GEMs of the Week

Volume 3 - Issue 6

What's in this week's issue?

Week of February 6 - 10, 2023

SPOTLIGHT: Do Not Sleep on the Importance of Sleep in Early Adolescence

Do Not Sleep on the Importance of Sleep in Early Adolescence

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Effects of sleep duration on neurocognitive development in early adolescents in the USA: a propensity score matched, longitudinal, observational study

Yang FN, Xie W, Wang Z. Effects of sleep duration on neurocognitive development in early adolescents in the USA: a propensity score matched, longitudinal, observational study. *Lancet Child Adolesc Health*. 2022;6(10):705-712. doi:10.1016/S2352-4642(22)00188-2

KEY TAKEAWAY: Less than nine hours of sleep a day in early adolescence negatively impacts behavior, reduces brain function, and impedes brain structural development.

STUDY DESIGN: Longitudinal observational cohort

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The American Academy of Sleep Medicine recommends adolescents get at least nine hours of sleep every night. However, few studies have shown the long-term impact of insufficient sleep on early adolescent brain development and account for confounding factors such as socioeconomic status, sex, and puberty.

PATIENTS: Nine- to 10-year-old children

INTERVENTION: Less than nine hours of sleep

CONTROL: Nine or more hours of sleep

PRIMARY OUTCOME: Combined behavioral metrics (behavioral problems, cognition, mental health), resting brain function, brain structure

Secondary Outcome: Structural and functional pathways mediating behavior changes associated with sleep deprivation

METHODS (BRIEF DESCRIPTION):

- Data was obtained using a central database from the ongoing, national Adolescent Brain Cognitive Development (ABCD) study. The ABCD study is a population-based study that uses technology to assess how certain childhood experiences affect adolescent brain development and multiple socio-behavioral outcomes. It involves 21 research sites across the U.S. and has about 11,880 children ages 9–10 currently enrolled.
- Participants were matched based on age, sex, race, body mass index, puberty status, and socioeconomic status.
- Participants were excluded if they did not have a baseline functional MRI or were missing other demographic information.
- Baseline data was obtained at the beginning of the study. Data was obtained again after two years when participants were 11–12 years old.
- Sleep duration was measured using a parent-reported Sleep Disturbance Scale for Children. The intervention group (insufficient sleep) was defined as getting less than nine hours of sleep on most nights in the last six months while the comparison group (sufficient sleep) was nine or more hours of sleep on most nights in the last six months. 6,042 matched pairs (3,021 in each group) had baseline data while 749 pairs had available data at the two-year follow-up.
- Behavioral problems were measured using the parent-reported Child Behavior Checklist. Cognition was measured using scores from the U.S. National Institutes of Health (NIH) Cognition Battery Toolbox. Mental health was measured using scores from the brief child version of the Prodromal Psychosis Scale, the youth version of the Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency (UPPS-P) Impulsive Behavior Scale, and the Behavioral Inhibition Scale.
- Brain function and brain structure elements were obtained using a resting-state functional MRI, a structural MRI, and a diffusion tensor imaging scale.
- Longitudinal mediation analysis was used to identify specific structural and functional pathways mediating behavioral changes associated with sleep deprivation.

INTERVENTION (# IN THE GROUP): 749

COMPARISON (# IN THE GROUP): 749

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- The intervention group who received less than nine hours of sleep a night had poorer combined behavioral metrics, defined as increased behavioral

problems, reduced cognition, and adverse mental health when compared to the control (r=0.85; 95% CI, 0.73–0.92).
    - The results for each individual behavioral metric were not available.
- Resting brain function was reduced in the intervention group when compared to the control group (r=0.54; 95% CI, 0.45–0.61).
- Some brain structure elements were reduced in the intervention group when compared to the control group.
    - Grey matter volume (r=0.61; 95% CI, 0.51–0.69)
    - Cortical thickness (r=0.47; 95% CI, 0.34–0.59)

Secondary Outcome –

- The cortico-basal ganglia connection and the anterior temporal lobe were identified as areas that mediate behavioral changes associated with sleep deprivation.

LIMITATIONS:

- Only 749 out of 3,021 pairs had all neuroimaging data at the two-year follow-up.
- This is an observational study using matched pairs to draw conclusions.
- The data only reflects two timepoints and does not show gradual or longitudinal change within or between each person.
- Results for each individual behavioral metric (behavioral problems, cognition, and mental health) were not separated but grouped together, which may affect the results.

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The opinions and assertions contained herein are those of the author and are not to be construed as official or as reflecting the views of the U.S. Navy Medical Department, the Navy at Large, or the Department of Defense.

A Safe and Effective Malaria Vaccine

Safety and Efficacy of a Three-Dose Regimen of *Plasmodium falciparum sporozoite* Vaccine in Adults During an Intense Malaria Transmission Season in Mali: A Randomised, Controlled Phase 1 Trial

Sissoko MS, Healy SA, Katile A, et al. Safety and efficacy of a three-dose regimen of Plasmodium falciparum sporozoite vaccine in adults during an intense malaria transmission season in Mali: a randomised, controlled phase 1 trial. *Lancet Infect Dis*. 2022;22(3):377-389. doi:10.1016/S1473-3099(21)00332-7

KEY TAKEAWAY: The three-dose regimen of *Plasmodium falciparum sporozoite* (PfSPZ) vaccine is safe and efficacious for protecting African adults from naturally occurring *P falciparum* infection, especially in endemic areas.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: In 2019, the World Health Organization (WHO) reported 229 million malaria cases and 409,000 deaths. Since then, there have been no meaningful reductions in case numbers or deaths. The three-dose regimen PfSPZ trial sought to prove similar efficacy when compared to the previous five-dose regimen trial.

PATIENTS: Healthy, non-pregnant adults

INTERVENTION: PfSPZ vaccine

CONTROL: Normal saline

PRIMARY OUTCOME: Safety and tolerability

Secondary Outcome: Vaccine efficacy

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria included participants who were healthy, non-pregnant African individuals between 18 and 50 years old, in good health without any significant clinical history. Women of childbearing age willing to use a reliable method of birth control were included.
- Exclusion criteria:
  - Known allergies, contraindications to vaccines or combined artesunate and amodiaquine
  - Malaria vaccine within five years, recent antimalarial medications, immunosuppressive medications, blood products
  - Abnormal lab findings, history of chronic illness, ECG abnormalities, positive HIV, Hep B, Hep C, or known Sickle Cell Disease
- Participants were randomly assigned (1:1) to receive three doses of $1{\cdot}8\times10^6$ PfSPZ or normal saline at one, 13, and 19-week intervals.
  - They were monitored for 30 minutes post-injection and assessed at three, seven, 14, 28, 42, and 56 days thereafter.
- Participants received anti-malaria treatment (artesunate & amodiaquine) two weeks before the first and third vaccination.
- *P falciparum* infection and serum antibodies were measured using thick blood smear and ELISA, respectively.
- Modified intention to treat (mITT) included all participants that received at least one dose of vaccine or placebo.

INTERVENTION (# IN THE GROUP): 60

COMPARISON (# IN THE GROUP): 60

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- The PfSPZ vaccine is well tolerated and safe.
  - Injection site pain was reported in both the vaccine (7%) and placebo groups (8%).
- Most study participants reported no local or systemic adverse effects.
  - Only 5% in both the vaccine and placebo groups reported any adverse effects (*P*>.005).

Secondary Outcome –

- Per protocol results of the three-dose regimen of the PfSZ vaccine conferred 51% efficacy against *P falciparum* transmission of malaria (95% CI, 0.20–0.70) (mITT: 39%; 95% CI, 0.04–0.62).

LIMITATIONS:

- The study had a small sample size; therefore, this needs to be validated with a larger population.
- The study only included one population, making it challenging to apply results to populations outside Africa.

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Sideline Vestibular and Oculomotor Tests May Not Be Sufficient to Diagnose Sports-Related Concussions

Do Sideline Tests of Vestibular and Oculomotor Function Accurately Diagnose Sports-Related Concussion in Adults? A Systematic Review and Meta-Analysis

Harris SA, Dempsey AR, Mackie K, King D, Hecimovich M, Murphy MC. Do Sideline Tests of Vestibular and Oculomotor Function Accurately Diagnose Sports-Related Concussion in Adults? A Systematic Review and Meta-analysis. *Am J Sports Med*. 2022;50(9):2542-2551. doi:10.1177/03635465211027946

KEY TAKEAWAY: Clinicians working sideline coverage of adult sports must consider using multiple assessment tools while assessing an athlete with a suspected sports-related concussion.

STUDY DESIGN: Systematic review (SR) of eight prospective cohort studies (N=763) and meta-analysis (MA) of four prospective cohort studies (N=368)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to low credibility of values)

BRIEF BACKGROUND INFORMATION: Vestibular and oculomotor impairments have been observed with sports-related concussions (SRC), such as nausea, dizziness, nystagmus, and blurry vision. SRC assessment tools are primarily dependent on subjective symptoms, which are underreported by athletes and practitioners. This study assesses if objective measures of vestibular and oculomotor impairments are useful as SRC diagnostic tools.

PATIENTS: Adults at risk for a sports-related concussion

INTERVENTION: King-Devick test in athletes with suspected SRC

CONTROL: King-Devick test in athletes without suspected SRC

PRIMARY OUTCOME: Diagnostic accuracy of SRC

METHODS (BRIEF DESCRIPTION):

- This study was completed in accordance with PRISMA guidelines as well as the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.
- Inclusion Criteria:
  - Included patients were at least sixteen years old and participated in a sport with a reasonable risk for SRC.
  - Test results were compared in those who had a suspected SRC to those who did not.
- Each study used the King-Devick Test as their intervention, and each had separate comparison tests:
  - The King-Devick test is a two-minute rapid number naming assessment evaluating impairments of eye movements, attention, and language function.

INTERVENTION (# IN THE GROUP): 178 (SR), 117 (MA)

COMPARISON (# IN THE GROUP): 570 (SR), 245 (MA)

FOLLOW-UP PERIOD: Range from immediately after the event to three years

RESULTS:

Primary Outcome –

- The King-Devick test for concussion had a diagnostic accuracy summary:
  - Specificity: 0.82 (95% CI, 0.66–0.91)
  - Sensitivity: 0.77 (95% CI, 0.31–0.96)

LIMITATIONS:

- The credibility of these values was rated very low due to the small population, varying comparison tests, and the King-Devick test specificity and sensitivity could differ substantially.
- Differences in each individual's "clinical phenotype" were not explicitly documented in the original cohort studies, which could have caused heterogeneity in the meta-analysis, such as a history of SRC or the presence of concussion symptoms before and after the injury.
- There is no definitive, objective diagnostic tool for SRC, which affects the accuracy of the cohort studies that make up this meta-analysis.
- Four of the authors of the systemic review portion of the meta-analysis were contributing authors of some of the included studies.
- There was missing data from the systematic review in 9/763 and 6/368 in the meta-analysis.

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Insulin Glargine and Liraglutide are More Effective in Diabetes Management Goals

Glycemia Reduction in Type 2 Diabetes – Glycemic Outcomes

GRADE Study Research Group, Nathan DM, Lachin JM, et al. Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. *N Engl J Med*. 2022;387(12):1063-1074. doi:10.1056/NEJMoa2200433

KEY TAKEAWAY: When added to metformin, insulin glargine and liraglutide significantly improve and maintain A1C levels better than sitagliptin or glimepiride.

STUDY DESIGN: Randomized, unblinded, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Over 500 million adults are affected by type 2 diabetes worldwide with more than 30 million adults affected in the United States alone. Type 2 diabetes has major economic costs and significant long-term complications. Current recommendations list metformin as the first-line medication to be used, but there is no clear recommendation on what is the best second medication to add to metformin therapy to improve A1C levels to 7.0%.

PATIENTS: Adults with type 2 diabetes

INTERVENTION: A second-line glucose-lowering medication + metformin

CONTROL: Not applicable (four second-line medications compared to each other)

PRIMARY OUTCOME: A1C ≥7.0%

Secondary Outcome: A1C ≥7.5%

METHODS (BRIEF DESCRIPTION):

- 5,047 participants with type 2 diabetes diagnosed at or after the age of 30 (or age at diagnosis over 20 years in Alaska Natives or American Indians), with the duration of diabetes less than 10 years, receiving only metformin with A1C of 6.8 to 8.5%.
- All participants were on immediate-release or extended-release metformin (1,000-2,000 mg/day)
- Patients were randomized to one of the following treatments:
  - Insulin glargine U-100, with an initial daily dose of up to 20 units, adjusted based on subsequent glucose levels.
  - Glimepiride with an initial dose of 1 to 2 mg to a max of 8 mg per day, adjusted based on glucose levels.
  - Liraglutide initial 0.6 mg increased to max dose 1.8 mg daily, adjusted depending on GI side effects.
  - Sitagliptin initial dose 100 mg, with adjustments subsequently based on kidney function.
- Participants and clinic staff were aware of the treatment assignments; however, investigators and committee members were unaware.
- Participants were evaluated quarterly using glycated hemoglobin levels, collected either in the clinic or using a mail-in kit.

INTERVENTION (# IN THE GROUP):

- Glargine: 1,263
- Glimepiride: 1,254
- Liraglutide: 1,262
- Sitagliptin: 1,268

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Five years

RESULTS:

Primary Outcome –

- When compared to pooled results of all other treatments:
  - Liraglutide reduced the risk of A1C ≥7.0% the most (hazard ratio [HR] 0.84; 95% CI, 0.78–0.91).
  - Glargine reduced the risk of A1C ≥7.0% (HR 0.87; 95% CI, 0.80–0.94).
  - Glimepiride did not affect the risk of A1C ≥7.0% (HR 1.0; 95% CI, 0.93–1.1).
  - Sitagliptin increased the risk of A1C ≥7.0% the most (HR 1.4; 95% CI, 1.3–1.5).

Secondary Outcome –

- When compared to pooled results of all other treatments:
  - Glargine reduced the risk of A1C ≥7.5% the most (HR 0.72; 95% CI, 0.65–0.79).
  - Liraglutide did not affect the risk of A1C ≥7.5% (HR 0.92; 95% CI, 0.84–1.01).
  - Glimeperide did not affect the risk of A1C ≥7.5% (HR 1.1; 95% CI, 1.0–1.2).

- Sitagliptin increased the risk of A1C ≥7.5% the most (HR 1.4; 95% CI, 1.3–1.5).

LIMITATIONS:

- Trial excluded SGLT2 inhibitors and thiazolidinediones, due to safety concerns and timing of FDA approval.
- The study used only a single agent in each drug class, though these classes have multiple other drugs available. These other drugs may have significantly different results leading to limited extrapolation.
- This trial was not blinded, which may lead to biases.
- Medication adjustments occurred frequently which may not reflect real-world practice.

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Could Magic Mushrooms Help People Quit Drinking?

Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients with Alcohol Use Disorder

Bogenschutz MP, Ross S, Bhatt S, et al. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder. *JAMA Psychiatry*. 2022;79(10). doi:10.1001/jamapsychiatry.2022.2096

KEY TAKEAWAY: Adjunct psilocybin administration may augment the therapeutic effects of psychotherapy for the treatment of alcohol use disorder (AUD).

STUDY DESIGN: Randomized, double-blind, controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of non-treatment group, underpowered, and short timeframe)

BRIEF BACKGROUND INFORMATION: Evidence-based treatment of AUD involves a multimodal, individualized approach including brief interventions and pharmacotherapy initiated by primary care providers; along with referrals to more intensive psychotherapy, 12-step programs, and residential programs. Psychotherapy approaches including motivational interviewing and CBT are effective treatment modalities but do not have additive effects when combined. Limited evidence exists identifying adjunct therapies to amplify the effectiveness of single psychotherapy approaches.

PATIENTS: People with alcohol dependence and recent heavy drinking

INTERVENTION: Psilocybin orally as an adjunct to psychotherapy

CONTROL: Diphenhydramine orally as an adjunct to psychotherapy

PRIMARY OUTCOME: Percent of heavy drinking days (PHDD)

Secondary Outcome: Percent of drinking days (PDD), drinks per day (DPD), alcohol abstinence, no heavy drinking, alcohol consumption risk level

METHODS (BRIEF DESCRIPTION):

- The population included 44% female and 21% Black, Indigenous, and people of color with AUD not receiving current therapy. Participants had no comorbid psychiatric disorders and were relatively hallucinogen naïve.
- All participants received 12 psychotherapy sessions. Treatments were given in a controlled environment as part of additional observed eight hour sessions.
- Psilocybin dosing at the first session was equal for all intervention-blinded participants, 25 mg/70 kg.
- Psilocybin dosing at the second session increased based on the participants' response to the initial dose. The second dose range was 30–40 mg/70 kg.
- Psychological experience and responses to the interventions were measured using the Pahnke-Richards Mystical Experience Questionnaire (MEQ) immediately after each session. Higher scores indicate a more intense psychedelic experience.
- PHDD was assessed at weeks eight, 12, 24, and 36 using Timeline Followback (TLFB), a validated self-reporting tool on alcohol consumption patterns (one drink = 14 g alcohol).
- PDD, DPD, abstinence, lack of heavy drinking days, and WHO drinking risk categories were also assessed at these intervals.
    - Self-reported alcohol volume was used to calculate WHO risk category and compared with self-reported drinking during the 12 weeks prior to screening.

INTERVENTION (# IN THE GROUP): 49

COMPARISON (# IN THE GROUP): 46

FOLLOW-UP PERIOD: 36 weeks

RESULTS:

Primary Outcome –

- All participants experienced a 27 to 32% reduction in PHDD in the first four weeks with psychotherapy alone (P<0.001).
- Psilocybin treatment during the subsequent 32 weeks resulted in 13% less PHDD (10%) as compared to the active control group (23%) (P=0.01).

Secondary Outcome –

- Psilocybin treatment did not decrease PDD (29%) compared to the active control group (42%) (P=0.05).

- Psilocybin treatment reduced DPD to 1 while there was no reduction in the active control group (*P*=0.01).
- Psilocybin adjunct therapy increased abstinence by the end of the trial compared to the active control group, confirmed by hair/fingernail ethyl glucuronide (EtG) testing (OR 2.8; 95% CI, 1.2–6.9; NNT=4.3).
- Psilocybin adjunct therapy increased the likelihood of having no days of heavy drinking in the study period compared to the active control group (OR 4; 95% CI 1.3–12; NNT=4.5).
- Psilocybin treatment lowered the risk for alcohol consumption more than the active control group:
    - One-point decrease in risk (OR 4.7; 95% CI 1.6–14; NNT=4)
    - Three-point decrease in risk (OR 2.8; 95% CI 1.1– 7.3; NNT=5.1).

LIMITATIONS:

- The active control, diphenhydramine, was easily distinguished from psilocybin by both participants and administrators which may have caused biased expectancies.
- Objective verification of self-reported drinking using EtG was only available for 54% of participants. Though objective verification supported the subjective claim in 100% of tested cases.
- The study's power was not adequate for subgroup analysis.
- There was no non-treatment control group to evaluate the effect of psychotherapy alone over 32 weeks.
- No information was provided about the duration of effects beyond the 32-week double-blinded period, which is important due to the high rates of relapse during AUD treatment.

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Got Non-Alcoholic Beer? The Effectiveness of Barley Malt as a Galactagogue

Barley Malt-Based Composition as a Galactagogue – A Randomized, Controlled Trial in Preterm Mothers

Wesolowska A, Pietrzak B, Kociszewska-Najman B, et al. Barley malt-based composition as a galactagogue - a randomized, controlled trial in preterm mothers. *Ginekol Pol*. 2021;92(2):118-125. doi:10.5603/GP.a2020.0107

KEY TAKEAWAY: Barley malt can be used effectively as a galactagogue for nursing mothers.

STUDY DESIGN: Multi-site, double-blind, randomized, placebo-controlled clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Many factors contribute to a mother's ability to produce milk; low milk supply and delayed production are common amongst breastfeeding mothers. Breast milk is especially critical for preterm infants. Galactagogues are substances that facilitate milk production and there are many substances that are anecdotally known to improve milk production, non-alcoholic beer being one of them. There is currently a lack of good evidence supporting the efficacy and safety of barely based galactagogues.

PATIENTS: Breastfeeding adult mothers

INTERVENTION: Galactagogue formula

CONTROL: Placebo

PRIMARY OUTCOME: Total volume of milk expressed

Secondary Outcome: Safety of the intervention

METHODS (BRIEF DESCRIPTION):

- Polish women >18 years old who delivered infants at <37 weeks gestation were enrolled and assigned to either placebo or galactagogue groups.
- Inclusion criteria: Enrollment within two days of birth and consented to utilize a breast pump and record lactation volume daily
- Exclusion criteria: Hypothyroidism and diabetes
- Mothers received 28 packages of identical-looking formulas to take twice daily for 14 days following delivery of the infant.
- Galactagogue formula consisted of lemon balm leaves and barley malt enriched with 70% barley-glucan.
- Mothers were instructed to pump breastmilk every four hours using the Symphony breast pump.
- Exact milk volumes collected were recorded by participants daily and confirmed by staff.
- Patients were monitored for any side effects of the intervention by research staff.
- Three hospital visits for follow-up were scheduled during the trial (one before day 2 post-partum, one before the end of the first week of the trial, and one on day 14 post-partum).

INTERVENTION (# IN THE GROUP): 40

COMPARISON (# IN THE GROUP): 40

FOLLOW-UP PERIOD: 14 days post-partum

RESULTS:

Primary Outcome –

- Galactagogue increased the total volume of milk expressed compared to placebo (6,036 mL vs 4,209 mL, respectively; *P*=.003).

Secondary Outcome –

- There were no adverse effects reported by participants in the galactagogue group.

LIMITATIONS:

- Other dietary considerations such as the use of other galactagogues or known anti-galactagogues were not controlled.
- Fluid intake was not controlled.
- The sample size was small.
- The study did not specify whether women were in the hospital or at home during the intervention.

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The Evolution of Monkeypox Spread: From Animals to Humans in Western Societies

The Changing Epidemiology of Human Monkeypox—A Potential Threat? A Systematic Review

Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. *PLoS Negl Trop Dis*. 2022;16(2):e0010141. Published 2022 Feb 11. doi:10.1371/journal.pntd.0010141

KEY TAKEAWAY: The age of those affected with Monkeypox has progressed to 21 years old in the 2010 decade compared to 4 years old in the 1970 decade. The mode of transmission has primarily changed from animals to humans.

STUDY DESIGN: Systematic review of epidemiology studies

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Recent reports of Monkeypox cases in the US have stemmed concern. Monkeypox is an orthopoxvirus that displays high similarity to the smallpox virus with similar clinical presentation. The incidence of Monkeypox is thought to have increased with the cessation of smallpox vaccination and subsequent cross-protection of disease. While cases remain highest in African countries, studies of the epidemiology of Monkeypox are useful to understand the potential threat of spread to Western countries.

PATIENTS: Confirmed and suspected monkeypox cases

INTERVENTION: Monkeypox cases from 1970 to 2020

CONTROL: Not applicable

PRIMARY OUTCOME: Description of monkeypox epidemiology (cases, clade, death rate, age of infection, mode of transmission)

METHODS (BRIEF DESCRIPTION):

- Systematic review comparing monkeypox cases from the 1970s, 1980s, 1990s, 2000s, and 2010s by age, death rate, and mode of transmission by country and clade.
- Cases of confirmed, suspected, probable or possible Monkeypox which include people in 10 African Countries and four countries elsewhere. Countries included CAR, DRC, the US, Nigeria, the Republic of Congo, Sierra Leone, Cameroon, Cote D'Ivoire, Gabon, the UK, Israel, Liberia, Singapore, and South Sudan.
- Median age of contraction per decade and case fatality rate and mode of transmission by country and/or clade (Western vs. Central Africa) were calculated.
- This included a systemic review of primary peer-reviewed literature (n=48 studies) and gray literature (n=18 studies taken primarily from government epidemiology reports [e.g., WHO, government ministries of health]), resulting in a review of 1,347 confirmed cases and 28,815 probable cases.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome – The incidence of Monkeypox cases has increased over the past five decades and the age of contraction has increased from children to young adults, suggesting a different mode of transmission. The cases from the Dominican Republic of Congo suggest a shift from animal to human vectors. The fatality rate is higher in the Central Africa clade, and less in the Western Africa clade (which is the most prevalent outside of Africa).

- Total Monkeypox cases (confirmed or probable) by decade:
  - 1970s: 47
  - 1980s: 356
  - 1990s: 520
  - 2000s: 139
  - 2010s: 280
- Death rates by country/clade:
  - All countries: pooled estimate 8.7% (95% CI, 7.0%–11%)
  - Central African clade: pooled estimate 11% (95% CI, 8.4%–13%)
  - West African clade: pooled estimate 3.6% (95% CI, 1.7%–6.8%)
  - West African clade (African countries only): pooled estimate 4.6% (95% CI, 2.1%–8.6%)

LIMITATIONS:

- Findings were dependent on the variable quality of the included research studies.

- There may have been underreporting in countries in Central Africa.

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