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A Review of Factors Affecting Vaccine Preventable Disease in Japan

Norimitsu Kuwabara MD and Michael S.L. Ching MD, MPH

Abstract

Japan is well known as a country with a strong health record. However its incidence rates of vaccine preventable diseases (VPD) such as hepatitis B, measles, mumps, rubella, and varicella remain higher than other developed countries. This article reviews the factors that contribute to the high rates of VPD in Japan. These include historical and political factors that delayed the introduction of several important vaccines until recently. Access has also been affected by vaccines being divided into government-funded "routine" (eg, polio, pertussis) and self-pay "voluntary" groups (eg, hepatitis A and B). Routine vaccines have higher rates of administration than voluntary vaccines. Administration factors include differences in well child care schedules, the approach to simultaneous vaccination, vaccination contraindication due to fever, and vaccination spacing. Parental factors include low intention to fully vaccinate their children and misperceptions about side effects and efficacy. There are also knowledge gaps regarding indications, adverse effects, interval, and simultaneous vaccination. These multifactorial issues combine to produce lower population immunization rates and a higher incidence of VPD than other developed countries. This article will provide insight into the current situation of Japanese vaccinations, the issues to be addressed and suggestions for public health promotion.

Keywords

immunization, Japan, vaccination rates, voluntary vaccines, vaccine preventable disease

Introduction

Japan ranks among the world leaders in the health of its citizens. The Japanese have the longest life expectancy and number of years lived in full health. Japan is among the leaders in the developed world in low obesity rates and low infant and cardiovascular disease mortality. The World Health Organization (WHO) ranked Japan first in overall health goal attainment in 2000. Japan is well known as a country with persistently high rates of vaccine preventable diseases (VPD) such as hepatitis B, measles, rubella, mumps, and varicella. The 2012-2013 rubella outbreak in Japan caused about 15,000 cases of rubella and 43 cases of congenital rubella syndrome. In June 2013, the US Centers for Disease Control (CDC) released an advisory against travel to Japan for expectant mothers who are not rubella-immune because of the risk of congenital rubella syndrome. People traveling from Japan have also repeatedly brought VPD overseas with them. Japan accounted for more measles importation to the United States than any other single country between 1993 and 2001. Between 1994 and 2013 there were 32 cases of measles, 156 cases of mumps and 16 cases of rubella imported to Hawai‘i from Japan.

Why are VPD so common in Japan? Japan is among the wealthiest countries in the world, has universal health care, and has access to the same vaccines as other developed countries. This paper seeks to review the historical and systemic factors that have affected the rates of VPD in Japan and offers suggestions for public health intervention.

Recent Historical Context

The Japanese Preventive Immunization Law enacted in 1948 made vaccination a duty of parents and physicians. In 1970, because of public concern in part due to smallpox vaccine adverse events, the Japanese government organized a compensation system for injuries for vaccinations carried out under the vaccine law. This led to increased scrutiny of adverse events associated with other vaccines such as the pertussis vaccine. In the 1940s, the estimated mortality rate by pertussis in Japan was more than 10,000 per year. Whole cell pertussis vaccination was initially introduced in 1950. Combined diphtheria, tetanus, and pertussis vaccination, with whole cell pertussis component (DTwP) was introduced in Japan in 1968. Pertussis mortality dramatically decreased to 206 deaths in 1971, and no deaths by pertussis were reported by 1974. Nevertheless there were concerns about adverse effects because more than half of vaccinated patients complained of local redness, swelling, and fever.

When two infants died within 24 hours of receiving DTwP in the winter of 1974-1975, the government suspended licensure of DTwP. Licensure was reinstated two months later with a change in the minimum recommended age from 3 months to 2 years as a precaution. Vaccination rates in young children fell dramatically, and the incidence of pertussis increased to 13,105 cases with 41 deaths by 1979. Japanese researchers then developed the first acellular pertussis vaccine, and it was added to the routine vaccination program as combined DTaP in 1981. In the subsequent decade, the incidence of pertussis fell back to nearly the same rates as before 1975.

The next major vaccine issue began in 1987 when the measles, mumps, rubella (MMR) vaccine was approved for use in Japan. Shortly after its introduction this version of MMR was linked to aseptic meningitis due to the urabe strain of the mumps vaccine. Subsequently, in 1993, the combination MMR vaccine was discontinued and replaced with separate measles, mumps, and rubella vaccines. This incident caused significant public scrutiny of all vaccinations and swayed the prevailing political attitude towards a more cautious approach.

In addition to the pertussis and MMR events, the Japanese government was sued several times in the 1980s and 1990s due to vaccine adverse events. Pressure by citizens and medical professionals led to the 1994 modification of the Preventive

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Immunization Law to make vaccination an individual responsibility instead of a mandatory act.\textsuperscript{17} Mass vaccination in regional Public Health Centers was replaced by vaccination by private physicians.

**Adoption Rate of New Vaccines**

After the discontinuation of MMR and the change in the Preventive Immunization Law, new vaccines were introduced in Japan at much slower rates than in other developed countries. Between 1993 and 2007 there was a “vaccine gap”, and only two new vaccines were brought to the Japanese market (hepatitis A and a combination measles and rubella vaccine).\textsuperscript{19} In contrast, 17 new vaccines were introduced over the same time frame in the United States.\textsuperscript{19}

Several important vaccines were delayed by years during this time including *Haemophilus influenzae* type b (Hib) vaccine, pneumococcal conjugate vaccine (PCV7) and inactivated polio vaccine (IPV). Japan began using Hib and PCV7 in 2009 while the United States licensed these in 1985 and 2000 respectively.\textsuperscript{19,21,22} Because of the relatively recent introduction of these important vaccines, Hib meningitis and epiglottitis, and invasive pneumococcal diseases have only recently seen decreases in incidence rates.\textsuperscript{23–26}

Live, attenuated oral polio vaccine (OPV) was introduced in Japan in 1960 when there were 5800 cases of paralytic polio reported. By 1980 there were 50 cases of paralytic polio caused by wild poliovirus; all cases were due to vaccination.\textsuperscript{17} The United States replaced OPV with IPV in 2000 because of this concern and the overall low rates of disease. However, this decision occurred during the “vaccine gap” in Japan. IPV was only introduced in Japan in 2012 despite numerous cases of vaccine-associated paralysis and five unvaccinated individuals contracting poliomyelitis from OPV between 2004 to 2008.\textsuperscript{27,28}

Despite recent introductions of new vaccines, the Japanese Ministry of Health, Labor, and Welfare (MHLW) has been quick to suspend vaccines. Both Hib and PCV7 were suspended for a month in 2011 because of seven deaths of children that were ultimately found to be unrelated to the vaccines.\textsuperscript{17,29} One recent vaccine to enter the Japanese market is the quadrivalent human papillomavirus virus (HPV) vaccine Gardasil. This was added in April 2013 following US licensure of Gardasil in 2006. However only two months after becoming available in Japan, the government ordered providers to cease active promotion of this vaccine and Cervarix (human papillomavirus bivalent vaccine) because of fears of complex regional pain syndrome.\textsuperscript{30} HPV vaccination is under further investigation in Japan and may be withdrawn from the market despite ongoing use in the United States and other countries, drawing parallels to the DTwP and MMR events decades earlier.\textsuperscript{30}

**Multiple Vaccine Systems**

Japan has a universal health care system that provides access to health for all citizens. However there are two kinds of vaccine systems in Japan, routine vaccination and voluntary vaccination (Table 2). The government pays for routine vaccinations while families must pay for voluntary vaccinations. Costs vary by vaccine (Table 3). In Japan the list of voluntary vaccinations includes hepatitis A, hepatitis B, influenza, and mumps.

Japanese rates of routine vaccinations are among the highest in the world. For example, in 2013, the rate of vaccination with three doses of DTP in Japan was estimated to be >99.5%, compared with 94% in the United States.\textsuperscript{31} Despite prior challenges with rubella coverage, in 2013, 95% of eligible Japanese children reportedly received one dose of rubella vaccine compared with 91% in the United States.\textsuperscript{31}

On the other hand, voluntary vaccines have lower rates of administration than routine vaccinations.\textsuperscript{32,33} In a Japanese survey conducted in the second half of 2011, only 53% of 18 month old children were reported to be vaccinated against Hib, 43% against pneumococcus, and 1.3% against hepatitis B.\textsuperscript{35} This compares with rates of 90%, 92% and 92% respectively for these vaccinations in the United States.\textsuperscript{31} At the time of that

<table>
<thead>
<tr>
<th>Disease</th>
<th>United States</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2011 reported cases\textsuperscript{a}</td>
<td>Incidence/100,000 population\textsuperscript{b}</td>
</tr>
<tr>
<td>Measles</td>
<td>220</td>
<td>0.06</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pertussis</td>
<td>18,719</td>
<td>6.0</td>
</tr>
<tr>
<td>Rubella</td>
<td>4</td>
<td>0.0013</td>
</tr>
<tr>
<td>Polio (paralytic)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tetanus</td>
<td>36</td>
<td>0.012</td>
</tr>
<tr>
<td>Mumps</td>
<td>404</td>
<td>0.13</td>
</tr>
</tbody>
</table>

\textsuperscript{b}Projections for 2011, estimated using US Census\textsuperscript{c} and Japan National Institute of Population and Social Security Research.\textsuperscript{d}
\textsuperscript{c}This number does not reflect the ongoing rubella epidemic in Japan. There were 3,936 laboratory confirmed cases of rubella in January-May 2013 in Japan including 10 cases of congenital rubella syndrome.\textsuperscript{d}
Table 2. Comparison of Vaccines Between Japan and United States

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Japan</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. influenzae type b (Hib)</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Pneumococcus (PCV)</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Pertussis</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Tetanus</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Polio (inactivated)</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Measles</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Rubella</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Mumps</td>
<td>▲</td>
<td>○</td>
</tr>
<tr>
<td>Varicella</td>
<td>Δ</td>
<td>○</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>▲</td>
<td>○</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>▲</td>
<td>○</td>
</tr>
<tr>
<td>Rotavirus (oral)</td>
<td>▲</td>
<td>○</td>
</tr>
<tr>
<td>Influenza</td>
<td>▲</td>
<td>○</td>
</tr>
<tr>
<td>Tuberculosis (BCG)</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>○</td>
<td>x</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>x</td>
<td>○</td>
</tr>
</tbody>
</table>

○ = Routine vaccine; ▲ = Voluntary vaccine (Δ = Varicella will become a routine vaccine in October 2014); x = Vaccine not ordinarily available.

Table 3. Approximate Costs for Voluntary Vaccines in Japan

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Cost per vaccination (varies by area, these examples are provided for illustration*)</th>
<th>Number of Doses</th>
<th>Cost for the vaccine series ($’s only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumps</td>
<td>¥6,000 (US $60)</td>
<td>2</td>
<td>$120</td>
</tr>
<tr>
<td>Varicella</td>
<td>¥6,000 (US $80)</td>
<td>2</td>
<td>$160</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>¥6,800 (US $68)</td>
<td>2</td>
<td>$136</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>¥5,000 (US $50)</td>
<td>3</td>
<td>$150</td>
</tr>
<tr>
<td>Rotavirus Rotarix</td>
<td>¥15,000 (US $150)</td>
<td>2</td>
<td>$300</td>
</tr>
<tr>
<td>RotaTeq</td>
<td>¥10,000 (US $100)</td>
<td>3</td>
<td>$300</td>
</tr>
<tr>
<td>Influenza</td>
<td>¥2,500 (US $25)</td>
<td>1 (annual)</td>
<td>$25</td>
</tr>
<tr>
<td>Human papilloma virus (Cervarix or Gardasil)</td>
<td>¥16,000 (US $160)</td>
<td>3</td>
<td>$480</td>
</tr>
</tbody>
</table>

Total Out of Pocket Costs | $1371


study, Hib and pneumococcal vaccines were voluntary vaccines and did not become routine until April 2013.

Part of the lower rate of vaccination with voluntary vaccines may be cost. Vaccine expense was cited as the most common discouraging factor among families not receiving voluntary vaccinations. In one study on HPV vaccine, 93% of mothers reported that they would accept the vaccine if it were free but only 1.5% would accept it at the recommended price of 40,000 yen (~US $390). In another study 20% of adults reported that they were unable to afford the influenza vaccine. Having free and non-free sets of vaccinations affects access and also communicates explicit government endorsement and prioritization of routine vaccinations.

A result of the lower rates of vaccination for voluntary vaccines is ongoing outbreaks of vaccine preventable diseases. Rotavirus has experienced significant declines in countries adopting universal vaccination programs, while Japan experiences ongoing seasonal outbreaks of this disease. Annual acute hepatitis B incidence in Japan was estimated to be 1.7-1.9 per 100,000 in 2007-2008. In the United States where hepatitis B vaccination rates exceed 90%, the incidence has fallen from 11.5 per 100,000 to about 1.5 per 100,000 in 2007 and has continued to fall to about 0.9 per 100,000 in 2011.

Schedule of Well Child Care and Vaccination Issues

The schedule for well child care may also present barriers to vaccination. In Japan, children are usually seen at 1 month of age, 4 months, 10 months, 18 months, and 3 years. This frequency may be insufficient to cover every vaccine. Parents may not bring their children for vaccines between well visits because they are busy working even when pediatricians open “immunization clinic” hours for patients.

The Japanese approach to vaccination in children with mild fevers may also contribute to missed opportunities for vaccination. The Japanese Immunization Vaccination Law does not allow vaccination if patients have a body temperature more than 37.5° C (99.5° F). This contrasts with the recommended practice in the United States, where there is not a specific threshold for body temperature. The US Advisory Committee on Immunization Practices (ACIP) recommends basing a decision to vaccinate on the overall clinical impression of the physician instead of a predetermined body temperature. Delaying vaccination of children who have mild fevers at well child visits increases the risk of missed vaccinations.

Recommendations about vaccine intervals also vary between the United States and Japan. If an inactivated vaccine or oral live vaccine is given, United States patients can return at any time to receive additional vaccinations if needed. If a parenteral live vaccine is administered, patients should wait at least 28 days before receiving another parenteral live vaccine. In Japan, patients need to wait at least one week for the next vaccination after any inactivated vaccine as well as 28 days for live vaccines.
A waiting period does not typically present an issue if multiple vaccines are given simultaneously, but in Japan multiple vaccines are less often given simultaneously than in the United States. In Japan, there has not historically been a need for simultaneous vaccination because many of the vaccines delivered in early childhood were not available until recently (eg, Hib, PCV) or not on the routine schedule (HBV). Only since the licensure of Hib and PCV has there been an opportunity to deliver multiple routine vaccines on the same day, but there are still reports of hesitation among families and providers to do so. Providing a combination vaccine might ameliorate this issue, but such vaccines are limited to Japanese-produced DTaP, diphtheria-tetanus (DT), and measles-rubella at this time. A diphtheria-tetanus-acellular pertussis plus Sabin derived injectable poliovirus vaccine (DTaP-sIPV) was introduced in November 2012, and may improve coverage but this will not eliminate the need for simultaneous vaccination.

In Japan, vaccinations also must be given within a predetermined schedule to be covered by the government. If parents do not return within this window, the routine vaccination fee may not be reimbursed. In this situation, patients who miss the window must pay for routine vaccinations themselves, producing a further barrier toward even routine vaccination.

**School Requirements**

While no federal vaccination laws exist in the United States, all 50 states require certain vaccinations prior to the entry of children into public schools. However, there is no domestic legislation to enforce vaccination for children entering school in Japan. This may result in a missed opportunity for vaccination. Studies following the introduction of varicella vaccine in the United States have shown that school entry requirements increased rates of this vaccination by an estimated 8%-28% within the first year of the mandate.

**Vaccine Administration Route**

Another issue that may affect vaccine effectiveness is the administration route. Japanese law requires subcutaneous administration of most vaccines except HPV. This contrasts to the intramuscular route for many vaccines in other countries. For many vaccinations, intramuscular shots are associated with decreased pain, lower adverse effect rates, and improved efficacy compared to the subcutaneous route.

The reason for this preference for subcutaneous vaccination is also rooted in history. The intramuscular route was popular in Japan until the 1970s. The anterior femoral site was the preferred injection location. However, multiple cases of quadriceps contractures were reported around this time. Despite the fact that the main medicines administered intramuscularly in this area were analgesics and antibiotics, not vaccines, these events became a significant social issue. Subsequently, the government changed the Preventive Immunization Law and adopted a cautious stance toward intramuscular administration. This aspect of the law has not been changed in the past 40 years.

**Parent and Provider Attitudes toward Vaccination**

Lower vaccination rates among voluntary vaccinations may also be driven by parent and provider attitudes. Japanese parents appear to have low intention to vaccinate their children against voluntary vaccines. In one study 33% of mothers reported an intent to fully vaccinate their children with 50% reporting a desire to vaccinate only for specific vaccines. In another study of parents who did not choose voluntary vaccinations, 39% worried about side effects, and 12.9% doubted the vaccine’s positive effects. Ten percent were motivated to acquire natural resistance to some voluntary vaccine pathogens (eg, varicella) despite the low likelihood of developing natural immunity to other voluntary vaccine pathogens (eg, hepatitis B).

Health professionals may also have misperceptions of vaccines. Japanese medical providers do not always have a basic knowledge of vaccines such as the adverse effects, indication of vaccination, interval, or possibility of giving multiple vaccines on the same day. A qualitative study of Japanese resident physicians demonstrated low personal vaccination rates for measles and themes of lack of awareness of disease severity and fear of adverse effects. Additionally large numbers of healthcare workers have been shown to be susceptible to VPD.

**Discussion**

While there are ongoing issues with vaccine adoption in Japan, there is great hope for progress. Recent changes in vaccine policy have led to licensing of Hib and pneumococcal conjugate vaccines. These vaccines have resulted in significant decreases in invasive *H. influenzae* and pneumococcal disease. The incidence rates of *H. influenzae* meningitis and non-meningitis infections were reduced by 92% and 82% respectively between 2008 and 2012. There have been similar decreases in pneumococcal meningitis (71% decrease) and non-meningitis invasive pneumococcal disease (52% decrease).

Nevertheless, despite the introduction of new vaccines, there are still large numbers of susceptible adults who may serve as a reservoir for ongoing infection. Adults constituted 92% of cases in the 2012-2013 rubella outbreak, and eighty percent of 20-39 year olds who developed rubella had not received the rubella vaccine. Because of prioritization of prior immunization efforts towards women to prevent congenital rubella syndrome, only 73%-86% of adult males demonstrated seropositivity to rubella. To interrupt natural transmission of disease, it is estimated that 87%-99% vaccination rates with rubella vaccine and 95%-99% with measles vaccine are required. Because of Japan’s high population density, even higher coverage may be required, particularly during an outbreak.

There has been progress towards improving population immunity rates. For example, in 2006, Japan increased the recommended frequency of measles and rubella (MR) vaccine from once to twice due to measles outbreaks in 2001-2002. Because the efficacy of a single dose of measles containing vaccine is estimated at 95%, a two dose schedule is critical for
ensuring that the herd immunity threshold is reached. Other changes such as catch up immunization with MR in 13 and 18 year olds, and public awareness campaigns were started after the development of the National Measles Elimination Plan in 2007. This has resulted in improved protection of children as only 5.6% of rubella cases in the recent outbreak were among children under 15 years old. However, until adult immunization levels increase, herd immunity effects may be limited.

On a political level, there has also been progress. In the United States, the ACIP is a federal committee that is mainly composed of specialists who have no interest in pharmaceutical companies. The ACIP evaluates evidence of vaccine efficacy and provides recommendations for their use. The Japanese government recently founded a similar vaccine subcommittee of its MHLW in April 2013. The purpose of this subcommittee is to evaluate the efficacy of vaccines and monitor their adverse effects. The MHLW appoints the committee members, and they provide only recommendations rather than set actual policy. Consumer representatives and patients provide only limited input on recommendations. Final policy decisions continue to be made by the MHLW.

Nevertheless the actions of this committee may be able to promote uptake of new and existing vaccines. Since the founding of this subcommittee, the MHLW has decided to shift varicella vaccine from the voluntary to the routine vaccine list starting in October 2014. The remaining voluntary vaccines (eg, mumps, hepatitis B, and rotaviruses) will be discussed for inclusion in the list of routine vaccines after the 2015 vaccine subcommittee meetings.

While the number of vaccines has been increasing, there are still barriers to increasing vaccination effectiveness such as rules regarding the route, interval, and payment systems. Increasing the number of government subsidized vaccines, improving the knowledge of physicians and parents, and reforming policies on subcutaneous injection and interval of vaccination may all contribute to improvements in Japanese VPD rates. In addition, public and practice-based vaccine recall strategies, monitoring of voluntary as well as routine vaccine delivery and safety systems, public health campaigns promoting catch-up vaccine coverage for adults, and creating quality or financial incentives for primary care providers to vaccinate children and adults are all strategies that have been recommended in the United States for enhancing vaccination and may be beneficial in Japan.

One example for improving parent and provider knowledge would be to standardize vaccination information efforts. In contrast to the national Vaccine Information Statements provided by the CDC in the United States, each municipal government in Japan provides its own vaccination information to citizens based on their own interpretation. This information is not standardized between municipalities. It may be beneficial for the Japanese government to standardize this information and make it widely available to improve parent and provider knowledge.

Another possible area for improvement would be to institute mandatory vaccination requirements for children attending school in Japan. While vaccination rates with the routine vaccines are already high, this would provide an opportunity for reviewing the vaccination status of all children. However, this would constitute a very significant change in public policy, and instituting such a policy, would require the unified support of many stakeholders.

Conclusion

Providers who may see Japanese nationals or their children should be aware of differences in rates of vaccinations. It will be important to carefully review vaccine records as the adults and their children may be missing vaccinations that would be important for disease prevention and school entry. In addition there should be a higher index of suspicion for VPD when these children present with febrile illnesses, especially among tourists or new arrivals to the country. Finally, Japanese parents may have attitudes towards vaccination that differ from many American parents, and providers should be prepared to address potential barriers to vaccination with cultural sensitivity. They should be ready to explain the differences in the vaccine systems in America and Japan.

The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

Conflict of Interest

None of the authors identify a conflict of interest.

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References

Prescription Drug Use During and Immediately Before Pregnancy in Hawai’i — Findings from the Hawai’i Pregnancy Risk Assessment Monitoring System, 2009-2011

Emily K. Roberson PhD, MPH and Eric L. Hurwitz DC, PhD

Abstract

There are relatively few population-based studies on prescription drug use during pregnancy. Hawai’i Pregnancy Risk Assessment Monitoring System (PRAMS) survey data from 4,735 respondents were used to estimate statewide prevalence of overall non-vitamin prescription drug use during and in the month before pregnancy. Data were weighted to be representative of all pregnancies resulting in live births in Hawai’i in 2009-2011. Of women with recent live births in Hawai’i, 14.2% (95% CI: 13.0 – 15.5) reported prescription drug use before pregnancy and 17.6% (95% CI: 16.2 – 19.0) reported prescription drug use during pregnancy. Prevalence of prescription drug use both before and during pregnancy was highest among women who had a pre-pregnancy chronic disease, were White, and had a pregnancy-related medical problem. Pain relievers (2.82%; 95% CI: 2.28 – 3.47), psychiatric medications (2.34%; 95% CI: 1.85 – 2.95), and anti-infectives (1.91%; 95% CI: 1.46 – 2.48) were the most common types of medications used before pregnancy. The most commonly-reported prescription medication types taken during pregnancy were anti-infectives (4.00%; 95% CI: 3.34 – 4.79), pain relievers (3.18%; 95% CI: 2.56 – 3.94), and gastrointestinal drugs (3.08%; 95% CI: 2.47 – 3.83). Of women who reported prescription drug use during pregnancy and attended prenatal care, 10.3% (95% CI: 8.0 – 13.2) reported that their healthcare provider had not counseled them during prenatal care on which medicines are safe to use during pregnancy.

Keywords

Prescription Drug Use, Pregnancy

Introduction

Despite the fact that some medications have documented teratogenic or otherwise harmful effects when used during pregnancy, prescription drug use among pregnant women is increasingly common. There are likely numerous factors that are influencing the increase in prescription drug use in pregnancy, with proposed explanations including rising prevalence of chronic disease in reproductive age populations, a greater number of pharmaceutical options for treating chronic diseases, and increasing maternal age at pregnancy. Although women with chronic diseases pre-pregnancy are more likely to report prescription drug use during pregnancy than women without chronic diseases, women without chronic diseases also report high usage of prescription medications during pregnancy. Another complicating factor is the fact that approximately half of all pregnancies in the United States are not intended. These unintended pregnancies often lead to accidental in utero exposures to prescription medication early in pregnancy, before the woman recognizes that she is pregnant. The research findings that do exist typically come from data sources with limited generalizability, such as electronic medical records, pharmacy dispensing records, or health insurance claims databases. This study aimed to use a population-based dataset to (1) determine the prevalence of non-vitamin prescription drug use before and during pregnancy in Hawai’i, (2) identify the types of medications used during these time periods, and (3) describe differences in non-vitamin prescription drug use during and immediately before pregnancy in Hawai’i by maternal demographic characteristics.

Methods

Data Source

A secondary analysis was conducted using Hawai’i Pregnancy Risk Assessment Monitoring System (PRAMS) survey data from 2009 to 2011. The PRAMS survey collects self-reported information on maternal behaviors, attitudes, and experiences before, during, and immediately following pregnancy. PRAMS programs operate according to a standardized data collection protocol developed by the Centers for Disease Control and Prevention (CDC), consisting of a mailed questionnaire (self-administered) with telephone follow-up for non-responders. Mothers are selected for the Hawai’i PRAMS survey using a stratified sample drawn from certificates of live birth in Hawai’i, and complete the survey 3-8 months postpartum. The majority of participants complete the Hawai’i PRAMS survey 3-4 months postpartum. The Hawai’i PRAMS analytic dataset includes information collected from Hawai’i PRAMS survey questions in addition to selected linked variables extracted from birth certificates. If PRAMS programs are able to achieve a minimum weighted response rate of 65% in each sampling stratum, survey results are considered generalizable to all live births in the state in a given year. Responses are then weighted according to CDC protocol to be representative of all pregnancies resulting in live births in Hawai’i in a given year. Hawai’i PRAMS weighted response rates for the years presented in this analysis ranged from 71%-73%. Additional information on PRAMS methodology can be found at: http://www.cdc.gov/prams/methodology.htm.

Data were available for 4,735 respondents, representing a weighted population of approximately 55,690 women with live births. Secondary analysis of Hawai’i PRAMS data is covered under pre-existing approvals granted by the Institutional Review Board of the Human Research Protection Office of the CDC, as well as by the Hawai’i State Department of Health Institutional Review Board.
Measures

The following questions pertaining to prescription drug use were used for this analysis:

During any of your prenatal care visits, did a doctor, nurse, or other health care worker talk with you about any of the things listed below? Please count only discussions, not reading materials or videos.

For each item, circle Y (Yes) if you used it or circle N (No) if you did not.

a. Prescription drugs

Did you use any of these drugs in the month before you got pregnant?

For each item, circle Y (Yes) if you used it or circle N (No) if you did not.

a. Prescription drugs

If yes, what kinds? Please tell us:

Did you use any of these drugs when you were pregnant?

For each item, circle Y (Yes) if you used it or circle N (No) if you did not.

a. Prescription drugs

If yes, what kinds? Please tell us:

Write-in responses were manually reviewed in order to properly adjust for misspellings, multiple drugs listed, and other factors. Responses were then coded into groups by medical indication using SAS 9.2 (SAS Institute Inc., Cary, NC) “string” and “upcase” commands. Medications with possible indications in multiple groups were cross-checked with maternal and/or birth certificate report of diagnoses to determine most likely group for categorization. An example of this would be the drug lamotrigine, which may be prescribed for psychiatric conditions, or for non-psychiatric seizure disorders. In this situation, the medication use was cross-checked with maternal report of medical conditions in order to determine the most likely categorization. Write-in entries that were larger than thirty characters were listed in separate comment file; these responses were also manually reviewed and coded into groups by unique ID number. In a very few cases, determination of which drug was being referenced was not possible. For each time period examined, there were fewer than five unweighted cases in which a drug listed was not reliably identified due to spelling errors, fewer than ten unweighted cases in which a respondent did not remember or state what type of medication was used, and/or did not provide additional information that could aid in drug identification, and fewer than twenty unweighted cases in which a participant selected “Yes” for prescription drug use, but then left the write-in box blank and did not provide additional information that could aid in drug identification. In cases where classifying an entry was not possible, it was coded as “Unknown”. Coding accuracy was verified on an ongoing basis throughout the analysis by manual review of SAS and SUDAAN outputs listing responses included and not included in each grouping.

Maternal age, race/ethnicity, nativity, education, and parity were determined based on linked birth certificate variables included in the Hawai‘i PRAMS analytic dataset. Approximately 23% of the population of Hawai‘i identifies as mixed race, however the maternal race/ethnicity variables included in the Hawai‘i PRAMS analytic dataset were sorted into single race groups based on a standard algorithm used by the Hawai‘i Department of Health Office of Health Status and Monitoring prior to their inclusion in the dataset. Federal Poverty Level (FPL) was based on maternal reports of household annual income and number of dependents in the year before delivery and was calculated according to Hawai‘i’s specific threshold guidelines. Prenatal counseling regarding medication safety, pre-pregnancy chronic disease, and pregnancy-related medical problems were based on maternal reports in the Hawai‘i PRAMS survey. The created variable for pre-pregnancy chronic disease included the following conditions, as reported in the Hawai‘i PRAMS survey only: Type 1 or Type 2 diabetes at any point before pregnancy; and asthma, hypertension, heart problems, epilepsy, thyroid problems, depression, and anxiety in the three months before pregnancy. The created variable for pregnancy-related medical problems included the following conditions, as reported in the Hawai‘i PRAMS survey: gestational diabetes, vaginal bleeding, kidney or bladder infection, severe nausea, vomiting or dehydration, cervical cerclage, hypertension, preeclampsia, toxemia during pregnancy, placental problems, preterm labor, or blood transfusion during pregnancy. SAS-callable SUDAAN 10.0 (RTI International, Research Triangle Park, NC) was used to generate prevalence estimates, confidence intervals, and P-values.

Results

Maternal demographic characteristics and prescription drug use before and during pregnancy are shown in Table 1. Of women with recent live births in Hawai‘i, 14.2% (95% CI: 13.0 – 15.5) reported non-vitamin prescription use (NVPU) immediately before pregnancy and 17.6% (95% CI: 16.2 – 19.0) reported NVPU during pregnancy. Women who had a pre-pregnancy chronic disease had the highest prevalence of NVPU both before (37.7%) and during (36.1%) pregnancy. By race-ethnicity, White women reported the highest prevalence of NVPU (22.9% before and 26.2% during pregnancy). Also, women who had a pregnancy-related medical problem were more likely to report NVPU both before (18.6%) and during (24.5%) pregnancy. Differences by demographic variables listed in Table 1 were statistically significant at the P < .001 level, with the exception of differences in use during pregnancy by maternal age (P = .002) and differences by parity, both before pregnancy (P = .891) and during pregnancy (P = .869).

Types of prescription drugs used before and during pregnancy are shown in Table 2. Pain relievers (2.82%; 95% CI: 2.28 – 3.47), psychiatric medications (2.34%; 95% CI: 1.85 – 2.95), and anti-infectives (1.91%; 95% CI: 1.46 – 2.48) were the most common types of medications used before pregnancy. The most commonly-reported prescription medication types taken during pregnancy were anti-infectives (4.00%; 95% CI: 3.34 – 4.79), pain relievers (3.18%; 95% CI: 2.56 – 3.94), and gastrointestinal drugs (3.08%; 95% CI: 2.47 – 3.83). Overall, 13.9% (95% CI: 12.7 – 15.2) of women reported not being counseled about medication safety during prenatal care. This estimate was
Table 1. Non-vitamin prescription use (NVPU) by maternal characteristics, Hawai'i PRAMS, 2009-2011

<table>
<thead>
<tr>
<th></th>
<th>Percent of total birth population* (95% CI)</th>
<th>Percent reporting NVPU before pregnancy* (95% CI)</th>
<th>Percent reporting NVPU during pregnancy* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100 (N/A)</td>
<td>14.2 (13.0 – 15.5)</td>
<td>17.6 (16.2 – 19.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 20</td>
<td>7.3 (6.4 – 8.3)</td>
<td>7.1 (4.5 – 11.0)</td>
<td>10.3 (6.9 – 15.2)</td>
</tr>
<tr>
<td>20-24</td>
<td>23.6 (22.1 – 25.3)</td>
<td>10.9 (8.7 – 13.4)</td>
<td>16.1 (13.4 – 19.3)</td>
</tr>
<tr>
<td>25-29</td>
<td>27.3 (25.7 – 29.0)</td>
<td>15.5 (13.1 – 18.2)</td>
<td>17.3 (14.8 – 20.1)</td>
</tr>
<tr>
<td>30-34</td>
<td>24.4 (22.9 – 26.0)</td>
<td>15.7 (13.3 – 18.5)</td>
<td>18.6 (15.9 – 21.7)</td>
</tr>
<tr>
<td>35 or older</td>
<td>17.4 (16.1 – 18.8)</td>
<td>17.5 (14.5 – 20.9)</td>
<td>21.5 (18.2 – 25.2)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hawaiiana</td>
<td>30.1 (28.4 – 31.7)</td>
<td>13.2 (11.2 – 15.5)</td>
<td>15.3 (13.1 – 17.8)</td>
</tr>
<tr>
<td>White</td>
<td>23.0 (21.5 – 24.6)</td>
<td>22.9 (19.8 – 26.4)</td>
<td>26.2 (23.0 – 29.8)</td>
</tr>
<tr>
<td>Filipino</td>
<td>17.8 (16.5 – 19.3)</td>
<td>12.3 (9.8 – 15.4)</td>
<td>16.1 (13.1 – 19.6)</td>
</tr>
<tr>
<td>Japanese</td>
<td>9.3 (8.3 – 10.5)</td>
<td>12.0 (8.8 – 16.3)</td>
<td>14.8 (11.2 – 19.4)</td>
</tr>
<tr>
<td>Other Pacific Islanderb</td>
<td>7.4 (6.4 – 8.5)</td>
<td>3.1 (1.6 – 5.9)</td>
<td>5.7 (3.2 – 10.1)</td>
</tr>
<tr>
<td>Other Asian</td>
<td>7.2 (6.3 – 8.3)</td>
<td>10.2 (6.7 – 15.1)</td>
<td>15.9 (11.5 – 21.6)</td>
</tr>
<tr>
<td>Other or unknownd</td>
<td>5.2 (4.4 – 6.1)</td>
<td>12.7 (8.4 – 18.8)</td>
<td>21.6 (15.5 – 29.3)</td>
</tr>
<tr>
<td>Nativity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born in United States</td>
<td>74.8 (73.1 – 76.4)</td>
<td>16.5 (15.0 – 18.1)</td>
<td>19.9 (18.3 – 21.7)</td>
</tr>
<tr>
<td>Born outside United States</td>
<td>25.2 (23.7 – 26.9)</td>
<td>7.3 (5.6 – 9.4)</td>
<td>10.8 (8.5 – 13.2)</td>
</tr>
<tr>
<td>Education Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>7.5 (6.6 – 8.5)</td>
<td>6.3 (4.0 – 10.0)</td>
<td>7.4 (4.7 – 11.3)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>39.7 (37.9 – 41.5)</td>
<td>12.8 (11.0 – 14.9)</td>
<td>15.5 (13.5 – 17.8)</td>
</tr>
<tr>
<td>1-3 years of college</td>
<td>23.5 (22.0 – 25.1)</td>
<td>15.5 (13.0 – 18.4)</td>
<td>21.4 (18.4 – 24.7)</td>
</tr>
<tr>
<td>4 or more years of college</td>
<td>29.3 (27.7 – 31.0)</td>
<td>17.4 (15.0 – 20.1)</td>
<td>20.3 (17.7 – 23.2)</td>
</tr>
<tr>
<td>Federal Poverty Level (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% or less</td>
<td>29.3 (27.6 – 31.0)</td>
<td>10.9 (9.1 – 13.1)</td>
<td>11.5 (9.6 – 13.8)</td>
</tr>
<tr>
<td>101% - 200%</td>
<td>26.0 (24.4 – 27.7)</td>
<td>13.0 (10.7 – 15.7)</td>
<td>17.9 (15.1 – 21.1)</td>
</tr>
<tr>
<td>201% or greater</td>
<td>44.7 (42.8 – 46.6)</td>
<td>17.9 (15.8 – 20.1)</td>
<td>21.8 (19.5 – 24.3)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primipara</td>
<td>40.6 (38.8 – 42.4)</td>
<td>14.1 (12.3 – 16.1)</td>
<td>17.7 (15.6 – 20.0)</td>
</tr>
<tr>
<td>Multipara</td>
<td>59.4 (57.6 – 61.2)</td>
<td>14.2 (12.7 – 16.0)</td>
<td>17.5 (15.7 – 19.4)</td>
</tr>
<tr>
<td>Pre-pregnancy Chronic Diseasee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19.7 (18.3 – 21.1)</td>
<td>37.7 (34.0 – 41.7)</td>
<td>36.1 (32.4 – 40.1)</td>
</tr>
<tr>
<td>No</td>
<td>80.3 (78.9 – 81.7)</td>
<td>8.4 (7.4 – 9.6)</td>
<td>13.0 (11.7 – 14.5)</td>
</tr>
<tr>
<td>Pregnancy-related Medical Problemf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52.8 (50.9 – 54.6)</td>
<td>18.6 (16.8 – 20.6)</td>
<td>24.5 (22.4 – 26.7)</td>
</tr>
<tr>
<td>No</td>
<td>47.2 (45.4 – 49.1)</td>
<td>9.2 (7.8 – 10.9)</td>
<td>9.8 (8.3 – 11.6)</td>
</tr>
</tbody>
</table>

*Weighted estimates; **Hawaiian includes part Hawaiian; ***Other Pacific Islander includes: Samoan, Guamanian, and other Pacific Islander; ****Other Asian includes: Chinese, Korean, Vietnamese, Asian Indian, and other Asian; ******Other or unknown includes: African American, American Indian, Puerto Rican, Cuban, Mexican, and all others; Pre-pregnancy chronic disease includes: diabetes, asthma, hypertension, heart problems, epilepsy, thyroid problems, depression, and anxiety; Pregnancy-related medical problem includes: gestational diabetes, vaginal bleeding, kidney or bladder infection, severe nausea, vomiting, or dehydration, cervical cerclage, hypertension, preeclampsia, or toxemia during pregnancy, placental problems, preterm labor, and blood transfusion during pregnancy.

Differences by demographic variables listed in this table were statistically significant at the P < .001 level, with the exception of differences in use during pregnancy by maternal age (P = .002) and differences by parity, both before pregnancy (P = .891) and during pregnancy (P = .869).
Table 2. Prescription drug use before and during pregnancy by type, Hawaii PRAMS, 2009-2011

<table>
<thead>
<tr>
<th>Prescription Type</th>
<th>Percent reporting use before pregnancy* (95% CI)</th>
<th>Percent reporting use during pregnancy* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy medications</td>
<td>1.52 (1.12 – 2.07)</td>
<td>1.71 (1.28 – 2.28)</td>
</tr>
<tr>
<td>Anti-infectives</td>
<td>1.91 (1.46 – 2.48)</td>
<td>4.00 (3.34 – 4.79)</td>
</tr>
<tr>
<td>Asthma medications</td>
<td>1.40 (1.05 – 1.86)</td>
<td>1.44 (1.07 – 1.93)</td>
</tr>
<tr>
<td>Birth control medications</td>
<td>0.80 (0.53 – 1.20)</td>
<td>N/A</td>
</tr>
<tr>
<td>Cardiovascular medications</td>
<td>1.42 (1.05 – 1.92)</td>
<td>1.69 (1.29 – 2.21)</td>
</tr>
<tr>
<td>Diabetes medications</td>
<td>0.83 (0.56 – 1.22)</td>
<td>1.39 (1.02 – 1.89)</td>
</tr>
<tr>
<td>Fertility treatment medications</td>
<td>0.81 (0.56 – 1.18)</td>
<td>N/A</td>
</tr>
<tr>
<td>Gastrointestinal medications</td>
<td>0.88 (0.58 – 1.33)</td>
<td>3.06 (2.47 – 3.83)</td>
</tr>
<tr>
<td>Other medications</td>
<td>1.27 (0.92 – 1.74)</td>
<td>1.28 (0.92 – 1.76)</td>
</tr>
<tr>
<td>Pain relievers</td>
<td>2.82 (2.28 – 3.47)</td>
<td>3.18 (2.56 – 3.94)</td>
</tr>
<tr>
<td>Pregnancy support medications</td>
<td>N/A</td>
<td>0.74 (0.50 – 1.10)</td>
</tr>
<tr>
<td>Psychiatric medications</td>
<td>2.34 (1.85 – 2.95)</td>
<td>1.38 (1.01 – 1.87)</td>
</tr>
<tr>
<td>Thyroid medications</td>
<td>0.86 (0.61 – 1.22)</td>
<td>1.02 (0.74 – 1.41)</td>
</tr>
<tr>
<td>Unknown medications</td>
<td>0.34 (0.20 – 0.58)</td>
<td>0.66 (0.41 – 1.05)</td>
</tr>
<tr>
<td>Vitamins/supplements</td>
<td>1.88 (1.42 – 2.47)</td>
<td>6.81 (5.94 – 7.81)</td>
</tr>
</tbody>
</table>

*Weighted estimates; Anti-infectives group includes: antibiotic, antiviral, antifungal, and antiparasitic medications; Other group includes all identifiable medications not otherwise grouped; for drugs taken during pregnancy, Other group also includes birth control; Psychiatric group includes antidepressant, antianxiety, and antipsychotic medications, as well as medications used to treat attention deficit disorder and attention deficit hyperactivity disorder; Vitamins/supplements group estimates include nonspecific responses indicating vitamin/supplement use (eg, prenatal vitamins) as well as specific references to individual supplements (eg, iron pills) and reflect only responses to the prescription drug use before and during pregnancy questions on the Hawaii PRAMS survey, not responses to other survey questions specifically addressing prenatal or multivitamin use.

Discussion

To the knowledge of the authors, this study is the first examining prescription drug use before and during pregnancy using maternally reported, population-based data from the Hawaii PRAMS survey. This data source provides a different perspective from other research findings relying on data from electronic medical records, pharmacy dispensing records, or health insurance claims databases. Data from those sources do not directly address what is arguably the most important question with regards to this line of research: what prescription drugs did women use? Instead, these data sources use proxy measures such as: what drugs were women prescribed, what prescriptions were filled, and what prescriptions were submitted for insurance coverage. However, many people are prescribed medications that they never fill, fill medication that they never use, or use medication that they never submit for insurance coverage.22,23 Also, none of these data sources address the usage of prescription medication not prescribed to the woman herself. This means that any use of medications provided by friends, family, or other means would not be captured. This is of concern because sharing and borrowing of prescription medication is exceedingly common among American women of reproductive age, with recent estimates indicating that more than one in four have shared or borrowed prescription drugs.26,27

Limitations of this study related to the Hawaii PRAMS survey itself include that the data are self-reported, and consequently subject to bias due to recall or reporting factors. This could affect the results of this study, as previous research has shown that women are more likely to recall use of some types of medications than others when retrospectively asked about medication use during pregnancy.28 Reporting of medication use on the PRAMS survey might also have been affected by individual-level factors related to patient compliance or noncompliance with medical recommendations, possibly resulting in underreporting, overreporting, or misclassification of prescription drug usage.23,29,30 Additionally, PRAMS nonresponse weights are calculated based on assumptions that women in a particular subgroup who responded would be predicted to have similar responses to those who did not respond. It is unclear how valid this assumption may be for the outcomes examined in this study.31

There are also limitations related to the Hawaii PRAMS prescription drug use questions in particular. Issues with comprehension of these specific questions might have posed problems for some individual respondents. For example, some medications listed as responses were likely not prescribed, and may have in fact been over-the-counter medications. However, because many drugs are available both over the counter and by
prescription (eg, ibuprofen), no attempt was made to exclude responses that may have been over the counter. This could mean that estimates for certain indication groups might include use of over the counter drugs, in addition to prescription drugs. The Hawai‘i PRAMS survey questions related to prescription drug use also did not have information on drug dosages, frequency of use, or pregnancy trimester of usage, all of which have important implications related to the effects of specific drugs on pregnancy and birth outcomes.

Conclusion
As prescription drug use among the general public becomes more widespread, there is an increased need for careful monitoring by health care providers of usage in pregnant and reproductive-aged women. The finding that 10.3% of women who report using prescription medication during pregnancy also reported not receiving counseling on medication safety during prenatal care is especially concerning for this reason. Counseling on potential risks to mother and fetus should be emphasized during prenatal care visits to assure that women are informed and empowered to make the best decisions for themselves and their infants.

Disclaimer
The findings and conclusions described in this article are those of the authors and do not necessarily represent the official position of the Hawai‘i State Department of Health, the Centers for Disease Control and Prevention, or any other organization.

Conflict of Interest
None of the authors have any financial or other conflict of interests to disclose.

Acknowledgements
The researchers would like to thank all of the women who have responded to the Hawai‘i PRAMS survey since the program began as a pilot project in 1999. Without their willingness to share information about their experiences before, during, and after pregnancy, this research would not be possible. Additionally, Tonya Lowery St. John and Ranjani Starr of the Hawai‘i State Department of Health, and Indu Ahluwalia of the Centers for Disease Control and Prevention provided valuable review and comment on an early version of this manuscript. The researchers would also like to acknowledge the Hawai‘i State Department of Health, and specifically the Family Health Services Division and Maternal and Child Health Branch, for supporting the Hawai‘i PRAMS program. This study was made possible in part by CDC grant #1U01DP003145.

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References
Project *Kealahou*: Improving Hawai‘i’s System of Care for At-Risk Girls and Young Women through Gender-Responsive, Trauma-Informed Care

Edward Suarez PhD; David S. Jackson PhD; Lesley A. Slavin PhD; M. Stanton Michels MD; and Kathleen M. McGeehan PhD, MS

**Abstract**

Project Kealahou (PK) is a six-year, federally-funded program aimed at improving services and outcomes for Hawai‘i’s female youth who are at risk for running away, truancy, abuse, suicide, arrest and incarceration. PK builds upon two decades of sustained cross-agency efforts among the state’s mental health, juvenile justice, education, and child welfare systems to promote system-of-care (SOC) principles of community-based, individualized, culturally and linguistically competent, family driven, youth-guided, and evidence-based services. In addition, PK emphasizes trauma-informed and gender-responsive care in serving its target population of females ages 11-18 years who have experienced psychological trauma.

Results from the first four years of the implementation of PK in the Department of Health’s (DOH) Child and Adolescent Mental Health Division (CAMHD) highlight the serious familial, socioeconomic, functional, and interpersonal challenges faced by the young women who receive services in Hawai‘i’s SOC. Despite the challenges faced by PK youth and their families, preliminary results of the evaluation of PK show significant improvements across multiple clinical and functional domains of service recipients. A financial analysis indicates that these outcomes were obtained with a minimal overall increase in costs when compared to standard care alone. Overall, these results suggest that PK may offer a cost effective way to improve access, care, and outcomes for at-risk youth and their families in Hawai‘i.

**Keywords**

Trauma, Youth, Girls, Mental Health, System of Care (SOC), Community Mental Health Initiative (CMHI), Trauma-Informed Care, Gender-Responsive Care.

**Introduction**

It is estimated that about two-thirds of children and youth with mental health challenges in the United States do not receive the mental health services they need.1 In many communities, services for youth with mental health challenges are unavailable, unaffordable, or insufficient, leaving them at risk for difficulties in school and the community.2 Hawai‘i, under the auspices of two decades of collaborative state and federal initiatives, is making sustained efforts to improve its mental health services and the overall system of care (SOC) for youth and their families. See Table 1 for an historical timeline of such efforts in Hawai‘i.

The foundation for these collaborative efforts—the Community Mental Health Initiative (CMHI)—is funded nationwide by the Substance Abuse and Mental Health Services Administration (SAMHSA) and is one of the most concentrated and sustained federal-state government mental health care partnerships. The CMHI has greatly advanced the SOC model for child and adolescent mental health nationwide,1,3 and recognizes the importance of family, school, and community contexts in seeking to promote the potential of every child, regardless of mental health challenge. SOC principles aim to ensure that services for youth and their families are family-driven, youth-guided, individualized, culturally and linguistically competent, accessible, community-based, least-restrictive; and provided through interagency, collaborative, and coordinated efforts.4

The goal of the SOC is to help families keep the youth at home, in school, out of trouble, and leading balanced, connected, responsible lives in the community. This requires not only extensive coordination and collaboration among disparate and often disconnected service sectors, such as mental health, education, juvenile justice, and child welfare—each a complicated system unto itself—but also requires strong trust and collaboration among youth, families, and their service providers. Continuously eliciting the trust and active participation of youth and their families in individualizing and completing mental health services is a key engagement strategy in Hawai‘i’s SOC project. Local treatment engagement efforts are grounded in and supported by the research literature which has found one of the most robust predictors of positive outcomes for CMHI youth to be greater participation in mental health treatment by youth and their caregivers.5,6

Project Kealahou (PK) intensively engages youth and families through a trauma-informed, culturally-resonant engagement process that includes time to “talk story” before committing to treatment as well as opportunities to make real choices about their service involvement. PK elicits active participation from

<table>
<thead>
<tr>
<th>Name (Translation)</th>
<th>Duration</th>
<th>Target Population/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Ho‘omohala (“Evolving Towards Maturity”)</td>
<td>2005-2010</td>
<td>Ages 15-21/Kaili-Palama, O‘ahu</td>
</tr>
<tr>
<td>Project Kealahou (“A New Pathway”)</td>
<td>2009-2015</td>
<td>Females ages 11-18/Central, Honolulu, and Windward O‘ahu</td>
</tr>
<tr>
<td>Project Laulima (“Working Together”)</td>
<td>2012-2017</td>
<td>CAMHD youth with developmental disabilities/Statewide</td>
</tr>
</tbody>
</table>
youth and families in coordinated service planning and project activities throughout the program. A Public Health Insights column in the September 2013 issue of this journal provides more information about the rationale and design of PK.7

Once engaged in services, PK girls and their families receive gender-responsive, trauma-informed, culturally-responsive, community-based services, including: intensive case management; community supports by paraprofessionals (ie, peer support for youth and caregivers); structured group activities; and evidence-based treatments (eg, Trauma-Focused Cognitive Behavioral Therapy and Girls Circle psychoeducational support groups). PK seeks to help girls who have experienced psychological trauma find “a new pathway” (kealahou) to a better future by healing past hurts and taking constructive steps toward a more hopeful future.

After two years of planning (2009-2011), and two-and-a-half years of services implementation (2011-2014), PK recently entered its fifth year of a six-year collaborative effort among the mental health, education, juvenile justice, and child welfare service sectors to enhance Hawai’i’s SOC for youth with complex needs. This report describes the basic demographic and clinical features at intake of the youth and families served to date (2011-2014). Preliminary results are presented regarding clinical and functional outcomes as well as participant satisfaction with various aspects of their treatment. Also, a cost analysis compares the level of mental health expenditures for PK participants prior to and after the implementation of PK services.

Methods
Participants
Youth were referred to PK primarily from the public education, juvenile justice, and mental health systems; details of programmatic structure are published elsewhere.7 Inclusion criteria were: age less than 18 years; meeting diagnostic criteria for an Axis I disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR); and a history of trauma. Of 304 referrals to PK between 2011 and 2014, eligibility criteria for PK services were met by 234. Of these, 144 chose to enroll in PK services. Once enrolled into PK services, one PK youth and/or one caregiver per family were eligible to participate in the project’s evaluation, which consisted of a baseline and four semiannual follow-up interviews. Of the 144 youth who chose to enroll in PK services, 75 declined to participate in the evaluation. After completing a University of Hawai‘i IRB–approved informed consent process, 69 youth and 31 caregivers (providing information on their youth’s behalf), for a total of 100 participants, agreed to participate in the evaluation. Twenty-four of these participants were youth who also had a caregiver participate in the evaluation; 45 were youth participating without a caregiver informant; and 7 were caregivers participating without a youth informant. These 100 informants provided information on 76 youth by completing a baseline interview upon enrollment into the evaluation. Twenty-eight youth and 16 caregivers completed both a baseline and a six-month follow-up interview, providing the data on which outcome analyses presented herein are based. Of the 41 youth enrolled in the evaluation without six-month follow-up data, 36 missed their six-month follow-up interview and 5 have not yet reached the six-month interview timeframe.

Variables and Measures
Data were collected through one- to two-hour-long structured interviews with youth and/or their caregivers at intake and at six-month intervals during the first two and a half years of PK services (September 2011 - April 2014). Data collected from respondents included demographic information, including age, race/ethnicity, gender, income, family/child history, presenting problems, clinical outcomes, and participant satisfaction, that was measured on a 5-point scale with “5” representing the highest level of satisfaction. Table 2 details measurement instruments and the participant characteristics derived from them.

For the Services and Cost Study, service types, durations, and costs were gathered on the 72 participants who were enrolled in the evaluation as of September 2013. For 41 of these participants, cost data was available for both the six months prior to and the six months after the start of PK services, allowing a comparison of the cost of PK and the cost of the standard care received prior to PK enrollment.

Table 2. Measures and Their Corresponding Variables

<table>
<thead>
<tr>
<th>Measure</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiver Information Questionnaire, Revised: Caregiver-Intake (CIQ-RC-I).9</td>
<td>Caregiver Custody Status, Family/Child History, and Household Income</td>
</tr>
<tr>
<td>Caregiver Strain Questionnaire (CGSQ).10</td>
<td>Caregiver Perceived Stress</td>
</tr>
<tr>
<td>Columbia Impairment Scale (CIS).12</td>
<td>Relationship, Behavioral, and Emotional Impairments</td>
</tr>
<tr>
<td>Education Questionnaire–Revision 2 (EQ–R2).13</td>
<td>School Performance, Referral Agency, and Agency Involvement</td>
</tr>
<tr>
<td>Enrollment and Demographic Information Form (EDIF).14</td>
<td>Age, Ethnicity, Youth Diagnosis, Presenting Problems, and Psychosocial/Environmental Problems</td>
</tr>
<tr>
<td>Revised Children's Manifest Anxiety Scale, Second Edition (RCMAS-2).15</td>
<td>Ratings of Youth Anxiety</td>
</tr>
<tr>
<td>Reynolds Adolescent Depression Scale, Second Edition (RADS–2).16</td>
<td>Ratings of Youth Depression</td>
</tr>
<tr>
<td>Youth Services Survey (YSS); YSS for Families (YSS-F).17</td>
<td>Ratings of Participant Satisfaction with Services</td>
</tr>
</tbody>
</table>

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Analyses
Pearson chi-squares, paired T-tests and ANOVA were calculated using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY) to compare differences in youth and caregiver reports at baseline and six-month follow-up, as well as differences between PK youth enrolled in the evaluation and PK youth not enrolled in the evaluation.

Results
Youth who participated (n = 76) in the evaluation did not differ demographically from youth who did not participate in the evaluation (n = 68). There were no significant differences between these two groups in terms of age (ANOVA; P = .398), racial/ethnic identity (Pearson’s chi square; P > .175) or diagnosis (Pearson’s chi-square; P > .243). Evaluation participants, however, reported more suicide attempts (Pearson’s chi-square; P = .034), greater persistent noncompliance with adults (Pearson’s chi-square; P = .031) and more problematic life domains, including social, legal, educational and primary support problems (ANOVA, P = .030) than those not in the evaluation.

Referral Sources and System of Care Involvement
During the first two-and-a-half years of PK, 304 youth were referred from SOC partners, primarily from the education, juvenile justice, and mental health systems. See Table 3 for details. Youth enrolled in PK services (N = 144) were typically receiving intensive and/or specialized services from several state agencies concurrently at intake, with 68% of PK youth reporting involvement with mental health, 52% school-based behavioral health or special education, 35% family court, 30% probation, 20% girls’ court, 15% corrections, 15% child welfare, 9% substance abuse, 4% other, and 2% physical health services agencies. Because youth could identify multiple agency involvement, the percentages of these categories sum to more than 100%.

PK Youth and Family Characteristics at Intake

Ethnicity and Age
The racial/ethnic backgrounds reported by PK girls (N = 144) at intake were: Native Hawaiian (57%), White (55%), Chinese (38%), Filipino (36%), Japanese (20%), Samoan (16%), Native American/Alaska Native (14%), Puerto Rican (12%), Other Pacific Islander (10%), African American (9%), Mexican (7%), Other Asian (6%) and Other Hispanic (2%). Because participants could choose more than one race/ethnicity, the percentages of these categories sum to more than 100%. The average age of youth at intake (N = 144) was 15.4 years (SD=1.7), with a range from 11 to 18 years.

Diagnoses
The most common diagnoses of PK youth at intake (N = 144) were mood disorders (42%), substance use disorders (32%), conduct disorders (29%), post-traumatic stress disorder (PTSD, 21%), adjustment disorder (14%), attention deficit hyperactivity disorder (ADHD, 13%), oppositional defiant disorder (13%), and disruptive behavior disorder (11%).

Family Circumstances and History
Caregivers for PK youth were primarily single biological mothers (57%), with only 17% of PK youth living in two-parent households, according to caregivers (n = 30; one caregiver participant did not complete a baseline interview) at study baseline. Median annual household income for PK youth at intake was in the $20,000 – $24,999 range (n = 27; 3 caregivers interviewed at baseline did not provide this information). Caregiver (n = 30) reports on the family and child history of PK youth at baseline are detailed in Table 4.

Legal and School Problems
At intake, PK youth (n = 69) reported extensive juvenile justice involvement, with 64% having a history of arrest and 44% having been convicted of a crime. PK caregivers (n = 30) at intake reported that 33% of PK youth had Individualized Educational Plans, 48% were in Special Education classes, and 26% had been suspended from school in the past six months.

Table 3. Sources for Project Kealahou Referrals (N=304)

<table>
<thead>
<tr>
<th>Referral Source</th>
<th>Percentage of Total Referrals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Health</td>
<td>40%</td>
</tr>
<tr>
<td>Juvenile Justice</td>
<td>25%</td>
</tr>
<tr>
<td>Education</td>
<td>23%</td>
</tr>
<tr>
<td>Homeless Shelter</td>
<td>5%</td>
</tr>
<tr>
<td>Child Welfare</td>
<td>3%</td>
</tr>
<tr>
<td>Self-Referred</td>
<td>2%</td>
</tr>
</tbody>
</table>

Table 4. Family and Youth History at Baseline: Project Kealahou (n=30) Versus Community Mental Health Initiative (CMHI) Sites (n=633)

<table>
<thead>
<tr>
<th>History of...</th>
<th>Project Kealahou Youth</th>
<th>CMHI Youth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression in Family</td>
<td>77%</td>
<td>75%</td>
</tr>
<tr>
<td>Substance Abuse in Family</td>
<td>77%</td>
<td>61%</td>
</tr>
<tr>
<td>Domestic Violence in Family</td>
<td>63%</td>
<td>44%</td>
</tr>
<tr>
<td>Runaway Youth</td>
<td>60%</td>
<td>46%</td>
</tr>
<tr>
<td>Substance Abuse by Youth</td>
<td>53%</td>
<td>27%</td>
</tr>
<tr>
<td>Household Member Convicted of Crime</td>
<td>53%</td>
<td>35%</td>
</tr>
<tr>
<td>Survivor of Physical Assault</td>
<td>45%</td>
<td>25%</td>
</tr>
<tr>
<td>Survivor of Sexual Assault</td>
<td>35%</td>
<td>23%</td>
</tr>
<tr>
<td>Suicide Attempt by Youth</td>
<td>30%</td>
<td>28%</td>
</tr>
</tbody>
</table>

*According to caregiver (n=30) responses to the Caregiver Information Questionnaire (CIQ-RC-I). 10
Includes data only from Community Mental Health Initiative sites serving female youth ages 11-21. 13
Outcomes at 6-Month Follow-up
Follow-up results, though preliminary, show significant improvement from baseline to six-month follow-up on measures of youth strengths \((P = .024)\), competence \((P = .027)\), depression \((P = .009)\), impairment \((P = .007)\), behavioral problems \((P = .017)\), emotional problems \((P = .007)\), as well as caregiver strain \((P = .001)\), as seen in Table 5. These results are based on paired T-tests of data gathered from PK youth \((n = 28)\) and caregivers \((n = 16)\) who completed both baseline and 6-month follow-up interviews during the first two-and-a-half years of PK services.

PK also received high marks from youth \((n = 29)\) and caregivers \((n = 17)\) who completed a six-month follow-up interview regarding their satisfaction with key aspects of PK. See Table 6 for details.

Services and Cost Study
In addition to its ongoing longitudinal outcome study, PK recently completed a study comparing the types and costs of services PK girls and their families received before and during PK. The Service Use and Cost Study is designed to examine PK’s service usage pattern and its costs of services in comparison to standard care in the public mental health system. Findings show that overall, PK youth and their families enrolled in the evaluation as of September 2013 \((n = 72)\) received more services \((1,819 \text{ service events})\) during their first six months of enrollment in PK compared to the six months prior to enrollment in PK \((1,680 \text{ service events})\). For those participants for whom cost data was also available both before and after the onset of PK services \((n = 41)\), the total cost for mental health services for the cohort during the first six months of PK enrollment \((\$365,803)\) was, however, only slightly higher \((\$21,662 \text{ more})\) than the total cost of mental health services for PK girls in standard care for the 6 months prior to PK enrollment \((\$344,141)\). Thus, the cost per service event was lower for PK \((\$201)\) compared to standard care \((\$205)\). Furthermore, these figures do not account for expected cost savings from decreased service usage and costs for PK girls in juvenile justice, child welfare, and educational settings, which have yet to be determined.

Whereas the frequency of most service types (ie, community therapeutic, psychiatric inpatient, and residential treatment) did not change substantially after the shift from standard care to PK-enhanced care, the frequency of one service type did increase substantially. While enrolled in PK, there was a substantial increase in the level of community support services (eg, peer support for youth and caregivers). Specifically, only 2.4% of PK girls received community support services in the six months prior to enrolling in PK compared to 68.3% of PK girls receiving this service during the first six months of enrollment in PK.\(^{19}\) Moreover, PK accomplished this sizable increase in community support services for a negligible cost increase of \$5,490 (over a 6-month time frame) compared to the cost of the community supports that were provided to the same 41 PK participants in CAMHD standard care for the six months prior to enrolling in PK.\(^{19}\)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measure</th>
<th>n</th>
<th>Source</th>
<th>Baseline Score</th>
<th>Follow-Up Score</th>
<th>Outcome</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiver Strain</td>
<td>CGSQ</td>
<td>16</td>
<td>Caregiver</td>
<td>10.62</td>
<td>8.41</td>
<td>Improved</td>
<td>(P = .001)</td>
</tr>
<tr>
<td>Youth Impairment</td>
<td>CIS</td>
<td>16</td>
<td>Caregiver</td>
<td>29.19</td>
<td>21.56</td>
<td>Improved</td>
<td>(P = .007)</td>
</tr>
<tr>
<td>Youth Emotional Problems</td>
<td>CBCL (6-18)</td>
<td>16</td>
<td>Caregiver</td>
<td>71.63</td>
<td>64.38</td>
<td>Improved</td>
<td>(P = .007)</td>
</tr>
<tr>
<td>Youth Depression</td>
<td>RADS-2</td>
<td>28</td>
<td>Youth</td>
<td>55.46</td>
<td>52.14</td>
<td>Improved</td>
<td>(P = .009)</td>
</tr>
<tr>
<td>Youth Behavioral Problems</td>
<td>CBCL (6-18)</td>
<td>16</td>
<td>Caregiver</td>
<td>73.44</td>
<td>67.75</td>
<td>Improved</td>
<td>(P = .017)</td>
</tr>
<tr>
<td>Youth Strengths</td>
<td>BERS-2Y</td>
<td>28</td>
<td>Youth</td>
<td>86.29</td>
<td>92.36</td>
<td>Improved</td>
<td>(P = .01)</td>
</tr>
<tr>
<td>Youth Competence</td>
<td>CBCL (6-18)</td>
<td>16</td>
<td>Caregiver</td>
<td>30.69</td>
<td>34.88</td>
<td>Improved</td>
<td>(P = .027)</td>
</tr>
<tr>
<td>Youth Strengths</td>
<td>BERS-2C</td>
<td>16</td>
<td>Caregiver</td>
<td>73.19</td>
<td>77.88</td>
<td>Improved</td>
<td>(P = .041)</td>
</tr>
<tr>
<td>Youth Anxiety</td>
<td>RCMA-2</td>
<td>26</td>
<td>Youth</td>
<td>55.31</td>
<td>54.12</td>
<td>Stable</td>
<td>(P = .488)</td>
</tr>
</tbody>
</table>

*Outcomes reported for participants who completed both intake and 6-month follow-up interviews.

Table 6. Caregiver \((n=17)\) and Youth \((n=29)\) Perspectives on Project Kealahou\(^{6}\)

<table>
<thead>
<tr>
<th>Satisfied with...</th>
<th>Project Kealahou Caregivers</th>
<th>Youth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to Services</td>
<td>82%</td>
<td>75%</td>
</tr>
<tr>
<td>Participation in Treatment</td>
<td>88%</td>
<td>76%</td>
</tr>
<tr>
<td>Cultural Sensitivity</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Satisfaction with Services</td>
<td>71%</td>
<td>83%</td>
</tr>
<tr>
<td>Outcomes</td>
<td>71%</td>
<td>79%</td>
</tr>
<tr>
<td>Functioning</td>
<td>77%</td>
<td>79%</td>
</tr>
<tr>
<td>Social Connectedness</td>
<td>82%</td>
<td>86%</td>
</tr>
</tbody>
</table>

*This table shows the percentage of respondents reporting positively (ie, a rating of 3.5 or more out of 5 possible points, with “5” representing that they “strongly agree”).
**Discussion**

Analysis of data from the first two-and-a-half years of PK’s ongoing services implementation shows that PK serves a diverse cohort of young women with serious personal, family, educational, and legal challenges that necessitate intensive and/or specialized services from multiple state agencies concurrently. Further analysis of outcome data demonstrates that PK youth and their caregivers achieved significant improvements in key functional, mood, and social domains. PK also ranks in the top 25% of all currently funded CMHI SOC sites nationwide on participant satisfaction with cultural sensitivity of services, quality of services, participation in services and overall satisfaction with services, and in the top 50% of CMHI sites on satisfaction with access to services and outcomes. Moreover, the analysis of service usage and cost data shows that, despite vastly expanded access to community support services in the form of peer support for PK youth and caregivers, the overall cost increase to enhance CAMHD’s standard care with PK services appears to be small.

Final results after the completion of PK in October 2015 are expected to confirm the findings to date of significant improvements for PK youth and caregivers. This expectation is based on significant positive outcomes seen as well as findings from other CMHI-funded SOCs nationally. The CMHI has shown that after completing such programs (ie, after 18-24 months of treatment), youth similar to those enrolled in PK evidence significant improvements in behavioral and emotional functioning, school performance, suicidal ideation/ attempts, and juvenile justice involvement, all of which have been shown to lead to decreased costs for the SOC. In particular, given the established link between service involvement of youth and positive outcomes discussed earlier, an especially promising finding from this preliminary evaluation of PK is the high rating by PK youth of their satisfaction with their level of participation in PK services. These findings are consistent with PK’s emphasis on intensively engaging and involving participants in all aspects of services.

**Strengths and Weaknesses of the Current Study**

This evaluation benefits from participation in the larger CMHI study cohort, which offers a depth and breadth of data from a battery of standardized measures administered to thousands of participants nationwide. While there is no evidence of systematic selection bias into this evaluation, a weakness of this study is the relatively low proportion of participants—28 of 69 youth and 16 of 31 caregivers—who completed both baseline and six-month follow-up interviews. Overall, however, the attrition rate is low at only 7%. Youth who did not complete a six-month follow-up interview may still participate in 12-, 18- and 24-month follow-ups, which would allow for more in-depth analyses as well as analyses of longer-term outcomes among this cohort.

Another weakness of this study lies in its inability to determine whether and which elements of PK services are responsible for its successful outcomes. Further research is needed to better understand the impact of PK’s unique components, with particular attention to the apparent cost-effectiveness of community supports provided by paraprofessional staff (ie, peer partners for youth and caregivers). In the future, a larger study cohort and the inclusion of a comparison group of matched CAMHD-only youth who are administered the same battery of tests at the same frequency as PK youth, could help distinguish any impact of PK above and beyond the impact of CAMHD standard care alone. Also, in the future, access to the national CMHI database could allow for direct comparisons of results from Hawai‘i and comparable mainland programs.

**Lessons Learned**

The apparent effectiveness of PK’s model of intensive and peer-delivered community-based supports is likely to be the key lesson learned from this innovative service model implementation for at-risk youth in Hawai‘i. As such, the task ahead for the state’s public mental health administration would be twofold: dissemination and sustainability. Regarding dissemination, the task for CAMHD is to translate this successful project into sustainable practices in its state-operated and/or contracted services. One particular challenge CAMHD faces in this regard is that peer support services for youth, though a key element of PK and other SOCs, are a new and untested practice throughout CAMHD standard care. Uptake of this element by CAMHD standard care will require substantial administrative support in the form of planning, resource allocation, and workforce development. The ultimate challenge for CAMHD, of course, will involve leveraging PK’s current funding and past successes in order to achieve sustainability and possible statewide expansion once federal funding ends in October 2015.

**Conclusion**

Significant clinical improvements, high satisfaction levels among PK participants, and a relatively low cost for services offer support for PK’s SOC enhancements for effectively serving youth with complex needs spanning multiple state agencies. By the conclusion of the evaluation, more outcome data derived from 6-, 12-, 18- and 24-month follow-up interviews will be available to help stakeholders and funders make data-based decisions about how to best serve this challenging at-risk population. At that time, the primary tasks for the State of Hawai‘i will be to sustain, integrate, and possibly expand on the system of care enhancements achieved by PK.
Conflict of Interest
None of the authors identify a conflict of interest.

Acknowledgement
Mahalo to the youth, families, service providers and administrators who make this project possible and who strive every day to provide a cohesive and responsive system of care for Hawai'i’s youth and their families. Mahalo to Project Director Tia Roberts and Project Consultant L. Pua Paul for their vision, dedication and guidance. PK is supported by Grant No. SM059024 under the direction of the Child, Adolescent and Family Branch, Center for Mental Health Services, Substance Abuse and Mental Health Services Administration, United States Department of Health and Human Services.

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References
MEDICAL SCHOOL HOTLINE

The Institute for Biogenesis Research: A Flower in the Pacific

W. Steven Ward PhD and Stefan Moisyadi PhD

The Medical School Hotline is a monthly column from the John A. Burns School of Medicine and is edited by Satoru Izutsu PhD; HJMPH Contributing Editor. 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 Institute for Biogenesis Research (IBR, www.ibr.hawaii.edu) was founded in September of 2000 to advance the study of reproductive and developmental biology. The incentive for the creation of the IBR was to propagate the legacy of the University of Hawai’i’s world renowned expertise in reproductive biology largely due to the outstanding research contributions of Dr. Ryuzo Yanagimachi. Since its inception, the IBR has grown from its first founding member to 9 full time faculty and 4 associate members. The success of the institute is measured in its worldwide recognition, its success in competing for federal grant funding, and its contributions to the university in teaching and extended research support.

Legacy of Dr. Yanagimachi
The University of Hawai’i decided to establish the IBR primarily to institutionalize the decades long research successes of Dr. Yanagimachi. He joined the University of Hawai’i (UH) in 1965, and has remained ever since. Before coming to Hawai’i, Dr. Yanagimachi had already distinguished himself as a leader in reproductive biology by making a major contribution to the development of techniques that would allow mammalian sperm to fertilize eggs in vitro.1 At UH, he again amazed the scientific world by injecting a sperm head into an egg to achieve fertilization.2 These two studies, supported by numerous other publications, became the basis for the two major treatments for human infertility, in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), that result in millions of babies born to infertile couples around the world. In 1997, Ian Wilmut and colleagues cloned the first mammal, Dolly the sheep,3 but this was only one animal, and the scientific community was not fully convinced it was possible to do this procedure routinely. The next year, Yanagimachi’s group demonstrated a novel method for cloning mammals. They cloned 50 mice, and five generations of cloned clones.4 This firmly established the discovery, and now their technique is used around the world to clone animals. Dr. Yanagimachi also developed a novel technique to create transgenic mice.5 For these and many other discoveries, Dr. Yanagimachi was elected to the prestigious National Academy of Sciences, USA, in 2001.

The press coverage of these latter discoveries awakened the state to Dr. Yanagimachi’s contributions, and the university decided to establish the IBR with some community support. The Castle Foundation provided a $1 million grant to recruit new faculty to populate the IBR, and the university contributed $5 million to construct a new 15,000 sq ft research facility in the BioMed Tower on the UH Manoa campus.

International Recognition for Reproductive and Developmental for the Biology Faculty Members of the IBR
As with any research institute, the strength of the IBR lies in its faculty members. The IBR has a particularly cohesive group with a large diversity of scientific interests and technical expertise, coupled with the common overall theme of fertilization and early development. Figure 1 depicts our current faculty members, 8 of whom are full time IBR and 3 associate members. In the fourteen years since its inception, the IBR has grown from three to twelve faculty with diverse, but related research projects. The faculty work together in various collaborations, increasing the productivity of the entire unit.

The IBR was started in September of 2000 with three faculty members and a lab manager. Dr. Yanagimachi was the founding director. He recruited Dr. Yusuke Marikawa who focuses currently on gene pathways that direct body plan formation,6,7 and Dr. W. Steven Ward who concentrates on sperm chromatin structure.8,9 Dr. Stefan Moisyadi was the first lab manager of the IBR, and oversaw the construction of the main facility located at 1960 East-West Rd., in the BioMed Tower on the Manoa campus of the University of Hawai’i. The IBR leadership quickly realized that Dr. Moisyadi was more than capable of heading his own research program, which he initiated in 2004. He developed a new molecular system to create transgenic animals and has been recognized for his major contributions to the field.10,11

Between 2002 and 2005, the IBR welcomed three additional faculty who came as postdoctoral fellows in 2000. All have made significant contributions, not only to the school, but to their areas of research. Currently, Dr. Vernadeth Alarcon, who trained with Dr. Marikawa, focuses on the earliest cell differentiation during development, the division of cells into those that will become the embryo and those that lead to the placenta12,13 Dr.
Monika Ward, who trained with Dr. Yanagimachi, developed a highly respected program that is determining the function of the genes on the Y chromosome in fertilization. Her group recently demonstrated that only two genes on the Y chromosome were needed for male mice to be capable of fertilization with assisted reproduction. Dr. Yukiko Yamazaki, who also trained with Dr. Yanagimachi, focuses on the embryonic development of sperm and oocytes and has recently developed new techniques to culture oocytes. In 2003, the IBR recruited Dr. Richard Allsopp who is interested in telomeres and in stem cell therapy. He has initiated a program to test the efficacy of stem cells as a therapy for heart injury.

In 2013, the IBR recruited four additional faculty as part of an application for a NIH center grant to support the program. Dr. Alika Maunakea was newly recruited to the Department of Native Hawaiian Health. His research interest is on how epigenetic modifications affect human disease. He is collaborating with Dr. M. Ward to test assisted reproductive techniques that might contribute to the development of epigenetic diseases such as autism. Dr. Lana Garmire is a new recruit to the University of Hawai‘i’s Cancer Center whose focus is bioinformatic analysis of genomewide sequences in cancer. Her focus in the IBR will be the relationship between obesity during pregnancy and the generation of epigenetic mutations that lead to cancer. Dr. Benjamin Fogelgren is a member of the same Department of Anatomy, Biochemistry and Physiology. He was invited to join the IBR when it became apparent that his research on cavity formation during kidney development had direct implications for blastocyst formation during early embryogenesis. Finally, Dr. Johann Urschitz who trained with Dr. Moisyadi, is working to use the transgenic methods developed in Dr. Moisyadi’s lab as gene therapy to address the problems of fetuses of obese mothers.

**Success of Grant Funding**

A measure of success of any research institute is its ability to compete for grant funding to support its work. In this, the IBR is following a predictable timeline in which the funding has increased over time (Figure 2). In the first four years IBR funding averaged about $1 million per year. This reflects both the small number of principal investigators in the early years, and the early development of the younger faculty. By 2008, the IBR faculty had developed a reputation that the team could successfully compete for a large NIH center grant to support its research. This brought in $10.5 million over the next six years. It also allowed the establishment of Hawai‘i’s first Transgenic Mouse facility, and the techniques for making transgenically modified mice in the IBR established important mouse mod-
Figure 2. Total Grant Funding per Year in the IBR. This graph depicts all the extramural funding for which the faculty of the IBR successfully competed. The data are accurate as of August 8, 2014, and does not include additional grants that have not yet been awarded after 2014.

The infrastructure of this grant established strengthened applications of IBR researchers for subsequent grant proposals. In July, 2014, the IBR was awarded a second phase of the center grant for an additional $11 million to support the IBR for the next five years. Individual faculty have also been productive in obtaining grant support for their respective research programs. In fiscal year 2013, the IBR had one fourth of all the NIH R01s in the medical school. These are the most competitive individual grants for principle investigators from the federal government, a hallmark of successful biomedical researchers.

To date, the IBR has brought in $38.6 million in extramural grant funding. It is significant that most of this federal funding enters directly into the Hawai‘i state economy. This is illustrated in Table 1 that details the expenditure of the IBR’s largest extramural award. About half of these funds will pay for salaries of employees that not only creates jobs, but contributes money into the economy. Another 30% is paid directly to the University of Hawai‘i to pay for the infrastructure that supports research. Eighty percent of the federal dollars that the IBR brings to the university goes directly into the state’s economy.

**The Graduate Program in Developmental and Reproductive Biology**

In addition to having established a world class biomedical research unit at UH and having contributed significantly to Hawai‘i’s economy, the IBR also plays a strong role in teaching. As a Research 1 university, the University of Hawai‘i at Manoa provides graduate training for Hawai‘i’s citizens giving them opportunities to develop skills for high-paying, technically advanced careers. The IBR is recognized world wide for its skills in micromanipulation and mouse genetics. With the success in grant funding, the IBR decided to develop a new graduate program to train local students. In 2008, with the success of the first center grant, a unique opportunity came about to do just this. The chair of the department, Dr. Scott Lozanoff, asked the IBR to propose a reorganization of the Graduate Program in Physiology. Drs. S. Ward and Allsopp made a proposal to change the name to, “Graduate Program in Developmental and Reproductive Biology (DRB; http://www3.jabsom.hawaii.edu)”.

The program has been successful in training MS and PhD. students. These graduate students are supported by teaching assistanceships that support undergraduate education at University of Hawai‘i at Manoa.

| Table 1. Budget for the IBR-COBRE Phase 2 (2014-2019) |
|-----------------|-----------------|-----------|
| **Grant Portion** | **Amount**      | **Percent** |
| Total Grant Award | $10,840,520     | 100%      |
| Salary           | $5,269,460      | 49%       |
| Indirect         | $3,390,520      | 31%       |
| Direct to Hawai‘i Economy | $8,659,980 | 80%       |
Conclusions
In the fourteen years since its inception, the IBR has become a world renowned center for biomedical research in the field of reproductive and developmental biology. The IBR also supports the educational missions of UHM and JABSOM, as well as contributing to other research endeavors throughout the state. By all measures, the institute can be counted as one of Hawai‘i’s success stories.

Conflict of Interest
None of the authors identify a conflict of interest.

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References

Community Strengthening Through Canoe Culture: Ho‘omana‘o Mau as Method and Metaphor

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Abstract
Historical trauma occurs across generations and is evidenced by indigenous disparities. Efforts made to address this issue commonly utilize European ethnocentric methods. Rather, a community-based approach should be used to empower indigenous communities. God’s Country Waimanalo (GCW) is a grassroots organization developed by Native Hawaiians for Native Hawaiians. Its wa’a (canoe) project, Ho’omana‘o Mau (everlasting memories; abbreviated Ho’o) is meant to perpetuate pre-colonial Hawaiian practices by educating Native Hawaiian communities and its partners through hands-on experience. Since 2012, GCW has opened its wa’a curriculum to educators, counselors, and students from the University of Hawai‘i at Manoa, Queen Lili‘uokalani Children’s Center, Alu Like, Hina Mauna, and the Youth Correctional Facility and contributed to Waimanalo based events such as funeral ash scattering and the papio fishing tournament. As metaphor, Ho’o is viewed as the catalyst to engage the next generation of Hawaiians to remember where they descend from, the lineage of chiefs and royalty, while establishing a solid foundation of independence and enhancing their ability to become self-sustaining. As a method, Ho’o is viewed as a classroom, a hands-on learning environment, and an ocean vessel, assembled according to traditional Hawaiian knowledge. Through this knowledge and practice, both indigenous and non-indigenous communities can work together in empowering Native Hawaiians to overcome historical trauma and reduce health disparities.

Background
As time progresses, many of ancient Hawai‘i’s cultural practices have all but disappeared. The influx of modern technology and the encroachment of foreign ideology, politics, and religion have greatly altered the homeostasis of a once thriving and self-sustaining Hawaiian community. The severity of these transformations from old world order to modern day life has caused the once thriving Hawaiian nation to become minorities in their own land. Previous research has shown that the trauma of western colonization has not only severed the connections to sources of sustenance but has also caused displacement of Hawaiian families and communities.

Prior to colonization, Native Hawaiians thrived in an existing culture, government, language, and religion. However, new worldviews dissolved the indigenous systems as foreigners judged the native ways of life based on western standards. In 2008, the United Nations recognized that the indigenous people have “suffered from historic injustices as a result of colonization.” Historical trauma can be defined as psychosocial trauma experienced by indigenous groups as a result of colonization, war, genocide, or cultural, social, and political subjugation. The literature suggests that historical trauma occurs across generations, beyond those who experience the traumatic events first hand. Evidence can be seen in the health disparities that Native Hawaiians face compared to other ethnicities in Hawai‘i. As a whole, Native Hawaiians experience high rates of acute diseases, depression, self-destructive behaviors, hostility, and chronic bereavement. Although previous efforts have been made to amend the outcomes of this disparity, the western-centric methods utilized continue to compare indigenous communities to European standards. Decolonizing methodologies such as community-based participatory research (CBPR) are recommended because they apply perspectives that challenge the European ethnocentric paradigms and empower indigenous people to improve their lives using their own approaches and aims. Further, Native Hawaiian health programs should be developed, implemented, and researched by Native Hawaiians.

Waimanalo is a town that lies along the windward coastline beside the Ko‘olau mountains. Prior to colonization, Waimanalo’s ahupua‘a (traditional land division) extended from present day Olomana to present day Hawai‘i Kai. During the 1960s, Henry J. Kaiser dredged part of the original Waimanalo and converted it to a series of luxury condominiums and homes now known as Hawaii Kai (“Kai” for Kaiser). Nearly one third of the Waimanalo residents are Native Hawaiians and the average family income is 31% less than that of the state. Many efforts in Waimanalo have been made to improve the circumstances of its indigenous residents. God’s Country Waimanalo (GCW) is a grassroots organization located in Waimanalo, O‘ahu, Hawai‘i. Their mission is to propagate and perpetuate the Hawaiian culture by incorporating the following values: (1) Kuleana – privilege, responsibility, (2) Malama – to care for, protect, and maintain, (3) Ike Pono – to know, see, feel, and understand, and 4) Ha‘aha‘a – humility and humbleness.

One of the projects implemented by GCW is the wa’a (canoe) project, Ho‘omana‘o Mau (Ho’o), which means “everlasting
memories.” Ho’o is a fifty-two foot long single-hull voyaging canoe moored off shore at Pa’u Honu, Waimanalo. It is used to build and strengthen the community through hands-on experiences guided by Native Hawaiians. Ho’o facilitates the emphasis of Hawaiian culture preservation and Hawaiian people empowerment as a metaphor and method.

As metaphor, Ho’o is viewed as the catalyst to engage the next generation of Hawaiians to remember where they descend from, the lineage of chiefs and royalty, while establishing a solid foundation of independence and enhancing their ability to become self-sustaining. As a method, Ho’o is viewed as a classroom, a hands-on learning environment and an ocean vessel, assembled according to traditional Hawaiian knowledge. According to Pukui,13 ma ka hana ka ʻike, translates as “in doing one learns.” Discovering cultural identity through cultural healing will allow Native Hawaiians to mitigate their own trauma, reduce internal discord, and heal wounds thus improving their social, mental, and physical health.14

Community Engagement

In January 2012, Mike Muller donated the wa’a, or canoe, Ho’omana’o O Mau to GCW to serve the Waimanalo community and its partners. Since then, with the help of Ho’o’s kahu (caretaker), Bob Lastimosa, GCW has been developing integrative curricula that involve cultural competency lessons for outsiders and cultural healing through practice for Native Hawaiians. The purpose of Ho’omana’o O Mau is two-fold: (1) to perpetuate Hawaiian culture and knowledge through educators and counselors by facilitating their understanding and utilization of this knowledge to improve and support the advancement of Native Hawaiians in today’s society, (2) to assist Native Hawaiians in regaining their cultural identity that was lost through historical trauma by bringing back canoe culture and reinstating Hawaiian cultural practices such as navigation, fishing, and the idea of ahupua’a through hands on learning.

So far a series of ocean perspective events known as Holo Kai (Ocean Voyage) has been offered to educators, counselors, and students from the University of Hawai’i at Manoa, Queen Lili’uokalani Children’s Center, Alu Like, Hina Mauka, and the Youth Correctional Facility. In addition, Ho’o has supported events and activities that help the community re-learn voyaging and navigation practices from thousands of years ago. Ho’o welcomed her kupuna (elder) wa’a, Hokule’a, (navigational star), to our shores on October 19, 2013, during her around the islands tour. On two occasions Ho’o and crew have supported scattering of ashes in waters off Waimanalo. Family members have shared aloha for the opportunity with heartfelt love and joy during a somber season of their lives. The annual papio fishing tournament in Waimanalo was established around the existence of Ho’o. Families come together to share food and knowledge through this cultural event.

Pilot Evaluation

In February 2014, educators, counselors, and their families from the University of Hawai’i at Manoa (UHM) were invited to participate in an integrative cultural competency training. A pilot evaluation was conducted by the students of School of Social Work and Office of Public Health Studies. The purpose of this pilot evaluation was to gather preliminary data that could guide the development of an effective curriculum that utilizes the wa’a to perpetuate Native Hawaiian knowledge, culture, and traditions to educators and counselors.

Participants were asked to complete a non-identifiable pre and post training paper survey that asks for demographics (age, zip code, and ethnicity), training expectations, reasons for attending the training, and their opinion on whether and how learning traditional Hawaiian practices is valuable in the area of social work. All survey questions besides demographics allowed for free-text responses. Survey results were evaluated using univariate analysis. Qualitative analysis methods were used to identify common themes in the free response sections.

A total of 29 participants attended the training. Since most were affiliated with UHM, 55% of the participants were from central O’ahu and the average age was 39 years old. Approximately half of the participants reported only one ethnicity whereas the others reported two or more. The majority of participants were of Asian or Pacific Islander descent.

The wa’a experience met, if not exceeded, the expectations of the participants. Participants were expecting to learn and experience Hawaiian cultural concepts. The knowledge they retained after the experience revolved around the meaning and importance of place, community, and individuals. Participants were asked if and how learning traditional Hawaiian practices is valuable in the area of social work, before and after the training. Substantial differences in survey responses were evident when comparing themes generated from the pre- and post-training surveys. In the pre-training survey, many simply stated that traditional Hawaiian practices were important, but did not have any specific insight into how they might be valuable in social work. However, in the post-training survey, participants were able to provide specific reasons for why this activity was important. Participants also enjoyed the wa’a ride and the interaction with the people who were present. Most participants did not suggest improvements to the wa’a experience. A few recommended that the shipments share their experiences, make the wa’a ride longer, and make the experience more interactive. This event was successful in familiarizing educators and counselors with Native Hawaiian culture, regardless of ethnicity.

Future Directions

GCW plans to recruit and train the next generation of Waimanalo community members through the new curriculum, Malama Ho’omana’o Mau (taking care of or working for Ho’omana’o Mau). Although still in its planning phases, this curriculum aims to train the next generation of crewmembers by transferring wa’a knowledge through hands-on learning opportunities with the veteran crew. Learning by doing is a Hawaiian mindset that is encouraged and infused at GCW in all activity areas and will be the cornerstone of the Malama Ho’omana’o Mau curriculum. The idea here is to take individuals who have
minimum knowledge of traditional voyaging and teach them all facets of operating Hoʻo, including sail and engine operation, rigging, anchorage, first aid, and rescue swimmer techniques. Furthermore, collaboration with researchers is needed to identify a non-invasive and effective evaluation approach for this new curriculum.

**Conclusion**
Practitioner Kalani Kaʻihue once said that “every ahupua’a needs a voyaging canoe.” Hoʻomanaʻo Mau is poised to bring function and form to canoe culture in the Waimanalo community and beyond with the development of curricula that brings method and metaphor to life in a meaningful way, steeped in the Hawaiian cultural value of ma ka hana ka ʻike for generations. With the resurgence of Hawaiian cultural practices looked upon in a positive light, more and more people want to engage and experience canoe culture, as well as other activities. Certainly, Hoʻo provides a foundation for young and old to see, feel and experience canoe culture from a practitioner’s perspective. Through the waʻa curricula, the Native Hawaiian community and its partners become knowledgeable and well acquainted with pre-colonial Hawaiian practices. This knowledge and practice in turn enable both indigenous and non-indigenous communities to work together in empowering Native Hawaiians to overcome historical trauma and reduce health disparities.

**Conflict of Interest**
None of the authors identify a conflict of interest.

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**References**
Areca (Betel) Nut Consumption: An Underappreciated Cause of Cancer

Adrian A. Franke PhD; Jennifer F. Lai MS; Crissy T. Kawamoto BS; Pallav Pokhrel PhD; and Thaddeus A. Herzog PhD

The Cancer Center Connection is a standing column from the University of Hawai‘i Cancer Center and is edited by Carl-Wilhelm Vogel MD, PhD; HJMPH Contributing Editor. Dr. Vogel is professor and former director of the University of Hawai‘i Cancer Center and has been the editor of this column since 2001.

Keywords
Betel nut; Betel quid; alkaloids; chewing; carcinogen; biomarkers

Introduction
The fruit from the palm Areca catechu (L.) commonly referred to as areca nut (AN) is botanically a drupe fruit with an outer leathery part (exocarp or skin; and mesocarp, which can be fleshy or hard) that surrounds a shell (hardened endocarp with a seed or pit) at all times during ripening (Figure 1). ANs in their variable preparations, commonly wrapped in a betel leaf therefore the widespread name “Betel nut” (BN; see below), are consumed worldwide by an estimated 600 million people among all age groups and social classes with prevalent consumption throughout the Indian subcontinent, East and Southeast Asia, and the Pacific Islands.1,2 In Guam, AN chewing is widely practiced among many populations (including Chamorros, Yapese, Palauans and Chuukese), and approximately 11% of Guam’s population chew on a regular basis.3 In some areas of India, the frequency of AN use has been increasing among the youth and has been speculated to serve as a gateway for tobacco use.4,5

There is considerable variation in the way ANs are consumed. They can be chewed alone, wrapped in a leaf of the betel pepper (Piper betle L.) then referred to as BN, or as a “betel quid” (BQ), whose recipes, despite varying regionally and locally within countries, generally consists of a whole or portion of an AN wrapped in a leaf of the betel pepper (Piper betle L.) together with other additives such as slaked lime (calcium hydroxide) and sometimes tobacco (from chewing tobacco or cigarettes) (Figure 1) and/or spices.6,9 Lime is typically obtained from the burning of coral or shellfish or extraction from limestone and is sold in paste, liquid, or powdered forms (Figure 1).7,8 Other ingredients such as cloves, cardamom, alcohol, nutmeg, aniseed, ginger, and sweeteners such as coconut are sometimes added to the various AN preparations for extra flavoring according to preference.7,8,10 In many countries such as those in South Asia, proprietary BQ mixtures are commercially manufactured and heavily advertised towards youth.11,12 Oftentimes, the nut is conveniently sold in proximity to tobacco products as to indirectly promote its concurrent use (eg, selling of single cigarettes).11

The chewing of AN in its various preparation forms is a socially accepted habit in many countries of the Western Pacific region13 and is used as a means of promoting social relationships and community ties. This habit also has cultural and religious significance among some populations where chewing is endemic.1,7,14 Factors thought to influence chewing commencement include encouragement from family members, friends, or role models at a young age, as well as peer pressure; in addition, some users have described AN chewing as a way to pass time or avoid boredom and loneliness.1,13,15

Reported Effects of Consumption
Globally, AN is the fourth most commonly used psychoactive drug after tobacco, alcohol, and caffeine.10,16 Its consumption has been claimed to produce feelings of euphoria, well-being, palpitation, salivation, diaphoresis, heightened alertness, hunger satisfaction, and increased stamina.1,12,17 Arecoline, the main AN alkaloid released upon mastication, has been reported to be responsible for several of these effects through activation of the sympathetic pathway13 although many other AN alkaloids could also have psychotropic activity. For example, arecaidine, the hydrolyzed product of arecoline, has been reported to relieve anxiety through its ability to inhibit gamma-aminobutyric acid reuptake, a property likely to result in potential abuse and dependence and, accordingly, its use with or without tobacco has been associated with dependency.10,18

Compelling evidence suggests strong associations between AN chewing and increased risks for developing oral cancer (particularly oral squamous cell carcinoma), leading to the classification of AN chewing both with BQ and without tobacco as carcinogenic to humans by the International Agency for Research on Cancer.9 Oral cancer mortality rates as high as 80% have been reported in some countries in the Western Pacific Region, which is in stark contrast to the average worldwide 5-year cumulative mortality rate of less than 50%.15 In Guam, the incidence of mouth cancer in some Micronesian groups who regularly chew AN is almost three times higher than it is in Caucasians, who rarely consume AN.19 In addition to oral
cancer, studies have reported associations between BQ chewing and esophageal, pharynx, lung, pancreas, cervical, and, albeit limited evidence, liver cancer.12,20,21

Oral cancer has functionally and cosmetically devastating consequences22 and is often preceded by clinically visible white (leukoplakia) or red (erythroplakia) lesions of the oral mucosa and/or the insidious, chronic condition oral submucous fibrosis (OSF), which has a high propensity for malignant transformation12,23-25 with relative risks ranging from 29 to 154 attributable to AN chewing.22 OSF is an irreversible condition that persists even after cessation of chewing22 and is characterized by changes in the fibroelasticity of the oral mucosa followed by progressive stiffness and, eventually, limited mouth opening that can lead to difficulty in eating.26

Both the duration and frequency of BQ use has been reported to increase the risk of developing OSF thereby suggesting a dose-response relationship,27 which is of particular concern for individuals who begin chewing at a young age as they are more likely to develop OSF and cancer due to the cumulative years of exposure.

Furthermore, BQ chewing has been associated with the practice of other risky habits such as alcohol and tobacco consumption.21,28 Not only are BQ chewers usually also smokers but chewers who smoke generally smoke more [cigarettes per day] than smokers who do not chew.21 BQ chewers have also been noted to be less physically active and have higher blood triglycerides and lower HDL levels when compared to non-smoking, non-chewing individuals.21

Prevention Initiatives
Globally, AN consumption has become a health burden of increasing significance, warranting an ongoing and urgent need for cessation programs. The use of biomarkers to identify areca exposure is of great need for measuring the success of cessation programs as it would assist in verifying self-reports of AN cessation.

In an attempt to identify such biomarkers, we recently completed a pilot study in Guam that analyzed the chemical composition of saliva at baseline and during chewing from habitual AN chewers who consumed one usual dose of a typical AN
preparation consumed in Guam; specifically, the participants were randomized to consume either the AN alone (AN group), the AN wrapped in a piper betle leaf (AL group), or a BQ consisting of one AN wrapped in betel piper leaf with slaked lime and cigarette tobacco (BQ group). The saliva obtained during chewing vs baseline showed significantly increased levels of guvacine (AN and BQ groups), arecoline (all three groups), guvacoline (AN group), arecaidine (all three groups), nicotine (BQ group), and chavibetol (AL and BQ groups).

We also found significant differences between the three AN preparation groups for total areca alkaloids (guvacine, arecoline, guvacoline, and arecaidine; \( P = .045 \)), total nicotine alkaloids (nicotine, cotinine, hydroxycotinine, N-nitrosoguvacoline, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosonornicotine (NNN), and N-nitrosoanatabine (NAT); \( P < .001 \)) and chavibetol (\( P = .006 \)). Chemical structures of these compounds are shown in Figure 2. From our results, we determined the following chemical patterns in saliva during...
chewing to be useful for future biomarker studies aimed at identifying extent and type of AN chewing: areca alkaloids indicates when an AN is chewed (AN group), areca alkaloids in combination with chavibetol indicates when an AN with the piper betel leaf is chewed (AL group), and areca alkaloids plus chavibetol and tobacco-specific alkaloids indicates when an AN with the Piper betle L. leaf, slaked lime, and tobacco is chewed (BQ group). The quantitative difference of these markers can be used to identify chewing type and also to distinguish from tobacco smoking. Pharmacokinetic studies for these markers are ongoing in our group.

Despite the global prominence of AN consumption, there is little information on how to help chewers quit. For that reason, we are currently developing AN cessation programs to be directed towards chewers in Guam and Saipan. Our new knowledge regarding AN biomarkers will allow us to test the efficacy of these programs with greater validity and precision. Ultimately, the development of successful AN cessation programs will help to reduce the incidence and overall burden of oral cancer in the Asia-Pacific region.

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The following guidelines are developed based on many common errors we see in manuscripts submitted to HJM&PH. They are not meant to be all encompassing, or be restrictive to authors who feel that their data must be presented differently for legitimate reasons. We hope they are helpful to you; in turn, following these guidelines will reduce or eliminate the common errors we address with authors later in the publication process.

**Percentages**: Report percentages to one decimal place (eg, 26.7%) when sample size is $\geq 200$. For smaller samples (<200), do not use decimal places (eg, 26%, not 26.7%), to avoid the appearance of a level of precision that is not present.

**Standard deviations (SD)/standard errors (SE)**: Please specify the measures used: using "mean (SD)" for data summary and description; to show sampling variability, consider reporting confidence intervals, rather than standard errors, when possible to avoid confusion.

**Population parameters versus sample statistics**: Using Greek letters to represent population parameters and Roman letters to represent estimates of those parameters in tables and text. For example, when reporting regression analysis results, Greek symbol ($\beta$), or Beta ($b$) should only be used in the text when describing the equations or parameters being estimated, never in reference to the results based on sample data. Instead, one can use “$b$” or $\beta$ for unstandardized regression parameter estimates, and “B” or $\beta$ for standardized regression parameter estimates.

**P values**: Using $P$ values to present statistical significance, the actual observed $P$ value should be presented. For $P$ values between .001 and .020, please report the value to the nearest thousandth (eg, $P = .123$). For $P$ values greater than .20, please report the value to the nearest hundredth (eg, $P = .34$). If the observed $P$ value is great than .999, it should be expressed as “$P > .99$”. For a $P$ value less than .001, report as “$P < .001$”. Under no circumstance should the symbol “NS” or “ns” (for not significant) be used in place of actual $P$ values.

**Trend**: Use the word trend when describing a test for trend or dose-response. Avoid using it to refer to $P$ values near but not below .05. In such instances, simply report a difference and the confidence interval of the difference (if appropriate), with or without the $P$ value.

**One-sided tests**: There are very rare circumstances where a “one-sided” significance test is appropriate, eg, non-inferiority trials. Therefore, “two-sided” significance tests are the rule, not the exception. Do not report one-sided significance test unless it can be justified and presented in the experimental design section.

**Statistical software**: Specify in the statistical analysis section the statistical software used for analysis (version, manufacturer, and manufacturer’s location), eg, SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

**Comparisons of interventions**: Focus on between-group differences, with 95% confidence intervals of the differences, and not on within-group differences.

**Post-hoc pairwise comparisons**: It is important to first test the overall hypothesis. One should conduct post-hoc analysis if and only if the overall hypothesis is rejected.

**Clinically meaningful estimates**: Report results using meaningful metrics rather than reporting raw results. For example, instead of the log odds ratio from a logistic regression, authors should transform coefficients into the appropriate measure of effect size, eg, odds ratio. Avoid using an estimate, such as an odds ratio or relative risk, for a one unit change in the factor of interest when a 1-unit change lacks clinical meaning (age, mm Hg of blood pressure, or any other continuous or interval measurement with small units). Instead, reporting effort for a clinically meaningful change (eg, for every 10 years of increase of age, for an increase of one standard deviation (or interquartile range) of blood pressure), along with 95% confidence intervals.

**Risk ratios**: Describe the risk ratio accurately. For instance, an odds ratio of 3.94 indicates that the outcome is almost 4 times as likely to occur, compared with the reference group, and indicates a nearly 3-fold increase in risk, not a nearly 4-fold increase in risk.

**Longitudinal data**: Consider appropriate longitudinal data analyses if the outcome variables were measured at multiple time points, such as mixed-effects models or generalized estimating equation approaches, which can address the within-subject variability.

**Sample size, response rate, attrition rate**: Please clearly indicate in the methods section: the total number of participants, the time period of the study, response rate (if any), and attrition rate (if any).

**Tables (general)**: Avoid the presentation of raw parameter estimates, if such parameters have no clear interpretation. For instance, the results from Cox proportional hazard models should be presented as the exponentiated parameter estimates, (ie, the hazard ratios) and their corresponding 95% confidence intervals, rather than the raw estimates. The inclusion of $P$-values in tables is unnecessary in the presence of 95% confidence intervals.

**Descriptive tables**: In tables that simply describe characteristics of 2 or more groups (eg, Table 1 of a clinical trial), report averages with standard deviations, not standard errors, when data are normally distributed. Report median (minimum, maximum) or median (25th, 75th percentile [interquartile range, or IQR]) when data are not normally distributed.

**Figures (general)**: Avoid using pie charts; avoid using simple bar plots or histograms without measures of variability; provide raw data (numerators and denominators) in the margins of meta-analysis forest plots; provide numbers of subjects at risk at different times in survival plots.

**Missing values**: Always report the frequency of missing variables and how missing data was handled in the analysis. Consider adding a column to tables or a footnote that makes clear the amount of missing data.

**Removal of data points**: Unless fully justifiable, all subjects included in the study should be analyzed. Any exclusion of values or subjects should be reported and justified. When influential observations exist, it is suggested that the data is analyzed both with and without such influential observations, and the difference in results discussed.
Macular degeneration occurs when the visual cells at the center of the retina break down. This tissue does not regenerate and eyesight may be severely impaired, a major cause of blindness in our aging population. In a report recently published in Lancet, researchers found that embryonic stem cells (EMC) planted in the retinas of patients with macular degeneration yielded amazing results. Although a small study (18 patients), results are extremely encouraging. Patients were followed for three years with no evidence of rejection, abnormal cell growth, tumor formation, or unwanted tissue. On average, patients’ visual acuity improved four lines on a standard eye chart. The control group showed no improvement. It is a small first step, but a very important one. Human embryonic stem cells are obtained from eggs that are fertilized in vitro and used for research. Therein lies the obstacle. The Dickey Wicker amendment was added on to another House bill in 1995 and served to ban HHS funds from research with human embryos. EMCs have the potential to develop into any cell type in the human body. Just as in Parkinson’s Disease, Alzheimer’s Disease, and stroke, the potential for EMC therapy is at the forefront in retinal research. It is time we joined the 21st century.

THOSE WHO GET TOO BIG FOR THEIR BRITCHEWS GET EXPOSED IN THE END.
A child was born HIV positive in 2010 and was treated with standard antiretroviral drugs. After the patient’s therapy was interrupted 15 months later, the virus did not return to detectable levels. Leading scientists shouted hooray and declared last year that the child was “functionally cured.” Oops. Last July researchers at the National Institute of Allergy and Infectious Diseases announced that the virus had bounced back. After a hiatus of four years the virus resurfaced in the patient’s blood and therapy was resumed. HIV lives in immune cells (T cells) that circulate in the blood and lymphatics. It can hide in lymph nodes where the cells become inactive and HIV is invisible. Later the T cell can awaken and the virus is activated. The opera isn’t over ‘til the fat lady sings, and with HIV the aria goes on.

GREAT SMILE. WHERE'D YOU BUY IT?
Why is the Supreme Court of the United States discussing tooth whiteners? The legal issue is much broader than a pearly smile and relates to the power of professional licensing boards. The North Carolina State Board of Dental Examiners made up primarily of dentists sought to prevent hair salons, day spas, shopping mall kiosks, and others from offering cosmetic teeth whitening services. The Federal Trade Commission (FTC) filed a lawsuit contending that the State Board was immune from antitrust suit because it is a government body. Just as in Parkinson’s Disease, Alzheimer’s Disease, and stroke, the North Carolina State Board is immune from antitrust suit because it is a government body. Just as in Parkinson’s Disease, Alzheimer’s Disease, and stroke, the potential for EMC therapy is at the forefront in retinal research. It is time we joined the 21st century.

HIPPOS IN THE NEW WORLD — A DRUG WAR BONUS.
About a quarter century ago drug lord Pablo Escobar built an exotic wild life zoo in Colombia. Subsequently Mr. Escobar was gunned down, the drug war subsided, and the zoo was abandoned. Four African hippopotamuses had been smuggled into the park. The hippos do not mosey up to the precise location where the robots provide the action. A bonus is the detailed data provided by the transponders the cows wear around their necks. The down side is for the dairy workers watching their jobs disappear.

THE CDC ACTUALLY MAKES ME FEEL LESS SAFE.
Tom Frieden, Director of Centers for Disease Control and Prevention (CDC) refused to ban entry of travelers from West African countries teeming with Ebola virus. His logic is that by leaving the door wide-open infection control units are better able to track potential victims. His inverted perspective is that a ban would increase the likelihood of travelers with Ebola gaining illegal access to our shores. The door will still be open for those who might lie about Ebola contacts and their own health to obtain care in the United States.

A GREAT STEP FORWARD. PROVIDED YOU CAN AFFORD IT.
Big Pharma scored bigtime with a drug for Hepatitis C. Gilead Sciences Inc, won United States approval to market the first pill that promises to cure hepatitis C patients without requiring other medicines. The drug named Harvoni is combined with Sovaldi, a previously approved medication, into a single orange pill to be taken once a day. The cost: $94,000 for a typical patient to be treated for 12 weeks. That’s over $1,000 per pill. And you thought illegal drugs were expensive.

AN UDDERLY SURPRISING DEVELOPMENT.
A report in the New York Times relates what looks like a “win-win” change in the dairy industry. A $250,000 robot can wash the cow’s milk sac, arrange nipple-cupping and milk the bovine dry without human interference. Amazingly, the cows have learned the drill and mosey up to the precise location where the robots provide the action. A bonus is the detailed data provided by the transponders the cows wear around their necks. The down side is for the dairy workers watching their jobs disappear.

ADDITIONS
- First president born outside the original 13 states: Abraham Lincoln.
- The first used car lot (17 cars) was opened in 1897.
- The used car lot line (17 cars) was opened in 1897.
- A Syrian rebel was shown in a video exhorting his troops from notes in his “Hello Kitty” notebook.
- The least favorite game at a nudist colony is dodge ball.
- What’s the difference between Washington and Las Vegas?
- In Vegas, the drunks gamble with their own money.
- I am a writer. I write checks, mostly fiction.

ALOHA AND KEEP THE FAITH.
Guidelines for Publication of HJM&PH Supplements

The following are general guidelines for publication of supplements:

1. Organizations, university divisions, and other research units considering publication of a sponsored supplement should consult with the editorial staff of HJMPH to make certain the educational objectives and value of the supplement are optimized during the planning process. It is important that the sponsoring editor is aware of all steps to its publication. Please contact Drs. Kalani Brady or Michael Meagher for further information.

2. Supplements must have educational value, be useful to HJMPH readership, and contain data not previously published to be considered for publication.

3. Supplements must have a sponsoring editor who will be involved in every step of the development, editing, and marketing of the publication since HJMPH staff will only be reviewing final proofs.

4. Supplements should treat broad topics in an impartial, unbiased manner. Please prefer specific classes of drugs, rather than products, unless there are compelling reasons or unique properties of the drug (product) that justifies its treatment.

5. The authors are solely responsible for the content of their manuscripts and the opinions expressed. They are also responsible for the replicability, precision, and integrity of the data and may be asked to sign a statement to that effect prior to publication. All authors are required to disclose any primary financial relationship with a company that has a direct fiscal or financial interest in the subject matter of products discussed in submitted manuscripts, or with a company that produces a competing product. The sponsoring editor must ensure that each article submitted incorporates a disclosure statement from the authors within the body of the text. For more information, please refer to the Disclosure Statement within “Instructions to Authors” on the journal website.

6. All supplement manuscripts should undergo editorial and peer review. It is the responsibility of the sponsoring editor to ensure the integrity of authorship and review process. In addition, sponsorship implies compliance with all federal, state and local laws, rules and regulations that may be applicable in connection with its publication.

7. Publication of a HJMPH supplement is a flat fee of $3,000 (electronic edition) plus the required State of Hawaii sales tax. The subscription manager will email an invoice to the designated editor for payment. Checks may be made out to UCERA. (There may be additional costs for hard copy prints. Please contact Drs. Brady or Meagher.)

8. The sponsoring editor may decide to include advertisements in the supplement in order to defray costs. Please consult with the HJMPH advertising representative Michael Roth at 808-595-4124 or email rothcomm@lava.net for assistance.

9. Supplement issues are posted online for full-text (PDF) retrieval on the HJMPH website at www.hjmph.org. An announcement of its availability will be made through our normal email distribution list. Full-text will also be available on PubMed Central.

10. It is the responsibility of the supplement editor and contributing team members to manage all editorial, marketing, sales, and distribution functions. If you need assistance, please contact our production manager. We may be able to help for an additional fee.

11. Timing of a supplement issue publication will be formalized once all required materials have been submitted to the production manager and payment made.
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