos of lectures and mini-talks are also posted on the Oceanic Time Warner on-demand channel "iAGE" at 1342/342. Currently, the focus remains on healthy aging, with the flexibility of future partnerships and expansion to address additional health issues and formats.

Conclusion

MMSs are an opportunity for medical schools and institutions to provide a community service and to promote and showcase their faculty and community health professionals. There are several focus areas and possible formats for MMSs. A few examples were provided: for youth, encouraging them to pursue careers in health care; for librarians, enabling them to assist patrons, from both the community and medical school, to find resources, decipher information, and thus improve health literacy; and, for community members, to understand the scientific basis of medicine which can improve effective communication with health care providers and increase their ability to make beneficial lifestyle selections.

Key qualities of MMSs that contribute to success of the programs include: strong administration and organizational support; speakers who are knowledgeable and excellent communicators; dynamic moderators; and, most of all, creation of a fun and engaging environment for learning.[1] Based on end of course evaluations, these qualities are evident to participants in JABSOM's MMS. The positive feedback from both students and lecturers has demonstrated that the program is educational but also provides an uplifting environment for socialization and networking. Students have attended multiple sessions and are recommending the program to friends and family, plus they share the information from the course with others. Students have become the teachers of healthy aging, which magnifies the impact of the information.

MMSs are a vehicle for empowering community members, students, and professionals to increase their knowledge, and thereby, make better informed health-related or educational/career decisions. Studies have shown that increased health literacy improves decision-making and promotes a stronger patient-centered relationship with physicians, thereby generating greater satisfaction with health care.[12] In contrast, low health literacy limits interaction with health care providers, which negatively impacts health decisions and outcomes.[13] Also, given the world-wide physician shortage, MMSs can be a valuable resource by encouraging our youth to pursue careers in healthcare and medicine.

Authors' Affiliations:
- Director, Institutional Planning and Special Projects, Dean's Office, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (KKC)
- Chancellor Emeritus, Professor of Tropical Medicine, Medical Microbiology and Pharmacology, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (VSH)

References

1. Moore L, Handfield-Jones R. Mini-medical school: A legitimate role for university CME offices. *Journal Of Continuing Education In The Health Professions* [serial online]. Winter2008 2008;28(1):55. Available from: Academic Search Complete, Ipswich, MA. Accessed October 25, 2016.
2. Stephenson J. Mini-med schools offer lay public lessons in the science of medicine. *JAMA* [serial online]. March 27,1996. 1996;275(12):897. Available from: Academic Search Complete, Ipswich, MA. Accessed October 19, 2016.
3. Lindenthal JJ, DeLisa JA. Promoting appreciation of the study and practice of medicine: inner workings of a Mini-Med program. *Advances in Medical Education and Practice*. June 16, 2012. 2012;3:73–78.
4. Chang A, Cavanaugh G, Kumar NS, Lee M, Stein D, Mulcahey MK. Mini-Medical School Programs' Influence on Students' Desire to Pursue Medicine. *Journal of the National Medical Association* [serial online].July 1, 2016. 2016;108(3):152-157. Available from: http://www.journalnma.org/. Accessed October 19, 2016.
5. Kaye K, Berns A, Cress L, Nazar A. Mini-medical school programs are an effective tool to introduce students to osteopathic medicine. *The Journal Of The American Osteopathic Association* [serial online]. February 2014;114(2):109-112. Available from: MEDLINE, Ipswich, MA. Accessed October 19, 2016.
6. Pathman D, Konrad T, Dann R, Koch G. Retention of primary care physicians in rural health professional shortage areas. *American Journal Of Public Health* [serial online]. October 2004;94(10):1723-1729. Available from: MEDLINE, Ipswich, MA. Accessed October 24, 2016.
7. Henderson R, Williams K, Crowshoe L. Mini-med school for Aboriginal youth: experiential science outreach to tackle systemic barriers. *Medical Education Online* [serial online]. December 23, 2015;20:29561. Available from: MEDLINE, Ipswich, MA. Accessed October 24, 2016.
8. Shaikh F, Babar M, Cross K. Mini-Med School: promoting awareness of medicine as a career for suburban and rural high-school students. *ANZ Journal Of Surgery* [serial online]. June 2013;83(6):481-486. Available from: MEDLINE, Ipswich, MA. Accessed October 24, 2016.
9. Dunn K, Crow S, Van Moorsel T, Creazzo J, Tomasulo P, Markinson A. «Mini-Medical School for Librarians»: from needs assessment to educational outcomes. *Journal Of The Medical Library Association* [serial online]. April 2006;94(2):166-173. Available from: Academic Search Complete, Ipswich, MA. Accessed October 19, 2016.
10. Werner S, Chimato M. Creating a More Informed Health Care Consumer: How One Medical Library Participates in Mini Medical School. *Journal Of Consumer Health On The Internet* [serial online]. October 2005;9(4):27-33. Available from: Academic Search Complete, Ipswich, MA. Accessed October 21, 2016.
11. Hinshaw V, Partika N. Medical school hotline: Educating current and future seniors: the mini-medical school on healthy aging; University of Hawaii at Manoa, John A. Burns School of Medicine. *Hawaii J Med Public Health* [serial online]. September 2014;73(9):292-294. Available from: MEDLINE, Ipswich, MA. Accessed October 19, 2016.
12. Vildan Altin S, Stock S. The impact of health literacy, patient-centered communication and shared decision-making on patients› satisfaction with care received in German primary care practices. *BMC Health Services Research* [serial online]. August 30,2016. 2016;16:1-10. Available from: Academic Search Complete, Ipswich, MA. Accessed October 26, 2016.
13. Lambert V, Keogh D. Health literacy and its importance for effective communication. Part 2. *Nursing Children And Young People* [serial online]. May 2014;26(4):32-36. Available from: MEDLINE, Ipswich, MA. Accessed October 26, 2016.

Leveraging Pacific Laboratories to Boost Global Health Security

A. Christian Whelen PhD; Scott J. Becker MS; Vasiti R. Uluiviti MS; and Nancy Maddox MPH

Insights in Public Health is a monthly solicited column from the public health community and is coordinated by HJMPH Contributing Editors Tetine L. Sentell PhD from the Office of Public Health Studies at the University of Hawai'i at Manoa and Donald Hayes MD, MPH from the Hawai'i Department of Health in collaboration with HJMPH Associate Editors Ranjani R. Starr MPH and Lance K. Ching PhD, MPH from the Hawai'i Department of Health.

Introduction

Just as the Ebola virus was claiming its first West African victims, world leaders gathered in Washington, DC, and Geneva, Switzerland, to inaugurate the Global Health Security Agenda (GHSA)—an ambitious framework intended to accelerate progress toward a world secure from infectious disease threats, particularly those with potential to spread across national borders. The GHSA was launched in February 2014, endorsed by the G7 (United States, Canada, France, Germany, Italy, Japan and the United Kingdom) in June 2014, and supported by 53 nations, as of August 2016.[1] All three core GHSA goals—preventing avoidable epidemics, detecting threats early, and responding rapidly and effectively to biological threats[2]—depend on adequate laboratory expertise to identify and characterize infectious pathogens in support of public health surveillance and response.

By virtue of its strategic location and access to sophisticated, reference-level laboratory services, Hawai'i is in a unique position to further GHSA goals in the Asia-Pacific region. The Hawaiian Islands lie about 2,500 miles southwest of the mainland United States, almost 4,000 miles east of the US territory of Guam and about 3,900 miles east of Tokyo, Japan. As a midway point between Asia and the continental US, Hawai'i attracts a large number of domestic and international visitors: 4.36 million air travelers and 56,555 out-of-state cruise ship passengers from January through June 2016, coming from Alaska and the US mainland (over 2.7 million), Japan (693,057), Australia (157,744), China (91,781), and other parts of the world.[3] In fact, in 2015, Honolulu was the port of entry for more non-US residents than any other domestic port, excepting New York City, Miami, and Los Angeles.[4] Hawai'i also engages in a robust maritime trade. In 2015, Hawai'i consumers purchased $2.27 billion worth of goods from the state's top five foreign import markets: (1) Indonesia, (2) Russia, (3) France, (4) Japan and (5) China.[5] Altogether, 85-90% of Hawai'i's food is imported from out of state.[6]

The mixing of international citizens and goods in Hawai'i's remote 6,422 square miles of land area makes the state a natural sentinel jurisdiction, well-positioned to monitor emerging (eg, Zika virus), re-emerging (eg, measles), and endemic (eg, leptospirosis) pathogens in the Asia-Pacific region. For example, the first US cluster of multi-drug resistant *N. gonorrhoeae* with enhanced cefixime resistance was detected here and associated with sex partners from Asia.[7] Similarly, 2009 H1N1 pandemic influenza was confirmed in a student and teacher from the same O'ahu school just 21 days after the Centers for Disease Control and Prevention (CDC) reported the first cases in the continental US.[8]

The Role of the Hawai'i State Laboratories

Of course, these disease investigations and ensuing interventions, were predicated on the existence of a strong, multidisciplinary Hawai'i public health infrastructure. Of particular relevance for this article are the services provided by the State Laboratories Division (SLD) of the Hawai'i State Department of Health. The SLD— which includes biosafety level 3 containment—tests over half a million air samples, 10,000-12,000 environmental samples, and 40,000 human specimens each year, licenses clinical laboratory scientists, conducts research, provides adjunct faculty to local colleges and universities, and participates in a range of activities for emergency preparedness and response. Importantly, the SLD leads the Hawai'i Laboratory Response Network, made up of several clinical (mostly hospital-based), veterinary, food testing, and military laboratories in the Hawaiian Islands. This network offers a highly trained workforce, proficient in classical and molecular disease testing; capability to test for priority bioterrorism agents, such as smallpox, *Bacillus anthracis* and *Brucella* species; surge capacity for high-volume outbreak response; and a platform for secure laboratory report-

Keywords
GHSA, USAPI, PIHOA, Hawai'i SLD, APHL, Specimen Transport, influenza, Zika

Abbreviations
GHSA: Global Health Security Agenda
SLD: Hawai'i State Laboratories Division
CDC: Centers for Disease Control and Prevention
APHL: Association of Public Health Laboratories
USAPI: US-affiliated Pacific Islands
PIHOA: Pacific Island Health Officers Association
LRN: Laboratory Response Network

ing and data exchange. The SLD is also a member of the US Laboratory Response Network (LRN) founded by the Centers for Disease Control and Prevention (CDC), the Association of Public Health Laboratories (APHL), and the Federal Bureau of Investigation. The LRN is integrated with the US Postal Inspectors, Department of Homeland Security, and other federal law enforcement agencies, and is considered a national security asset. As a member, the SLD has access to specialized training and standardized testing reagents and protocols for certain biological select agents and toxins monitored by the CDC Select Agent Program, as well as for emerging and re-emerging pathogens of public health significance.

In recent years, the SLD substantially increased its public health reach, serving as a hub of laboratory expertise for the six US-affiliated Pacific Islands (USAPI) jurisdictions, which include the US flag territories of American Samoa, Commonwealth of the Northern Mariana Islands, and Guam, plus the Compact of Free Association nations of the Federated States of Micronesia (includes the islands of Chuuk, Pohnpei, Kosrae, and Yap), the Republic of the Marshall Islands (includes the island atolls of Majuro and Ebeye), and the Republic of Palau. These are resource-poor states with limited laboratory infrastructure; for example none has a Biosafety Level 3 "containment room" with one-way, filtered air flow to enable safe handling of highly infectious pathogens. With the exception of Guam, all send clinical infectious disease specimens off-island for any testing other than routine bacteriology. Before 2009, however, specimens were referred to laboratories in Australia, Hawai'i, Puerto Rico, or the US mainland on an ad hoc basis entailing complicated logistical arrangements and high costs. In 2009, the influenza A (H1N1) pandemic exposed the need for a more economical and efficient transport system. This article describes the USAPI's transition to a unified specimen transport mechanism, coordinated by the Pacific Island Health Officers Association (PIHOA), and the subsequent working relationship among USAPI, PIHOA, APHL, and the Hawai'i SLD. This partnership is boosting disease surveillance in the Asia-Pacific region, improving health outcomes, and advancing the GHSA vision of a world secure from infectious disease threats.

USAPI Laboratories and Off-island Specimen Shipment

Of the six USAPI, only one, Guam, has a dedicated public health laboratory; all other USAPI laboratories serve a dual role, providing both clinical testing for individual patient diagnosis and testing to support public health surveillance and outbreak response within their jurisdictions. The Commonwealth of the Northern Mariana Islands has a unique arrangement: instead of a freestanding public health department, the islands use the Commonwealth Healthcare Corporation, a combined 86-bed municipal hospital/public health department organized as a public corporation. The hospital laboratory offers the only biosafety level 2 testing available in the Northern Mariana Islands and primarily performs standard metabolic test panels for hospital patients and limited tests for priority public health pathogens, such as tuberculosis, chlamydia, and gonorrhea. None of the USAPI public health laboratories are able to test for agents of bioterrorism, and only Guam is able to perform influenza typing and molecular detection of some arboviruses (eg, Zika, dengue, and chikungunya) via the US Food and Drug Administration Emergency Use Authorization-approved Trioplex assay developed by CDC. All USAPI jurisdictions routinely ship specimens off-island for specialized analytical services, including confirmatory testing for measles, leptospirosis, and foodborne disease pathogens.

As the most advanced public health laboratory among the USAPI, the Guam Public Health Laboratory has assisted other USAPI laboratories in various capacities, including confirmatory testing for syphilis and a few other pathogens, outbreak response testing for a 2014 measles outbreak in Chuuk, and routine specimen packing and shipping to distant reference laboratories, such as CDC in Atlanta and the World Health Organization Regional Measles Reference Laboratory in Melbourne, Australia. Guam has the only daily supply of dry ice needed for long-distance specimen shipping, and the Guam Public Health Laboratory is hopeful that an ambitious renovation/construction project (funded in large part by the US Department of Defense[9]) will substantially increase its reference microbiology capabilities.

Yet, as stated in a PIHOA training document, "The USAPI are resource-limited and face significant challenges developing public health infrastructure, especially laboratory testing capacity for infectious diseases… The USAPI are truly a weak link in the global network for the prevention and mitigation of pandemic influenza and other infectious diseases. This fact underscores the need for a coordinated, region-wide approach to upgrading the USAPI lab network and increasing the capacity of the USAPI to provide timely and effective epidemiological surveillance and [disease] notifications."[10]

Pandemic Response Changes Public Health Practice

Before 2009, USAPI public health laboratories referred relatively few specimens to the Hawai'i SLD. During the 2009 influenza A (H1N1) pandemic, however, CDC included resources for virologic surveillance in its cooperative agreement with APHL, which, in turn, enabled SLD to test hundreds of specimens from USAPI patients over the next four years. This emergency response support strengthened the relationship between the SLD and the USAPI laboratories and highlighted the advantages of working with Hawai'i, including fewer shipping days compared with other reference laboratories used by the USAPI, negating the need for packing specimens with dry ice; faster reporting of positive test results (24-48 h from SLD specimen receipt), via line list or a password-protected electronic information system; and lower costs. For example, a shipment from the USAPI to Honolulu costs about $250 per 50 mL package for a Category A (highest risk) specimen and $100 per 4 kg/4L package for a Category B (lower risk) specimen, compared with $800 and $500, respectively, to ship the same specimens, with dry ice, to Melbourne, Australia.

In May 2010, APHL—whose members include the SLD and some USAPI public health laboratories—provided PIHOA with a year of funding support to subsidize further shipments of USAPI influenza specimens to the SLD for ongoing public health surveillance. PIHOA provided training in specimen packaging and shipping to all USAPI shippers, developed influenza specimen shipping protocols, and secured an agreement with the Honolulu-based Diagnostic Laboratory Services Inc, (DLS) to transport USAPI influenza specimens to Honolulu along with the tuberculosis specimens it tests for USAPI laboratories under its own contract with CDC. Unfortunately, the cost structure prohibited DLS from continuing this arrangement past December 2012. Instead, PIHOA drew from a revolving fund established in 2007 with $20,000 of seed money from the US Department of Interior. The intent was for PIHOA to front shipping costs, to avoid delays, and for laboratories to reimburse the fund afterward. In addition, fund reserves were supplemented with 17 months of financial support for influenza shipments to the SLD from the Secretariat of the Pacific Community. However, support from the Secretariat ceased in December 2014, and, by January 2015, the revolving fund was depleted due to delayed and incomplete reimbursements. At this time, the Association of USAPI laboratories devised the current funding mechanism for off-island shipments of infectious disease specimens (not limited to influenza specimens): a revolving account managed by PIHOA and funded by initial and periodic contributions of $2,000-$3,000 from each of the ten USAPI laboratories. Thus, instead of reimbursement after-the-fact, laboratories draw down the prefunded account. This mechanism remains in use today.

Altogether, from 2009 to 2016, between 700 and 800 shipments have been sent from USAPI public health laboratories to the Hawai'i SLD for either routine surveillance testing or emergency response testing during infectious disease outbreaks, including an ongoing Zika virus outbreak on Majuro, Republic of the Marshall Islands and American Samoa. During this period, SLD has tested 2,641 USAPI specimens for one or more disease agents, including, but not limited to, influenza virus, dengue virus, chikungunya virus, Zika virus, foodborne disease bacteria, measles virus, and *Leptospira* bacteria. The SLD has also provided viral transport media and other shipping supplies to PIHOA public health laboratories, as well as technical support, as requested, to improve USAPI laboratory services. For its part, PIHOA has established accounts with various airlines serving the Pacific-Asia corridor and with courier services in Honolulu and Guam; developed shipping protocols outlining the roles of the public health partners and transport providers; and managed the revolving fund. PIHOA also ensures that each USAPI public health laboratory has at least three staff members certified to package infectious disease specimens in accord with International Air Transport Association requirements and provides periodic training in specimen packaging and shipping.

Boosting Global Health Security

Enhanced SLD testing for USAPI laboratories since 2009 has had a strong, positive public health impact in the region. A few notable SLD accomplishments include the following:

- Performing chemistry and microbiological testing of seawater used for thawing frozen tuna, so the American Samoa StarKist® factory could reopen after a major submarine earthquake and tsunami in 2009 threatened seawater quality.

- Determining the causative agent—Staphylococcal enterotoxin—of two 2011 food poisoning outbreaks in Guam, one of which affected five schools and sickened over 300 children.

- Confirming measles as the pathogen responsible for outbreaks in 2014 in Chuuk, Guam, Kosrae, and Pohnpei.

- Determining that Chikungunya virus, and not measles, was the cause of a 2014 outbreak of acute fever and rash in American Samoa that coincided with the measles outbreaks occurring elsewhere in the region. This was the first confirmation of Chikungunya virus in American Samoa.

- Providing testing support for a large dengue 3 outbreak in American Samoa in summer 2015.

An ongoing focus of SLD support for USAPI is testing for influenza virus and other respiratory pathogens. In 2013, for example, the Hawai'i SLD tested 345 specimens from the region for influenza virus, including 121 from the Commonwealth of Northern Mariana Islands in the single month of June. Subsequent subtyping of positive specimens revealed an upsurge of influenza A (H1N1) in the region. In 2014, the SLD tested 165 USAPI specimens for influenza (50 received in a single month from Republic of Palau), and determined that influenza A (H3) was the predominant strain. Circumstances in both Palau and the Marianas raised concerns of potential avian influenza transmission to humans, and laboratory results alleviated those fears. In addition, the SLD performed pyrosequencing on a subset of 21 USAPI influenza specimens—including both H1 and H3 strains from 2013-14—to assess the presence of mutations associated with resistance to one of the most common, first-line anti-influenza drugs, oseltamivir (a neuraminidase inhibitor marketed under the trade name, Tamiflu), and found all specimens to be wild type with no oseltamivir resistance.[11]

Such information is of critical importance to inform patient care management, as well as public health interventions to stop the spread of disease. The virulence and drug-resistance profiles of different seasonal influenza strains vary greatly, and CDC estimates that between the 1976-77 flu season and the 2006-07 flu season, US influenza-associated deaths ranged from a low of about 3,000 to a high of about 49,000 people, mostly adults aged 65 years and older.[12] Additionally, CDC reports an average of more than 200,000 US influenza-related hospitalizations each year.[13]

The SLD selected 175 influenza-negative USAPI specimens from 2013-14 for additional testing by a molecular respiratory viral panel that simultaneously detects and identifies multiple respiratory virus nucleic acids. Among the 85 specimens positive for various non-flu viruses, 49 were positive for rhinovirus, 21 for respiratory syncytial virus, 5 for adenovirus, 4 for human

metapneumovirus, and 5 for a combination of these. These data were similar to viral panel results from Hawai'i surveys indicating minimal difference in the types of respiratory viruses causing illness in the Pacific region.

Battling Zika Virus in the Pacific

More recently, in 2015 and the first half of 2016, the SLD performed over 1,000 analyses of USAPI patient specimens for a range of endemic and emerging pathogens. Even as the SLD was in the midst of seasonal influenza testing and also responding to a dengue outbreak detected in October 2015 on the Big Island of Hawai'i, the laboratory began the process of bringing two new diagnostics tests on-line: one for molecular detection of Zika virus (via real-time reverse transcriptase polymerase chain reaction) and one for detection of IgM antibodies to the Zika virus. By March 2016, SLD was one of few US laboratories with capability for both molecular and antibody testing for the Zika virus. Subsequent SLD testing provided the first laboratory evidence that Zika had emerged in American Samoa, the Marshall Islands (Majuro), and Micronesia (Kosrae and Chuuk). CDC and local epidemiologists responding to the large American Samoa outbreak collected specimens from 50 pregnant women to rule out Zika virus exposure, and SLD's IgM tests demonstrated presumptive evidence of exposure in about half the women.

The interpretation of confirmatory serological testing by the plaque reduction neutralization test (PRNT) of Zika IgM screen positives, performed at CDC's Fort Collins, Colorado, facility is very complex, and suffers from cross-reactivity in patients from areas with active dengue transmission. Consequently, SLD convened several conference calls with health officials in American Samoa and Guam to help health officials understand the test reports. By spring 2016, the turn-around-time for CDC Zika testing on the US mainland was at least six weeks, making the availability of Zika testing in Hawai'i even more valuable to inform patient diagnoses and timely public health interventions, such as travel advisories, mosquito control activities, and outreach to pregnant women. In addition, SLD data provided Hawai'i and CDC health officials with situational awareness of Zika risks in the USAPI, which is necessary for evaluating potential imported cases.

Summary

In conclusion, PIHOA, Hawai'i SLD, CDC, and APHL have partnered to strengthen health security in the Pacific by providing or assuring access to testing services, providing technical support, improving specimen transport systems, and nurturing the fragile USAPI laboratory network. This work continues and will expand with resources allocated through the GHSA. Future projects include a potential laboratory "twinning" relationship between SLD and Vietnam public health laboratories—in which Vietnamese scientists will train on-site at the SLD, and SLD scientists will provide on-site support in Vietnam—and activities to achieve Hawai'i Department of Health recognition of clinical training rotations to enable state licensure of medical technologists/clinical laboratory scientists trained in the Philippines. Rigorous laboratory data are critical to enhance our understanding of health issues in the vast Pacific region and, thus, to protect Hawai'i and the US mainland from health threats we may not otherwise even know exist.

Conflict of Interest

None of the authors identify any conflicts of interest.

Authors' Affiliations:
- State of Hawai'i, Department of Health, State Laboratories Division, Honolulu, HI (ACW)
- Association of Public Health Laboratories, Honolulu, HI (SJB, NM)
- Pacific Island Health Officers Association, Honolulu, HI (VRU)

References

1. Global Health Security Agenda Web Site. https://ghsagenda.org/about.html. Accessed August 29, 2015.
2. Global Health Security Agenda: Frequently Asked Questions. Centers for Disease Control and Prevention Web Site. http://www.cdc.gov/globalhealth/healthprotection/ghs/faqs.htm#ui-id-3. Page last updated January 29, 2016. Accessed August 29, 2015.
3. Hawai'i Tourism Authority. Press release, "Visitor Arrivals (4.4 Million), Expenditures ($7.7 Billion) Increased in First Half of 2016." http://www.hawaiitourismauthority.org/default/assets/File/research/monthly-visitors/June%202016%20Visitor%20Stats%20Press%20Release%20(FINAL).pdf. Published July 28, 2016. Accessed August 30, 2016.
4. US Department of Commerce, International Trade Administration, National Travel and Tourism Office Web Site. Top airports for overseas non-resident arrivals to the US. http://travel.trade.gov/view/m-2015-I-001/index.asp. Accessed August 31, 2016.
5. United States Census Bureau. State Imports for Hawaii. Top 25 Countries Based on 2015 Dollar Value. US Census Bureau Web Site. https://www.census.gov/foreign-trade/statistics/state/data/imports/hi.html. Accessed August 30, 2016.
6. Leung P, Loke M. *Economic Impacts of Increasing Hawaii's Food Self-Sufficiency*. Honolulu, HI: Cooperative Extension Service, Economic Issues, College of Tropical Agriculture and Human Resources, University of Hawaii at Manoa; December 2008 (EI-6).
7. Kidd S, Lee MVC, Maningas E, Komeya A, Kunimoto G, et al. Gonococcal susceptibility to cephalosporins—Hawaii, 2003 to 2011. *Sex Transm Dis*. 2013;48(8):1-4.
8. Park SY, Nakata MN, Elm JL, Ching-Lee MR, Rajan R, et al. Outbreak of 2009 pandemic influenza A (H1N1) at a school — Hawaii, May 2009. *MMWR*. 2010;58(51&52);1440-1444.
9. Public Law 113-66. National Defense Authorization Act for Fiscal Year 2014.
10. Uluiviti V. *Sustaining Effective Specimen Shipping in the US-affiliated Pacific Islands: 2006-2016*. Honolulu, HI: PIHOA;2016.
11. Miller HB, Gose RB, Nagata MT, Sciulli RH, Whelan AC. Pacific region influenza surveillance for oseltamivir resistance. *Journal of Clinical Virology*. 2012;54:73-75.
12. Thompson MG, Shay DK, Zhou H, Bridges CB, Cheng PY, et al. Estimates of deaths associated with seasonal influenza — United States, 1976-2007. *MMWR*. 2010;59(33):1057-1062.
13. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004;292(11):1333-1340.

APPOINTMENT DESCRIPTION

Are you seeking to expand your knowledge of public health and improve your writing skills? Push the envelope of career possibilities and gain an edge in the publishing industry. The Hawaii Journal of Medicine & Public Health (*HJM&PH*) is searching for motivated, ambitious professionals in the fields of medicine, public health or allied health to serve as Junior Editors in a **one year** unpaid appointment. If you are looking for a place where you can showcase your writing skills and your creativity, HJM&PH is the place for you!

Junior Editors will work closely with the Journal office and one of our Associate Editors. Preference will be given to individuals with: a master's degree or higher; a background in public health or medicine; previous editorial experience; social media presence.

Duties & Responsibilities:

- Work with an Associate Editor to review submitted manuscripts to determine their relevance to the diverse *HJM&PH* audience and appropriateness for further peer review;
- Carefully suggest suitable peer reviewers and monitor the review process;
- Provide timely feedback on the contents and readability of manuscripts requiring revision; and
- Work with an Associate Editor to generate final decisions that will be rendered by the editor-in-chief.
- Workload includes about 2-3 reviews per week.

Requirements:

- Applicant must hold a master's degree or higher in public health, medicine, or a related field
- A responsible candidate with a terrific attitude who can work well with a team as well as independently
- A creative self-starter who can work well under constant deadlines
- Varying Hours: We will do our best to work with your schedule
- This is a non-paid appointment
- Must commit to a 1-year term

Appointment responsibilities/duties can be performed remotely. The Junior Editor's tenure will begin in early January 2017 and can be extended for another year depending on performance evaluation.

To Apply: Please submit a resume and a brief cover letter describing your interest in serving as a Junior Editor for the Journal as well as prior editorial experience to hijmph@gmail.com.

Deadline: November 1, 2016. Applications received by this date are guaranteed consideration. Applicants will be considered on an ongoing basis until the position is filled.

THE WEATHERVANE

RUSSELL T. STODD MD; CONTRIBUTING EDITOR

BRAIN INJURIES ARE NEVER TRIVIAL.
Following multiple reports about concussion injuries in athletes, more information is coming down. According to a study in Medicine and Science in Sports and Exercise, data showed that college athletes were nearly twice as likely to suffer a serious knee, ankle or lower extremity injury for as long as one year following injury compared with the previous twelve months. Information was collected from 2010 to 2013 with two-thirds of the athletes male. 85% of concussed athletes return to competition within 7 days after their head injury. Repeat injuries are not too surprising when one considers that the concussion may impair the brain's ability to coordinate physical movement. Subtle disruptions in brain pathways may increase synapsis time and delay reaction and motion. Too often both coaches and athletes are very eager to get back in action when the remedy is R&R.

BUCKLE UP AND STOW THE IPHONE.
Despite a steady downturn in traffic fatalities in recent years, the first half of 2016 saw a dramatic increase of 10.4% in highway deaths. What is going on? Adding these figures to the uptick at the end of 2015, has the National Highway Traffic Safety Administration (NHTSA) partnering with the National Safety Council to examine factors. It is too early to pinpoint specific reasons for the increase, because final data for 2015 and 2016 will not be available until the fall of 2017. What is obvious is that 35,000 people died from motor vehicle crashes in 2015, an increase of 7.2%, the largest since 1966. "We have an immediate crisis on our hands" as NHTSA chief Mark Rosekind stated at a conference in Washington DC. Drunken driving is historically a major cause in vehicle deaths, but motorists today are inundated with smart phones, digital dash screens, and other exotic electronic distractions. Frequently drivers may want to answer a call instead of watching the road. It should be noted that younger drivers remain among the highest risk of dying although they drive less. Teenagers crash at rates nearly three times that of drivers over the age of 20, according to the Insurance Institute for Highway Safety.

CORNEAS RECOGNIZE GENDER?
A corneal transplant is a corneal transplant, except when it isn't. Researchers reporting in the American Journal of Transplantation studied almost 17,000 transplants and found that rejections of 220 per 1,000 male-to-female occurred versus 180 for every 1,000 sex-matched donations. For males donor's gender didn't matter. The gene that encodes H-Y is on the Y chromosome so women don't have it. If their immune systems haven't encountered the H-Y antigen before they may assume it is a sign of a foreign invader, and attack the transplant. Co-author Stephen Kaye, ophthalmologist at the Royal Liverpool University Hospital in England stated that H-Y appears to be more of an issue in the conea than other organs. Kidney and other organ recipients show no gender problems.

MEDICARE MUST DEFINE CHIROPRACTIC LIMITS.
A Review by the Department of Health and Human Services Office of the Inspector General (OIG) revealed that the Medicare program for senior citizens spent roughly $359 million on unnecessary chiropractic care in 2013 for treatment of strains, sprains, or other joint conditions. The OIG called on Medicare to tighten oversight of the payments. The office noted that its analysis was one of several in recent years to find questionable Medicare spending on chiropractic care. Unless CMS implements strong guidelines it is likely to continue to make improper payments to chiropractors, the OIG said. Medicare should limit how often patients can return to the chiropractor, it should determine whether there should be a cutoff in visits. Patients who received more than a dozen treatments were more likely to get medically unnecessary care. All return visits after the first 30 were not indicated. John Fatardeau, senior vice president of public policy and advocacy for the American Chiropractic Association said the industry "worked aggressively" to educate chiropractors on how to correctly document treatment and bill Medicare. The group also rejects a numerical limit on chiropractic care. What a surprise.

TROLLING FOR MORE FEMININE FANS.
The National Football League (NFL) goes pink in October to accentuate the drive for breast dancer research. Their boast is that the NFL has raised "almost $15 million" for awareness and screening programs since 2009. Big Deal—or is it; that amounts to about 2 million annually for an organization that enjoys $12 billion each year. Yet the NFL does not contribute one nickel for breast cancer research. Estimates vary, but roughly 33% to 45% of viewers are female, so is this a veiled effort to attract more women to become NFL fans? Moreover, adding in the NFL's attempts to address domestic violence, "go pink" is an excellent vehicle for women to reach for the remote.

PLEASE, NO CUDDLING WITH DUCKS.
The Centers for Disease Control and Prevention (CDC) noticed a recent increase in "live poultry associated salmonella." CDC repeated its previous warning to avoid kissing chickens, turkeys or ducks and not to bring them into the house regardless of how clean they appear. The current popularity of urban egg farming makes 'hipsters' vulnerable to bacteria for which humans are unprepared.

FAST FACILITY FOR FIXING FAILING FILLINGS.
He works like a regular dentist replacing fillings, restoring crowns, patching dentures and whatever, except that his dental practice is at JFK airport in the big apple. Anxious patients can't believe their good fortune in finding a dentist while waiting between flights. For 30 years Dr. Robert Trager, age 76, has responded to emergencies, like patching up two boys who damaged their teeth horsing around on a carousel. He has helped immigration authorities with his X-ray machine estimating ages of people seeking asylum. His practice sweet spot is the routine business he gets from airport workers, airline crew member who stop for checkups between flights. He has the practice on airport signs, "JFK dentist. Join the smile high club."

ADDENDA
- The speed of a roller coaster increases an average of 10 mph when it's raining.
- The Elvis hit "Hound Dog" was written in about 10 minutes. I can believe that.
- Is that a beard or are you eating a muskrat?
- Now that I have learned how to make the most out of life most of it is gone.
- Sex is like air. It is only important if you're not getting any.
- It's only kinky the first time.

ALOHA AND KEEP THE FAITH rts
(Editorial comment is strictly that of the writer.)

HAWAIʻI JOURNAL OF MEDICINE & PUBLIC HEALTH

The Hawai'i Journal of Medicine & Public Health invites students and professionals at public health, medical, nursing, pharmacy, and dental schools or programs to enter in its **2nd Annual Writing Contest**.

Submissions must be original works related to the practice of medicine or public health, with a focus on the Hawaiian Islands or Pacific Rim region.

Eligibility:

- Undergraduates, masters- and doctoral-level students, post-doctoral fellows, and residents.
- Applicants must have an advisor who can attest to the individual's contributions and provide final approval of the submitted work.

2nd Annual

WRITING CONTEST

DEADLINE 12/30/2016

Win $500

Up to three $500 cash prizes will be awarded.

- Undergraduate Prize
- Graduate Student Prize
- Post-Graduate Prize

Winners will have their photographs featured along with their works in a future issue of HJM&PH. Selected manuscripts will be announced **January 20, 2017**.

For more info scan:

www.hjmph.org/contest

MIEC Belongs To Our Policyholders!

Gary Okamoto, MD
Board of Governors

Over the last 20 years Hawaii policyholders have saved an average of 26% on premiums with MIEC's Dividend Program*

Keeping true to our mission

MIEC has never lost sight of its original mission, always putting policyholders (doctors like you) first. For almost 35 years, MIEC has been steadfast in our protection of Hawaii physicians with conscientious Underwriting, excellent Claims management and hands-on Loss Prevention services; we've partnered with policyholders to keep premiums low.

Added value:

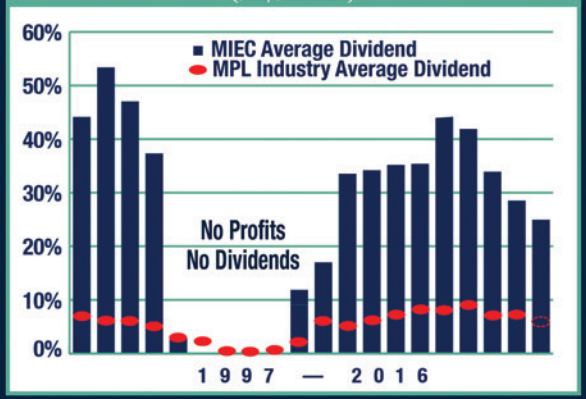
- No profit motive and low overhead
- Local Honolulu claims office

For more information or to apply:

- www.miec.com
- Call 800.227.4527
- Email questions to underwriting@miec.com

* On premiums at $1/3 million limits. Future dividends cannot be guaranteed.

Hawaii Dividends as % of premiums
($1m/$3m limits)



MIEC 6250 Claremont Avenue, Oakland, California 94618 • 800-227-4527 • www.miec.com

UCERA_ad_09.01.16

MIEC

Owned by the policyholders we protect.