Acute Lung Injury

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Outline

Definition
Etiologies
Mechanism
Symptoms
Pathology
Treatment
Outcomes
Other inhalants
Prevention

Definition

- EVALI—E-cigarette or vaping product related acute lung injury
- Officially recognized by the CDC in the summer of 2019
- Peaks in incidence June through September 2019 with a decrease since, likely due to information/surveillance



EVALI—National Statistics

- As of February 18, 2020
 - 2807 hospitalizations—all states
 - 68 deaths—29 states, not AZ, age range 15-75
- Hospitalizations: 66% male, median age 24, range 13-85 years, 15% under 18 y.o., 37% 18-24 y.o., 24% 25-34 y.o., 24% over 35 years
- As of January 14, 2020
 - 82% using THC products, 33% exclusively—78% getting "informally"
 - 57% using nicotine products, 14% exclusively—69% getting commercially



1-9 cases

10-49 cases

50-99 cases

100-149 cases

150-199 cases

200-249 cases

Pathology

- Acute fibrinous pneumonitis, diffuse alveolar damage, organizing pneumonia
- Acute eosinophilic pneumonia
- Diffuse alveolar hemorrhage
- Lipoid pneumonia
- Bronchiolar interstitial lung disease
- All suggest more than one mechanism and a continuum of disease



THE MANY FLAVORS OF EVALI...

HYPERSENSITIVITY PNEUMONITIS

- OFTEN SYMMETRICAL - MIP-TO-UPPER LUNG GROUNP-GLASS MOSAICISM
- ILL-PEFINED CENTRILOBULAR NOPULES



ORGANIZING PNEUMONIA

- OFTEN PENSE AND/OR GROUND GLASS CONSOLIDATIONS - OFTEN PERIPHERAL OR PERI-LOBULAR PISTRIBUTION - CLASSICALLY SUBPLEURAL SPARING

LIPOID PNEUMONIA

MAY CONTAIN ANY OR ALL OF:

- CRAZY PAVING (ABOVE)

- GROUND GLASS

- CONSOLIDATIONS

PIFFUSE ALVEOLAR PAMAGE

- HETEROGENOUS CONSOLIDATIONS (CRAZY PAVING, GROUND GLASS, ETC) - GRAVITY DEPENDENT - ORGANIZING PHASE WITH TRACTION BRONCHIECTASIS AND RETICULATIONS





ACUTE EOSINOPHILIC PNEUMONIA

- SYMMETRICAL GROUND GLASS WITH SEPTAL THICKENING AND PLEURAL EFFUSIONS (NON-SPECIFIC)
- PERIPHERAL EOSINOPHILIA ABSENT ON PRESENTATION
- PIAGNOSIS CLINCHEP BY BAL WITH 25% EOSINOPHILS

PIFFUSE ALVEOLAR HEMORRHAGE

- MAY HAVE CENTRILOBULAR NOPULES
- GROUNP GLASS
- CONSOLIPATIONS
- COMBINATION OF ANY OF ABOVE

E-liquid component	Chemical or compound
Carrier solution	Propylene glycolVegetable glycerin
Flavourants	 Diacetyl 2,3-Pentanedione Acetoin
Additives	 Nicotine Tetrahydrocannabinol Cannabidiol Butane hash oil Other oil-rich additives
Adulterants	 Vitamin E acetate (tetrahydrocannabinol adulterant)
Aerosol emissions	 Carbonyls from heating propylene glycol and vegetable glycerin Particulates Trace metal elements Volatile organic compounds
Contaminants	Bacterial endotoxinsFungal glucans



Patterns of disease shown in case reports of vaping-associated pulmonary illnesses: an overview of the medical literature up to Oct. 30, 2019*.

Type of lung injury or predominant disease pattern	No. of cases	Age and sex	Associated imaging findings	Level of care required
Organizing pneumonia ^{10–13,26}	12	64M, 40F, 54M, 22M, 20M, 21M, 28M, 19M, 28M, 38M, 35M, 39M	1 patchy infiltrates, 11 diffuse GGO, 1 tree in bud, 1 pneumothorax with bilateral central opacities, bilateral reticulonodular opacities with subpleural sparing	7 hospital ward, 2 ICU, 3 unknown
Acute fibrinous pneumonitis with organization ²⁶	11‡	44M, 42M, 51M, 25M, 21M, 34F, 28M, 54F, 67M, 19M, 40M	5 diffuse GGO, 2 bilateral centrilobular GGO, 1 perihilar GGO, 1 tree in bud, 1 diffuse bronchocentric micronodular GGO, 1 diffuse bilateral opacities	11 unknown
Lipoid pneumonia ¹⁷⁻²¹	10	42F, "young" F, 35F, 31F, 20§, 23§, 23§, 25§, 29§, 47§	8 diffuse GGO, 3 "crazy paving," 1 consolidation, 1 basilar GGO	6 hospital ward, 4 ICU
Acute alveolitis or diffuse alveolar damage ^{9,13,26–28}	8¶	46M, 33M, 35M, 61M, 47F, 21M, 34F, 28M	6 bilateral diffuse GGO, 1 traction bronchiectasis	1 hospital ward, 6 ICU, 1 unknown
Pneumomediastinum or pneumothorax ²⁹⁻³³	6	17M, 16M, 21M, 15M, 16M, 18M	2 pneumomediastinum, 1 tension pneumothorax, 3 nontension pneumothorax	6 hospital ward
Hypersensitivity pneumonitis ^{5–8}	4	73F, 16F, 23M, 18F	2 diffuse GGO, 2 septal thickening, 1 traction bronchiectasis, 1 honeycombing, 1 diffuse nodules	2 hospital ward, 1 ICU with ECMO, 1 ICU without ECMO
Granulomatous disease ^{34,35}	2	43F, 34F	2 bilateral nodules	2 hospital ward
Eosinophilic pneumonia ^{15,16}	2	18F, 20M	2 diffuse GGO, 1 airspace disease, 1 coalescing nodules	1 ICU, 1 hospital ward
Status asthmaticus ³⁶	2	16M, 14F	2 pneumomediastinum	2 ICU with ECMO
Bronchitis ^{37,38}	2	43M, 56F	1 no acute abnormality, 1 diffuse GGO, 1 "crazy paving"	1 outpatient, 1 hospital ward
Inhalational injury ^{39,40}	2	35F, 60M	1 nodular infiltrates, 1 mediastinal adenopathy, 1 bilateral GGO	1 ICU with ECMO, 1 hospital ward
Respiratory bronchiolitis– associated interstitial lung disease41	1	33M	Tree in bud	Hospital ward
Diffuse alveolar hemorrhage ⁹	1	33M	Diffuse GGO	ICU
Hypereosinophilia with eosinophilic asthma ⁴²	1	18F	NA	Outpatient
Transient nodules in lung and liver ⁴³	1	45F	Multiple pulmonary and hepatic nodules	Hospital ward
Pleural effusion44	1	63M	Left-sided pleural effusion	Hospital ward
Severe persistent airflow obstruction in a long-standing smoker†45	1	45M	Patchy GGO, mosaic attenuation	Outpatient
Upper airway damage ⁴⁶	1	30M	Moderate uvulitis and edema of the paratracheal musculature	ICU

Note: ECMO = extracorporeal membrane oxygenation, F = female, GGO = ground-glass opacities, ICU = intensive care unit, M = male, NA = not available.

**Case reports" refers to individual cases reported with pathology and imaging findings. Table 1 does not include the 53-person case cohort published by Layden et al.²² or 805 cases reported by Perrine et al.⁴⁷

†Patient was a long-standing smoker. No baseline pulmonary function tests before illness.

‡One death.

§Sex not defined

¶Two deaths.



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EVALI—Clinical Features

- Shortness of breath
- Cough
- Chest pain
- Pleuritic chest pain
- Hemoptysis
- Fever and chills
- Nausea, vomiting, diarrhea
- Abdominal pain
- Present days to months ahead of acute process

Clinical Characteristics of Nonhospitalized Patients



- 85% (47/55) initially experienced respiratory symptoms
 - e.g., cough, chest pain, and shortness of breath
- 57% (27/47) had gastrointestinal symptoms
 - e.g., abdominal pain, nausea, vomiting, and diarrhea
- 76% (41/54) had symptoms accompanied by constitutional symptoms
 - e.g., fever, chills, and weight loss

Proposed criteria for EVALI

Confirmed case

- Use of an e-cigarette ("vaping") or "dabbing" in the previous 90 days*
- Lung opacities on chest radiograph or computed tomography
- Exclusion of lung infection based on:
 - Negative influenza PCR or rapid test (unless out of season)
 - Negative respiratory viral panel
 - Negative testing for clinically-indicated respiratory infections (eg, urine antigen test for *Legionella* and *Streptococcus pneumoniae*, blood cultures, sputum cultures if producing sputum, and bronchoalveolar lavage if performed)
 - Negative testing for HIV-related opportunistic respiratory infections (if appropriate)
- Absence of a plausible alternative diagnosis (eg, cardiac, neoplastic, rheumatologic)

Probable case

- Use of an e-cigarette ("vaping") or "dabbing" in the previous 90 days*
- Lung opacities on chest radiograph (diffuse hazy or consolidative opacities) or computed tomography (ground glass or consolidative opacities)
- Infection identified via culture or PCR, but clinical team believes this infection is not the sole cause of the underlying lung injury OR

Minimum criteria to rule out pulmonary infection not met (testing not performed) and clinical team believes infection is not the sole cause of the underlying lung injury

• Absence of a plausible alternative diagnosis (eg, cardiac, neoplastic, rheumatologic)

Risks

- THC—present in lung lavage samples from 75-80% of acute injury victims
- Vitamin E acetate—used as a thickener, usually with THC—present in lung lavage of over 90% of acute injury victims
- Nicotine—present in lung lavage of over 60% of acute injury victims. Also present in lavage of smokers without symptoms
- Other elements—CBD, plant oils, medium chain triglycerides, petroleum products, byproducts

Presentation, Characteristics, and Outcome of Six Patients in Utah with Pulmonary Illness Related to E-Cigarette

Table 1. Presentation, Characteristics, and Outcome of Six Patients in Utah with Pulmonary Illness Related to E-Cigarette Use.*							
Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	
Age (yr)	20	25	29	23	23	47	
Approximate time from symptom onset to presentation†	9 days	9 days	2 wk	2 mo	5 days	6 wk	
Initial laboratory studies†							
Blood white-cell count (per mm ³)	16,300	18,200	10,600	4800	12,300	13,800	
Differential count (%)							
Granulocytes	92.0	93.7	92.2	84.5	90.2	89.2	
Lymphocytes	1.5	3.8	6.0	8.9	5.7	7.0	
Eosinophils	0.9	0.0	0.3	2.9	0.8	0.0	
ESR (mm/hr)‡	NA	122	105	90	128	60	
C-reactive protein (mg/dl)§	30.7	20.4¶	22.6	28.0	25.8	21.7	
Bronchoalveolar lavage							
Lipid-laden macrophages (%)	>50	Approx. 50	30	25	>75	Approx. 60	
Differential count (%)							
Macrophages	32	79	71	61	43	46	
Bronchial lining cells	12	2	7	1	5	0	
Lymphocytes	5	0	3	9	14	25	
Neutrophils	49	18	19	26	38	27	
Eosinophils	12	1	0	3	0	2	
Management and outcomes							
Medical therapy	Antibiotics; high-dose glucocorticoids	Antibiotics; high-dose glucocorticoids	Glucocorticoids; anti- biotics**	Glucocorticoids; anti- biotics**	Antibiotics	None	
Other interventions	Mechanical ventilation; venovenous ECMO	High-flow nasal cannula	None	Supplemental oxygen by nasal cannula	Supplemental oxygen by nasal cannula	Supplemental oxygen by nasal cannula	
Outcome	Alive; hypoxemia resolved	Alive; oxygen at discharge	Alive; fevers resolved	Alive; hypoxemia resolved	Alive; hypoxemia resolved	Alive; hypoxemia resolved	

* ECMO denotes extracorporeal membrane oxygenation, ESR erythrocyte sedimentation rate, and NA not available.

Shown are data at admission to our facility.

The reference range is 0 to 10 mm per hour.

The reference range is 0.0 to 0.8 mg per deciliter.

Shown are data for high-sensitivity C-reactive protein; the reference range is less than 0.3 mg per deciliter.

Lipid-laden macrophages were measured by means of oil red O staining.

** With respect to glucocorticoids, a short course of prednisone was prescribed by an outpatient provider before hospitalization.

SD Maddock et al. N Engl J Med 2019;381:1488-1489.

Computed Tomographic Scans of the Chest Obtained from Patients with Vaping-Associated Lung Injury.





Chest Radiographs and High-Resolution Computed Tomographic Imaging in a 17-Year-Old Male Patient with Diffuse Lung Disease.





Treatment

- Hospitalization
- Respiratory support—oxygen, ventilation, ECMO
- Antibiotics to cover community acquire pneumonia
- Consider steroids
- Prognosis complete resolution to death—no clear associations

Management algorithm

Initial clinical

Patient arrives with signs and symptoms such as:







Outpatient clinical evaluation

- Consider CXR (chest pain, dyspnea, clinical exam findings)
- Consider influenza testing per established guidelines

Outpatient clinical management

Manage for possible EVALI



- Discontinue use of e-cigarette, or vaping, products
- Consider corticosteroids with caution Manage other possible infections, if present
- Consider early initiation of antivirals for possible influenza or appropriate antibiotics for community acquired pneumonia Ensure follow-up within 24-48 hours Emphasize importance of routine influenza vaccination Offer cessation services

Inpatient clinical evaluation

- Conduct laboratory and infectious disease testing guided by clinical findings
- Obtain a chest X-ray and consider CT if chest X-ray is normal
- Consider consultation with specialists
- Additional testing with bronchoalveolar lavage or lung biopsy as clinically indicated, in consultation with pulmonary specialists

Inpatient clinical management

- Discontinue use of e-cigarette, or vaping, products
- Consider empiric use of antibiotics, antivirals, or both
- Consider corticosteroids with timing, depending on severity
- Offer cessation services
- Ensure follow-up no later than 1-2 weeks after discharge
- Emphasize importance of routine influenza vaccination

Ask about Use

- Ask about the use of e-cigarette, or vaping, products and types of substances used
- Confidentiality is essential especially for young adults and adolescents
- Empathetic, nonjudgmental, and private questioning of patients*
- Continue to ask questions during follow-up encounters



Exposure History

Types of substances used

 THC/cannabis [oil, dabs], nicotine, modified products or the addition of substances not intended by the manufacturer

Where products were obtained

- THC containing products obtained through informal sources such as friends, family members, or in-person or online-dealers have been implicated
- Clinicians might seek additional information to inform the ongoing investigation



Physical Examination

- Should include vital signs and pulse-oximetry
 - Vital signs findings include tachycardia, tachypnea, O₂ saturation <95% at rest on room air
- Pulmonary findings on auscultation exam have been unremarkable, even among patients with severe lung injury



Considerations for Management Setting

- Some patients may be candidates for outpatient management
 - Normal oxygen saturation (≥95%)
 - No respiratory distress
 - No comorbidities that might compromise pulmonary reserve
 - Reliable access to care, strong social support systems
 - Ensure follow-up within 24–48 hours



Outpatient Clinical Evaluation

- Consider influenza testing
- Consider chest radiograph (CXR), if indicated by
 - Chest pain
 - Dyspnea
 - Clinical exam findings



Outpatient Management: Manage Possible EVALI

- Advise patient to discontinue use of e-cigarette, or vaping, products
 - Some patients have had recurrences with continue use
- Corticosteroids might worsen respiratory infections and should be considered with caution in the outpatient setting
 - Not well studied; consider with caution
 - Might worsen commonly seen respiratory infections
 - Most patients had rapid improvement with corticosteroids
 - Some patients who have not received corticosteroids had clinical improvement with e-cigarette cessation

Blagev DP, Harris D, Dunn AC, Guidry DW, Grissom CK, Lanspa MJ. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: a prospective observational cohort study. Lancet 2019;19:32679–0.

Outpatient Management: Manage Other Infections

- Manage other infections, if present, in accordance with established guidelines^{*}
 - Early initiation of antivirals for possible influenza
 - Appropriate antibiotics for community acquired pneumonia



* CDC Summary of Influenza Antiviral Medications; IDSA Clinical Practice Guidelines for Seasonal Influenza; Pneumonia guidelines; Pneumonia guidelines for infants and children

Outpatient Management: Cessation Counseling

- Offer or connect all patients to services to stop using e-cigarette, or vaping, products
- Adults tobacco smokers should be
 - advised not to return to smoking cigarettes, if using e-cigarette, or vaping, products to quit cigarette smoking
 - provided with evidence-based interventions: behavioral counseling,
 FDA-approved cessation medications
- Adolescents and young adults might benefit from specialized services like
 - addiction treatment services
 - providers who have experience with counseling and behavioral health

Outpatient Management: Follow-Up Instructions

- Ensure follow-up within 24-48 hours; additional follow-up might be indicated, based on clinical findings
- Patients should return immediately if they develop new or worse respiratory symptoms
- Emphasize importance of routine influenza vaccination



Inpatient Clinical Evaluation

- Urine toxicology, influenza testing, other laboratory and infectious disease testing guided by clinical findings
- Obtain a chest x-ray and consider CT if chest x-ray is normal
- Consultation with pulmonary, critical care, medical toxicology, infectious disease, and others
- Consider bronchoalveolar lavage or lung biopsy as clinically indicated

Inpatient Clinical Management

- Discontinue use of e-cigarette, or vaping, products
- Consider empiric use of antibiotics, antivirals, or both, in accordance with established guidelines
- Consider corticosteroids, with timing depending on severity
- Offer cessation services
- Ensure follow-up no later than 1-2 weeks after discharge from hospital
- Emphasize importance of routine influenza vaccination

Follow-up From Hospital Admission

- Initial: within 1–2 weeks after discharge
 - Repeat pulse-oximetry
 - Consider repeat CXR
- Additional follow-up: 1–2 months after discharge
 - Consider spirometry, diffusion capacity testing, and CXR
- Long-term effects and the risk of recurrence of EVALI are not known
 - Many patients have symptom resolution
 - Some patients relapsed during corticosteroid tapers or with resumption product use
 - Some had hypoxemia requiring home oxygen and pulmonary follow up
 - Some treated with high-dose corticosteroids might require monitoring of adrenal function and endocrinology follow up

WHAT ARE E-CIGARETTES?

- » E-cigarettes are known by many different names. They are sometimes called "e-cigs," "e-hookahs," "mods," "vape pens," "vapes," "tank systems," and "electronic nicotine delivery systems."
- » Some e-cigarettes are made to look like regular cigarettes, cigars, or pipes. Some resemble pens, USB sticks, and other everyday items.
- » E-cigarettes produce an aerosol by heating a liquid that usually contains nicotine—the addictive drug in regular cigarettes, cigars, and other tobacco products—flavorings, and other chemicals that help to make the aerosol. Users inhale this aerosol into their lungs. Bystanders can also breathe in this aerosol when the user exhales into the air.



» E-cigarettes can be used to deliver marijuana and other drugs.

CS284159-8



U.S. Department of Health and Human Services Centers for Disease Control and Prevention



WHAT ARE E-CIGARETTES?

Electronic cigarettes (e-cigarettes) are battery-powered devices that deliver nicotine, flavorings, and other ingredients to the user. Using e-cigarettes is sometimes called "vaping." E-cigarettes do not create harmless "water vapor" – they create an aerosol that can contain harmful chemicals.

HOW MANY YOUTH ARE USING E-CIGARETTES?

- E-cigarettes have been the most commonly used tobacco product among U.S. youth since 2014.
- In 2019, CDC and FDA data showed that more than 5 million U.S. youth, including over 1 in 4 high school students and about 1 in 10 middle school students, used e-cigarettes in the past 30 days.
- During 2017 and 2018, e-cigarette use skyrocketed among youth, leading the U.S. Surgeon General to call the use
 of these products among youth an epidemic in the United States.

WHAT ARE THE RISKS FOR YOUTH?

- Most e-cigarettes contain nicotine, which is highly addictive. Nicotine exposure during adolescence can:
 - » Harm brain development, which continues until about age 25.
 - » Impact learning, memory, and attention.
 - » Increase risk for future addiction to other drugs.
- · Young people who use e-cigarettes may be more likely to go on to use regular cigarettes.
- Many e-cigarettes come in kid-friendly flavors including mango, fruit, and crème which make e-cigarettes
 more appealing to young people.
- E-cigarette aerosol is not harmless. It can contain harmful substances, including:
 - » Nicotine »
 - » Ultrafine particles
 - » Cancer-causing chemicals » Flavorings that have been linked to lung disease
 - » Volatile organic compounds » Heavy metals such as nickel, tin, and lead



U.S. Department of Health and Human Service: Centers for Disease Control and Prevention



CDC.gov/e-cigarettes







7 out of 10 middle and high school students who currently use tobacco have used a **FLAVORED** product.







of students who currently use e-cigarettes have used **flavored** e-cigarettes. (1.6 million) of students who currently use hookah have used **flavored** hookah. (1 million) of students who currently use cigars have used **flavored** cigars. (910,000)



Source: Morbidity and Mortality Weekly Report (MMWR)







TOBACCO PRODUCT USE IN ANY FORM, INCLUDING E-CIGARETTES, IS UNSAFE FOR YOUTH.

Cigarette Smoking

- Declining but still 12% of high school students actively smoking cigarettes
- Over 80% of adolescent smokers persist into adulthood
- Symptoms—chronic cough, exacerbations of asthma, pulmonary exacerbations, atherosclerosis
- Clear risk of development of lung cancer and many other cancers as well as heart disease and COPH
- Nicotine dependence—as little as 100 cigarettes
- 31% of adolescent cigarette smokers vaped previously



Marijuana

- Current use of 12th graders 23%
- Prevalence of vaping marijuana at 14% in 2019
- Combustibles of tar and hydrocarbons
- Youth are using THC in vaping devices more and more

Canabis Lung Manifestations

- Symptoms—cough, sputum productions, wheezing, dyspnea
- Acutely actually increased FEV1 and decreased EIB in asthma patients
- Chronic use associated with obstructive lung disease with decreased FEV1, decreased MMEF, decreased airway conductance and diffusing capacity
- Associated with lung cancer
- Much higher likelihood of EVALI if used via vaping vs nicotine products alone

Outpatient Management: Cannabis Use Disorder

- People with cannabis use disorder should receive evidence-based interventions, such as
 - Cognitive-behavioral therapy
 - Contingency management
 - Motivational enhancement therapy
 - Multidimensional family therapy
 - Addiction medicine services consultation
 - <u>www.findtreatment.gov</u> or

1-800-662-HELP (4357).



Our children at risk

- Previous experimentation
- Previous vaping
- Smoking by parents and peers
- Attitudes and beliefs about the social implications and health consequences of smoking
- Depression
- Poor school performance
- Adverse experiences
- Substance use disorder

Our Children at Risk

- Children with underlying lung disease at increased risk
- Children and adolescents believe vaping to be "safer"
- Approximately 30% of children and adolescents who are actively vaping have asthma—may be more prone to EVALI
- Approximately 5-10% of adolescents with cystic fibrosis smoke cigarettes or vape

The 6 A's

- Anticipate the risk of initiating
- Ask about smoking/vaping/exposure
- Advise risks and cessation
- Assess readiness to quit
- Assist those ready to quit—develop a plan
- Address nicotine withdrawl or other barriers

CDC Public Health Recommendations

CDC recommends that people should NOT

- Use e-cigarette, or vaping, products that contain THC
- Buy any type of e-cigarette, or vaping, products, particularly those containing THC, from informal sources (such as family, friends, or in-person or online dealers)
- Modify or add any substances to e-cigarette, or vaping, products that are not recommended by the manufacturer

CDC Public Health Recommendations



Since the specific cause or causes of lung injury are not yet known, the only way to assure that people are not at risk while the investigation continues is to consider refraining from use of <u>all</u> e-cigarette, or vaping, products

CDC Public Health Recommendations

- E-cigarette, or vaping, products should never be used by used by youth, young adults, or women who are pregnant
- People who do not currently use tobacco products should not start using e-cigarette, or vaping, products
- Adults using e-cigarettes to quit smoking should not go back to smoking; they should weigh all risks and benefits and consider utilizing <u>FDA-</u> <u>approved nicotine replacement therapies</u>*
- If people continue to use e-cigarette, or vaping, products, they should:
 - Carefully monitor themselves for symptoms
 - See a health care provider immediately if symptoms develop

References

- cdc.gov
- COCA presentations (many of the slides)
- State health offices