# Quaternary Ammonium–Based Disinfectants: Advantages, Disadvantages and Safety Concerns

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# Background

- **Quaternary ammonium compound (QACs), first emerged in 1935 with the introduction of benzalkonium chloride (BAC), a frequently used quaternary ammonium compound**
- **In 1947, the first QAC-based disinfectant was marketed in U.S.**
- **QACs have been widely used in the U.S. for decades**
  - **Over 1 million pounds/yr manufactured or imported**
- **QACs are used in multiple industries and types of products**
  - **Including disinfectants used in homes and healthcare facilities, mouthwashes, nasal rinses, shampoos & hair conditioners, ophthalmic medications, fabric softeners, durable consumer goods**

Hora PI et al. Environ Sci Technol Lett 2020;7:622-31
Arnold WA et al. . Environ Sci Technol 2023;57:7645-7665

# Background

- **For decades, QAC-based skin antiseptics (e.g. Zephiran) were commonly used in healthcare settings**
  - **Used less frequently during the last 20 years due to their propensity to become contaminated**

- **For years, healthcare personnel have been recognized as an occupational group that is frequently exposed to QAC disinfectants and their potential adverse effects**
  - **Especially housekeepers and nurses**

Bello A et al. Environ Health 2009;8:11
Saito R et al. Am J Ind Med 2015;58:101
Gonzalez M Clin Experiment Allergy 2014;44:393

# Routes of Exposure to QAC Disinfectants

- **Dermal**
  - Hands may become contaminated with QACs during the process of applying disinfectants, although dermal absorption is low (< 10%)
  - Touching surfaces previously disinfected with a QAC disinfectant
- **Oral**
  - Accidental or intentional ingestion of QACs has occurred rarely
  - Surface-to-hands-to-mouth transfer may occur; not well documented
- **Inhalation**
  - QACs are not volatile compounds, and inhalation of QAC disinfectants when cleaning surfaces with a QAC wipe is unlikely
  - Spraying QAC disinfectants creates aerosols than can be inhaled
  - Dried QACs on surfaces can be found in dust, which can be inhaled

Dewey HM. ACS Chem Health Saf 2022;29:27

# Significant Increase in Usage of QAC disinfectants During the COVID-19 Pandemic

- **274/594 (46%) of disinfectants effective against SARS-CoV-2 listed on the EPA's List N contained QACs**

- **In 1 month in 2020, one company produced an amount of QAC disinfectants that was equal to its entire 2019 production**

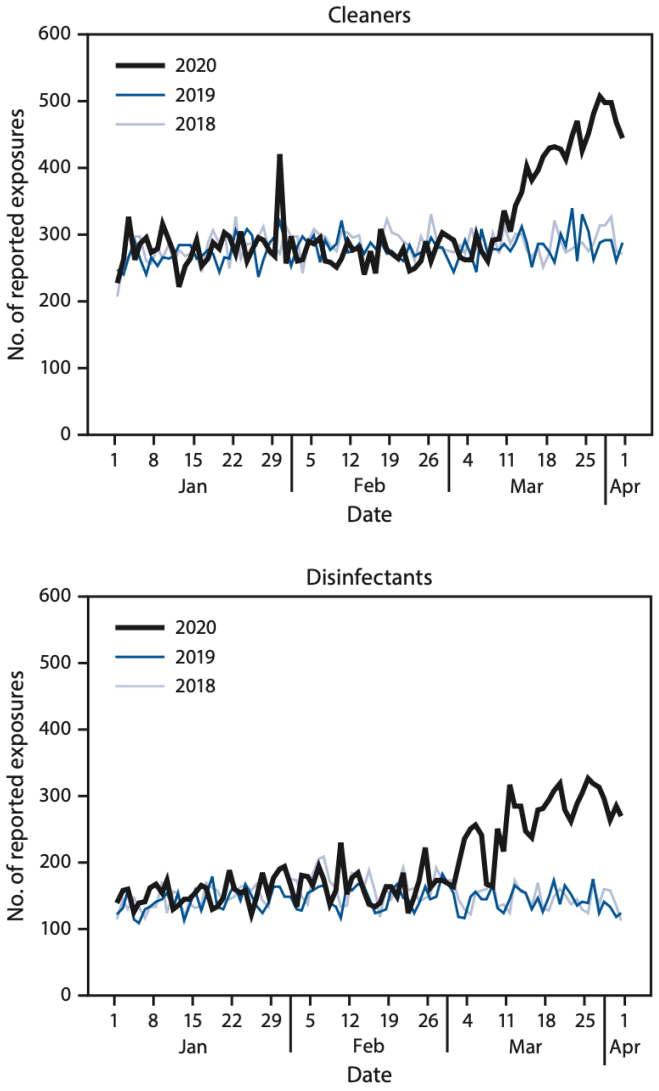
- **One study estimated that a 62% increase in the concentration of QACs in residential dust samples occurred during the pandemic**

- **Amount of QACs in raw wastewater increased by 331% in a study performed in Athens, Greece**

Mohapatra S et a. J Haz Mat 2023;445:130393
Zheng G. Environ Sci Technol Lett 2020;7:760-765
Alygizakis N etal. Sci Total Environ 2021;799:149230

# Increased Exposures to Cleaning & Disinfectant Chemicals During the Early COVID-19 Pandemic

- **National Poison Data System and CDC compared number of reported exposures to cleaners and disinfectants**
  - **January – March: 2018, 2019, and 2020**
- **Reported exposures to cleaners & disinfectants in Jan – Mar 2020 increased**
  - **20.4% increase from 2019**
  - **16.4% increased from 2018**
- **Bleaches accounted for largest (62.1%) increase in reported exposures to cleaners**
- **Nonalcohol disinfectants had largest (36.7%) increase in disinfectant exposures**
- **108.8% increase in inhalation exposures to disinfectants**



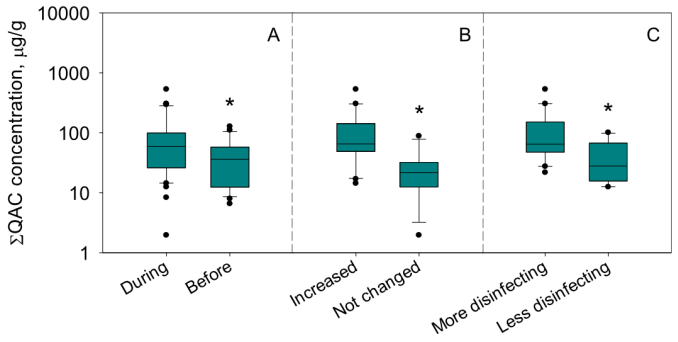

Chang A et al. MMWR 2020;69:496

# Increased Indoor Exposure to QAC Disinfectants During the COVID-19 Pandemic

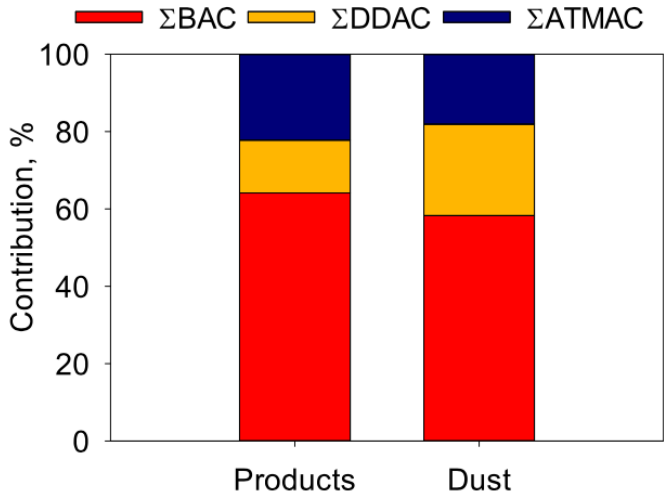
- **QAC levels in household dust were measured**
  - Before and during the COVID-19 pandemic
  - Dust samples were examined for 19 QACs
  - Data on household use of disinfectants were collected

- **Results**
  - QACs were detected in > 90% of samples collected during the pandemic, with dust QAC concentrations ranging from 1.95 – 531 ug/g (median = 58.9)
  - Median QAC levels were significantly higher during the pandemic than before (58.9 vs 36.3 ug/g)
  - Higher QAC levels were found in homes that disinfected more frequently
  - QAC profiles in products used and in dust samples were similar, suggesting that disinfectants could be a substantial source of QACs found in household dust

∑QAC concentrations in dust from homes, during and before COVID-19 pandemic




Average contributions of 3 frequently used QACs to ∑QAC concentrations in products and household dust




Zheng G et al. Environ Sci Technol Lett 2020;7:760

# Rationale for QAC Review

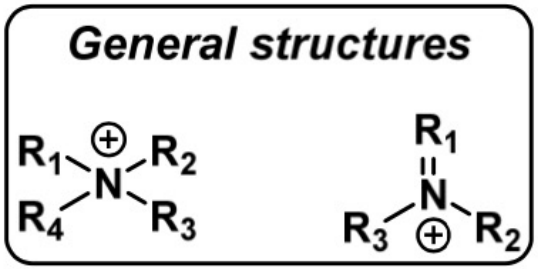
- **Healthcare personnel have been exposed to QACs for many years, and exposures increased dramatically among healthcare personnel and among individuals in the community during the COVID-19 pandemic**

- **As a result, there is increasing concern regarding the safety of frequent use of QACs**

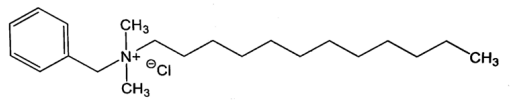
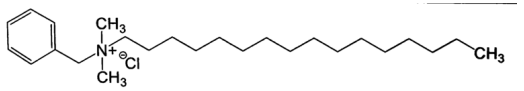
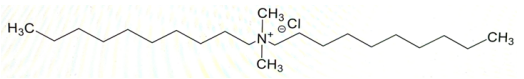
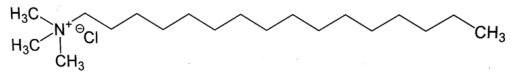
- **Purpose of my talk is to review data regarding the safety and potential toxicity of QACs with a healthcare focus**

# Quaternary Ammonium Structures

- **Basic structure of QACs:**
  - Positively-charged nitrogen (head)
  - 4 bonds to alkyl or aryl chains (tails) with varying number of carbon atoms, ranging from 10-18 (C10-C18)



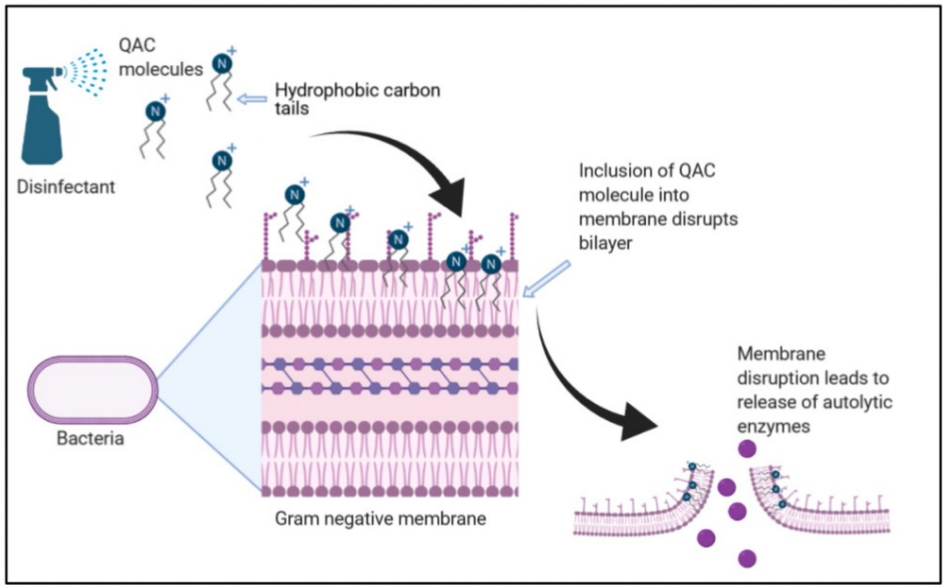

  - The attached negatively-charged moiety is usually a chloride or bromide anion

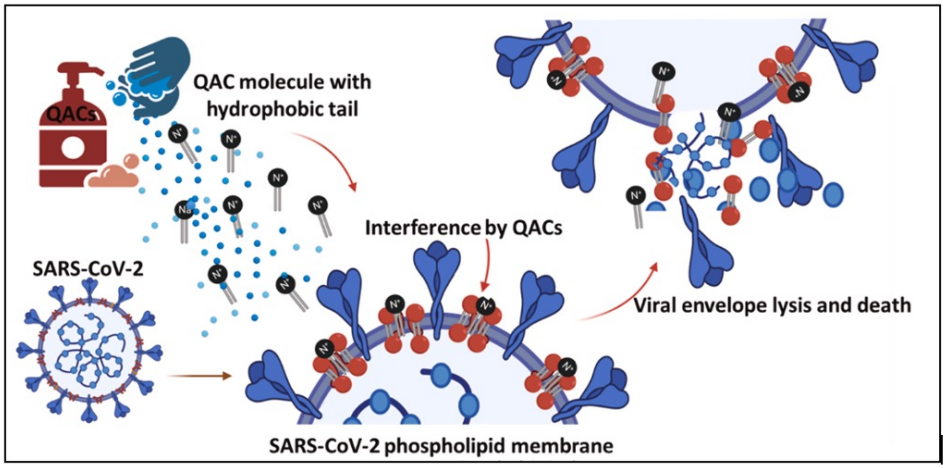
| QAC Compound | Chemical Structure |
|---|---|
| Benzyl dimethyl dodecyl ammonium chloride (BAC-C12 or ADBAC-C12) |  |
| Benzyl dimethyl dodecyl ammonium chloride (BAC-C18 or ADBAC-C18) |  |
| Didecyl dimethyl ammonium chloride (DDAC) |  |
| Hexadecyl trimethyl ammonium chloride (ATMAC – C16) |  |

Adapted from Dewey HM et al. ACS Chem Health Saf 2022;29:27-38

Vereshchagin AN et al. Int J Molec Sci 2021;22:6793

# Mechanisms of Antimicrobial Action of QACs




Jones IA et al. Molecules 2021;26:2276 Mohapatra S et al. J Haz Materials 2023;445:130393

# Advantages of QACs

- **Possess a broad range of antimicrobial activity**
  - **Bactericidal, fungicidal, virucidal against enveloped viruses**
    - **Example viruses: Herpes simplex, HIV, influenza, coronaviruses (SARS-CoV-2)**
  - **Good cleaning agents**
  - **EPA registered**
  - **Good materials compatibility**
    - **Compatible with many types of surfaces**
  - **Persistent antimicrobial activity when left undisturbed**
  - **Inexpensive in dilutable form**

Rutala WA et al. Am J Infect Control 2023;51(11S):A3-A12

# Advantages of QACs

- **QACs can be produced in many different chemical configurations, with varying features**
  - **Many disinfectants contain a mixture of several QACs**
    - **Combination of BACs is very common**
    - **Combinations of BAC + DDAC**
- **Many types of QACs are not expensive to manufacture**
- **Been widely available for decades, and marketed by numerous companies**
  - **Large number of disinfectants available helps keep costs down**
- **Generally considered to be safe**
  - **Based mainly on animal studies performed years ago**

# Additional Features Favoring Use of QAC Disinfectants

- **Widely available in different formats**
  - Concentrated solutions that are diluted prior to use and placed in buckets containing wipes

  - Ready-to-Use solutions
    - Trigger sprays, foams
    - Can be used with a variety of dry wipes

  - Pre-impregnated wipes available in cannisters


- **As a result, QAC disinfectants are among the products most commonly used for disinfection of high-touch surfaces and floors in non-contact isolation rooms**

Leas BF et al. AHRQ Pub No. 15-EHC020-EF  Han Z et al. Am J Infect Control 2021;49:34

# Disadvantages of QAC Disinfectants and Antiseptics

- **Poor antimicrobial activity against some pathogens**
- **Binding to certain types of wipes**
- **Safety-related issues**
- **Ability of some healthcare pathogens to become tolerant or resistant QACs**
- **Propensity to become contaminated with Gram-negative bacteria**
- **Possible role of widespread QAC to promote tolerance, or less often, resistance to antibiotics**

# Poor Antimicrobial Activity Against Some Pathogens

- **Limitations of QAC disinfectant antimicrobial activity**
  - Not sporicidal (e.g., no useful activity vs *C. difficile*)
  - Generally not mycobactericidal
  - Poor activity vs non-enveloped viruses (norovirus, adenovirus)
  - Relatively poor activity vs *Candida* species, including *C. auris*
  - Affected by organic matter

Rutala WA et al. Am J Infect Control 2023;51(11S):A3-A12
Cadnum JL et al. Infect Control Hosp Epidemiol 2017;38:1240

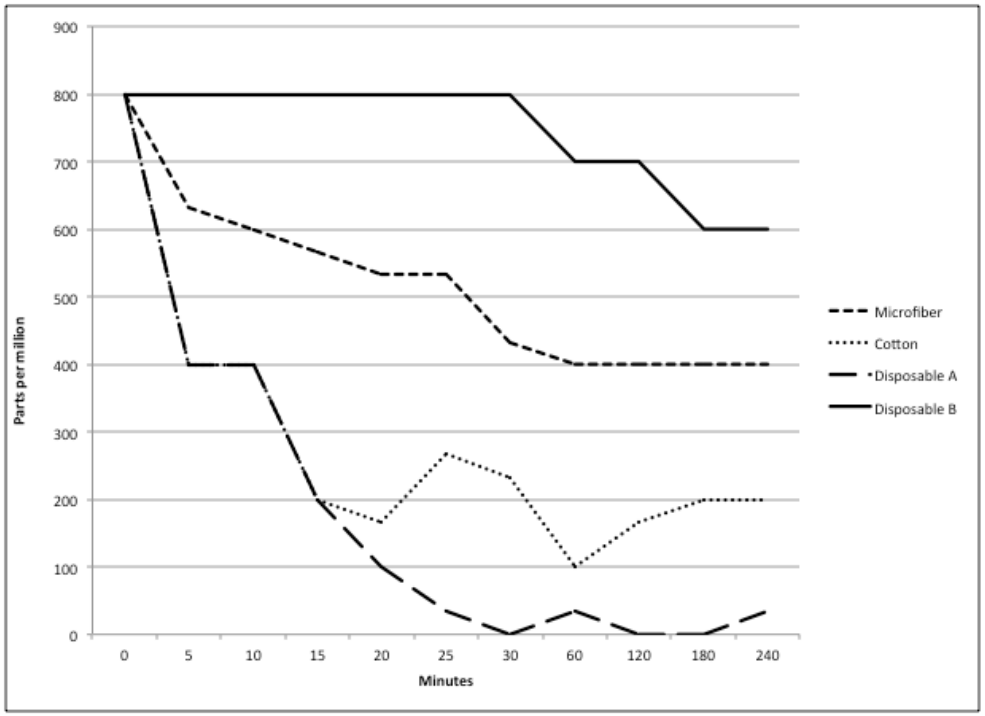
# QAC Binding to Certain Types of Wipes

- **Prolonged soaking of cotton towels, cellulose-based wipes and some microfiber wipes in dilutable QACs can result in binding of the QAC to wipe material**

- **Reduces QAC concentration**
  - **In the disinfectant bucket**
  - **Released by wipe onto surfaces**
  - **Quat binding may occur after relatively short soak times**

- **Periodic measuring the concentration of dilutable QAC disinfectants used in buckets is recommended**

Quaternary ammonium concentrations in fluid expressed from microfiber cloths, cotton towels, and 2 types of disposable wipes




**Boyce JM et al. ICHE 2016;37:340**

*** Engelbrecht K et al. Am J Infect Control 2013:41:908**
**MacDougall KD et al. Infect Control Today 2006;10:62**

# QAC Safety-Related Issues

- **Safety of QACs has been addressed in multiple studies**

- **10 well-conducted studies performed in rats and rabbits from 1998-2008 did not reveal any developmental or reproductive toxicity (DART) adverse endpoints**
  - **These studies are often cited as evidence of the safety of QACs**
  - **Only BAC and DDAC were studied as representative QACs**
  - **None of the studies exposed animals to BAC + DDAC, and combination often used in hospital disinfectants**

- **More recent *in vitro* and *in vivo* studies in animals and humans have been conducted**
  - **Some studies have raised safety and toxicity concerns**

# *In Vitro* studies in Animal Cell Lines

| QACs | Animal Cell Line | Effects |
|---|---|---|
| Alkyl trimethyl ammonium chloride (TAB C10) | Madin-Darby canine kidney cells | Mitochondrial dysfunction |
| BAC C10-C16 | Mouse neuroblastoma cells | Significant inhibition of DHCR7- final step in cholesterol synthesis.<br>Changes in glycerides, sphingomyelins |
| BAC C12 & C16 | Mice neurospheres (derived from mouse embryonic neural progenitor cells) | Size & growth of neurospheres affected;<br>BAC C12 inhibited cholesterol synthesis |

Inacio AS et al. Antimicrob Agents Chemother 2021;113:2631
Herron J et al. Toxicol Sci 2016;151:261
Herron JM et al. Chem Res Toxicol 2021;34:1265

# *In Vitro* Studies in Human Cell Lines

| QACs | Human Cell Line | Effect |
|---|---|---|
| BAC | Human neuroblastoma cells | Inhibit DHCR7 synthesis, affecting cholesterol synthesis |
| | Human hepatic microsomes | Metabolism of BAC by P450 enzymes, with effect on cholesterol synthesis |
| | Human osteosarcoma cytoplasmic hybrid cells | Inhibit mitochondrial function and estrogen metabolism |
| | Human corneal epithelial cells | Disrupt mitochondrial function at concentration significantly lower than BAC level in some eye drop medications |
| BAC C12 C14 C16 | Human A549 alveolar cells<br><br>Pulmonary surfactant monolayer | Cytotoxicity via caspase-3-dependent apoptotic pathway<br>Altered alveolar surfactant activity |
| DDAC | Human bronchial epithelial cells | Significant cell membrane damage; reductions in mitochondrial volume, calcium content, and cell viability |


Herron J et al. Toxicol Sci 2016;151:261
Sequin RP et al. Chem Res Toxicol;32:2466
Datta S et al. Environ Health Perspect 2017;125:087015
Datta S et al. Invest Ophthalmol Vis Sci 2017;58:2406
Kanno S et al. Chemico-Biologic Interact 2020;317:108962
Park EJ et al. Toxicol Appl Pharmacol 2020;404:115182

# *In Vivo* Animal Studies

- **2 academic research labs reported reproductive problems in mice following introduction of a BAC + DDAC disinfectant used for disinfection of animal facilities**
  - **Mouse reproductive activity increased when disinfectant was stopped**

- **Additional studies by one lab reported reproductive abnormalities in both male and female mice exposed orally to large doses of the combination of BAC + DDAC**

- **Mice exposed orally to BAC + DDAC produced embryos with open neural tube defects at day 10, which were considered abnormal**
  - **Other experts have disagreed, noting that such findings are not abnormal in early embryos**

Melin VE et al. Reprod Toxicol 2014;50:163
Melin VE et al. Reprod Toxicol 2016;59:159
Hrubec TC et al. Birth Defects Res 2017;109:1166
DeSesso JM et al. Birth Defects Res 2021;113:1484

# *In Vivo* Animal Studies

| QAC | Animals Tested | Effects |
|---|---|---|
| BAC C12, C16 | Pregnant female mice | BACs crossed blood-placental and embryonic blood-brain barriers, with alteration of sterol & lipid metabolism in neonatal brain tissue |
| DDAC | Mice | Dermal irritation; increased B- and T-cells and dendritic cells in local lymph node drainage, suggesting possible dermal sensitivity |
| BAC | Mice | Concentration-dependent decreases in tidal volume, increased respiratory rates when exposed to BAC aerosols |
| | Mice | Large oral doses of BAC caused sneezing, cough, breathing difficulty in some mice that were assumed to have inhaled some BAC. Symptomatic mice had significantly higher BAC blood levels than mice which did not aspirate. |
| BAC | Rats | Exposure to BAC aerosols caused pulmonary cell damage & inflammation; changes in bronchial alveolar lavage fluids |

Herron JM et al. Toxicol Sci 2019;171:32
Anderson SE et al. J Immunotoxicol 2016;13:557
Xue Y et al. Toxicol Lett 2004;148:113
Swiercz R et al. Int J Occup Med Environ Health 2008;21:157
Kwon D et al. Toxicol Appl Pharmacol 2019;378:114609

# Evidence of QAC Adverse Effects in Humans

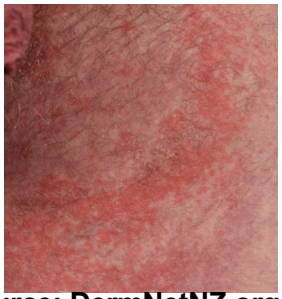
- **BAC and DDAC are known causes of acute eye & skin irritation**
  - Classified as Category I (highly toxic, corrosive) by EPA
    - Based on studies conducted in rabbits
  - Eye protection is recommended when handling concentrated solutions of QAC disinfectants

- **Eye drops that contain BAC as a preservative can cause inflammation of the ocular surface & anterior segment**
  - May be prudent to avoid BAC as a preservative in topical glaucoma meds, especially in patients with ocular surface disease

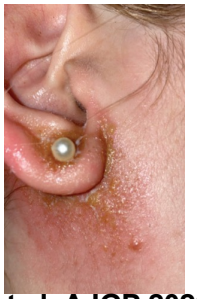

EPA ADBAC Final Work Plan 2017
EPA DDAC Final Work Plan 2018
Goldstein MH et al. Eye (Lond) 2022;36:361
Steven DW et al. Br J Ophthalmol 2018;102:1497
Kestelyn PA et al. Int Ophthalmol 2019;39:105
Stevens AM et al. Acta Ophthalmol 2012;90:e221
D'Andrea L et al. Br J Pharmacol 2022;88:3947

# Dermatitis Due to QACs

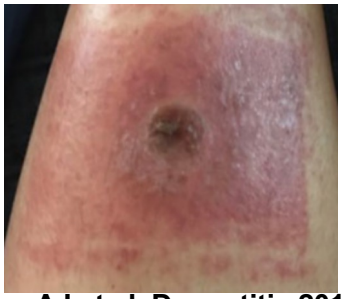
- **QACs are an occasional cause of**
  - Irritant contact dermatitis (ICD)
  - Allergic contact dermatitis (ACD) – less common



Source: DermNetNZ.org



Sun C et al. AJGP 2020;49:670



Zhang AJ et al. Dermatitis 2018;79:387

- **Several studies found that sensitization (allergy) to QACs has increased recently**

- **In recent trial of a handwash product containing 0.13% BAC,**
  - 21.4% of volunteers experienced adverse effects during the trial
  - 1 reaction was severe; frequency of erythema not reported
  - Systemic absorption was below the FDA level of concern (0.5 ng/ml)

DeLeo PC et al. Regul Toxicol Pharmacol 2021;124:104978

# Asthma: Possibly Due to Exposure to Disinfectants

- **Meta-analysis of 16 epidemiologic studies of professional cleaners (many were nurses) found significant association between occupational exposure to disinfectants and asthma**

- **Recent population-based study revealed that chronic occupational exposure to cleaning/disinfection products**
  - **Associated with current adult-onset asthma**
  - **Poorly-controlled asthma**

- **Cormier et al. reported that professional cleaners, including HCP, who were exposed to disinfectants (including QACs)**
  - **Had increased risk of asthma**
  - **HCP accounted for 16% of work-related asthma in the United States**

De Matteis S et al. Clin Ches Med 2020;41:641
Sit G et al. J Allergy Clin Immunol Pract 2022;10:3220
Cormier M et al. Int J Tuberc Lung Dis 2020;24:101

# Exposure to Disinfectants and Asthma

- **However, other studies do not provide convincing evidence that QACs cause asthma**
  - Many cleaning/disinfection products contain QACs plus other potential irritants, which may have been the cause of symptoms
  - Personnel did not always know if the products they were using contained QACs
  - Degree of exposures not always described in sufficient detail
- **3 studies published from 2012-2014 found that specific exposure to QACs was associated with asthma**

Dumas O et al. Occup Environ Med 2012:69:883
Paris C et al. Occup Environ Med 2012;69:391
Gonzalez MM et al. Clin Exp Allergy 2014;44:393

# Exposure to Disinfectants and Asthma

- **Other studies have failed to find a significant association between exposure to QAC disinfectants and asthma**
  - 10-year hospital study found that asthma related to low-level disinfectants was exceedingly rare
  - A study of HCP found that poor asthma control as associated with several types of disinfectants, but not exposure to QACs
  - A large study of nurses in the US failed to find a significant association between disinfectants (including QACs) and new-onset asthma
  - 2021 study revealed that bleach & glutaraldehyde increased the risk of asthma, but information was not adequate to implicate QACs
  - 2 other recent reviews concluded that there is insufficient evidence to link QACs with occupational asthma

Weber DJ et al. Am J Infect Control 2016;44:e85
Dumas O et al. Eur Respir J 2017;50:1700237
Dumas O et al. Am J Ind Med 2020;63:44
Romero Starke K et al. Int J Environ Res Public Health 2021;18:5159
Clausen PA et al. Int J Hyg Environ Health 2020;229:113592
Dumas O et al. JAMA Netw Open 2019;2:e1913563

# Respiratory Irritation Caused by QACs

- **Several inhalational challenge studies where HCP with a history of work-related asthma were challenged by inhaling BAC solutions suggest that BAC or other QACs can cause occupational asthma**

- **BAC can induce bronchospasm in patients with a history of asthma**

- **Use of BAC preservative in albuterol solutions used for continuous nebulization therapy in pediatric patients is of concern**
  - **2 retrospective studies found that patients receiving nebulization therapy with albuterol-containing BAC required more prolonged therapy than patients receiving BAC-free albuterol therapy, perhaps due to BAC-related irritation**


Bernstein JA et al. J Allergy Clin Immunol 1994;94:257 Burge PS et al. Thorax 1994;49:842
Purohit A et al. Int Arch Occup Environ Health 2000;73:423
Vandenplas O et al. BMJ Open 2013;3:e003568
Asmus MJ et al. J Allergy Clin Immunol 2001;107:68
Zhang YG et al. Am Rev Resp Dis 1990;141:1405
Prabhakaran S et al. Pharmacolther 2017:37:607
Pertzborn MC et al. Pediatrics 2020;145:e20190107

# Role of QACs in Causing or Exacerbating Asthma

- **Role of QACs in causing or exacerbating asthma is still debated, based on conflicting data and expert opinion**
- **Additional clinical studies of the mechanisms by which QACs may cause irritant-induced asthma are needed**
- **Epidemiologic studies should focus on individuals with**
  - **Frequent occupational exposure**
  - **Especially those exposed to QAC disinfectant sprays**

# Human Adverse Effects Reported to EPA, Sep 2006 – Mar 2016

- **2,176 incidents related to BAC (ADBAC)**
  - Types of exposure
    - 37.4% Handling concentrated liquid products
    - 26.7% RTU spray or trigger spray products
    - 10.8% RTU wipes
  - Severity
    - 94% moderate
    - 3.9% major
    - 0.3% fatal

- **781 incidents related to DDAC**
  - Types of exposure
    - 73.9% Handling concentration solutions
    - 7.4% Handling RTU solutions
    - 6.5% RTU trigger spray products
  - Severity
    - 93% moderate
    - 4.5% major
    - 0.6% fatal

EPA ADBAC Final Work Plan 2017
EPA DDAC Final Work Plan 2018

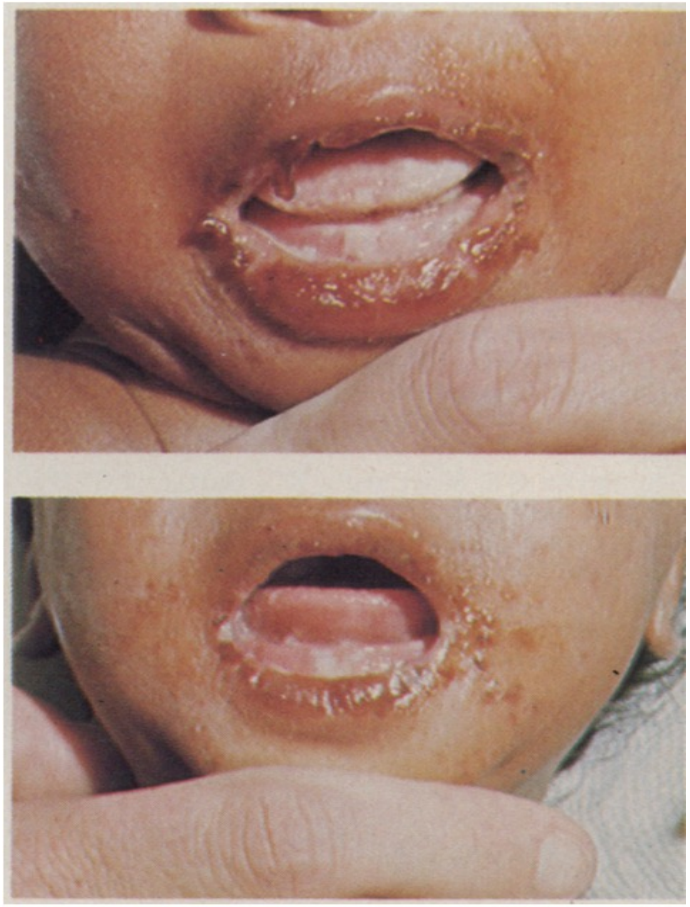
# Additional Cases of Severe Reactions Due to QAC Ingestion

- **At least 69 additional cases have been published over a period of many years**
  - **18 cases were fatal**
  - **Most involved accidental or intentional ingestion of products containing high QAC concentrations (e.g. 10% [100,000 ppm])**
    - **Most commercial disinfectants contain 90 – 16,000 ppm BAC or DDAC**

- **Reactions were due to known direct irritant and corrosive effects of QACs**

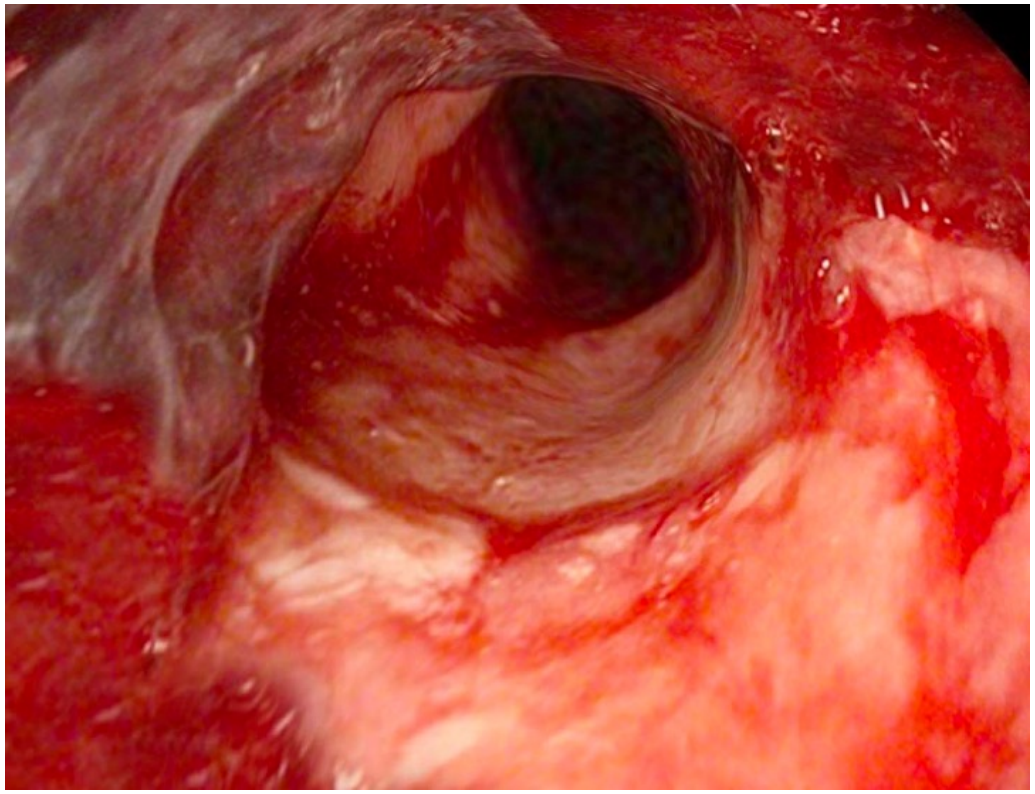
Xue YH et al. Legal Med 2002;4:232
Mishima-Kimura S et al. Legal Med 2018;32:48

# Examples of Severe Reactions to Oral Ingestion



**Circumoral scaly erythema around lips & necrotic lesions on tongue of twin infants**

**Wilson JW et al.**
**Am J Dis Child 1975;129:1209**



**Upper GI endoscopy view of esophagus, consistent with severe esophagitis**

**Kumar A et al. Int J Med Students 2021;9:231**

# Recent Detection of QAC Levels in Human Blood

- **Until recently, experts thought that BAC and DDAC, which are poorly absorbed via oral and dermal routes, were not absorbed in sufficient quantities to reach the systemic circulation**

- **In 2021, a study involving 43 volunteers detected QAC levels in blood specimens of 81% of participants**
  - **Blood levels of QACs were associated with dose-dependent changes**
    - **Increased inflammatory cytokines (Stimulated IL-10, IL-6, TNFα)**
    - **Decreased mitochondrial function**
    - **Disruption of cholesterol homeostasis**
  - **Total QAC concentrations ranged from 10-150 nM (0.01-1.58 ng/ml), a range shown to have physiological effects in cell culture models**

- **Limitations: small sample size; lack of data on QAC use**

Hrubec TC et al. Toxicol Rep 2021;8:646

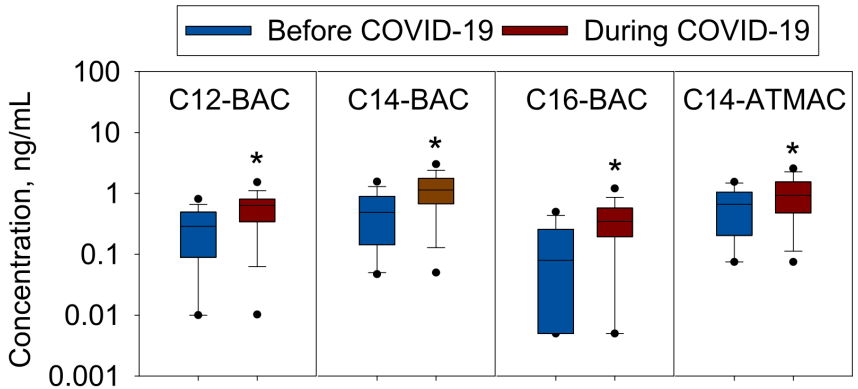
# Recent Detection of QAC Levels in Human Blood

- **Another study included**
  - 111 pre-COVID serum samples
  - 111 samples during COVID

- **Blood samples were assessed for**
  - C8-C18 BAC
  - C8-C18 DDAC
  - C8-C18 ATMAC
  - Total BAC, DDAC, and ATMAC levels

- **15/18 targeted QACs were found in blood specimens**
  - Maximum ∑QAC level = 68.6 ng/ml
  - Median ∑QAC levels during COVID were significantly higher than those collected before the pandemic

Blood Levels of C12, C14, C16 BAC and ATMAC C14 Before & During COVID-19 Pandemic




Note: Samples collected before and during the COVID-19 pandemic were not paired specimens, but demographics of the 2 groups of participants did not differ

Zheng G et al. Environ Sci Technol 2021;55:14689

# Detection of QACs in Breast Milk

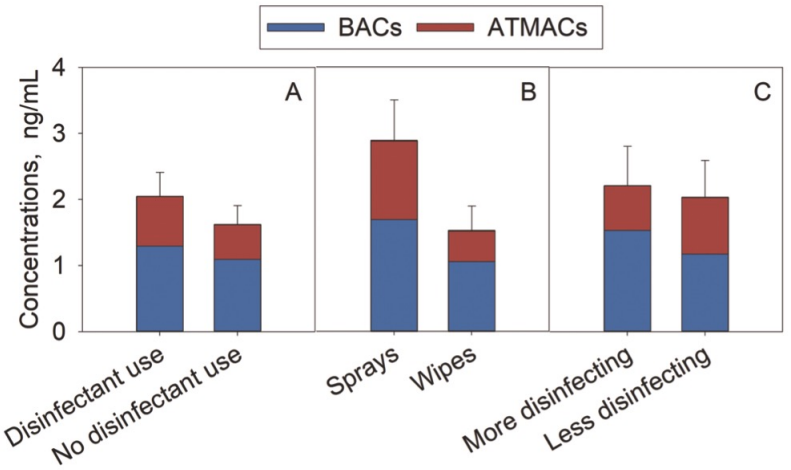
- **Breast milk from 48 mothers planning to or currently breast feeding was tested**

- **Samples were measured for 18 QACs**
  - C8-C18 BAC, C8-C18 DDAC, C8-C18 ATMAC
  - ∑BAC, ∑DDAC, ∑ATMAC and ∑QAC levels

- **Data were obtained on use of**
  - Disinfectant products (including sprays)
  - Personal care products (with, w/o ATMAC)

- **Results**
  - 13/18 QACs were detected in breast milk
  - ∑QAC levels ranged from 0.33-7.4 ng/ml, with median of 1.5 ng/ml
  - C14 BAC was the most abundant QAC
  - ∑QAC levels were highest in women who used spray disinfectants

∑BAC and ∑ATMAC concentrations in breast milk, Based on mothers' disinfection habits




**Estimated daily intake for infants < 1 month of age ranged from 230 – 750 ng/kg body wt/day**

Zheng G et al. J Expos Sci Environ Epidemiol 2022;32:682

# Limitations of Blood and Breast Milk Studies

- **Hrubec et al. and Zheng et al. did not check volunteers' cholesterol, LDL or HDL levels, or triglyceride blood levels to assess effects of metabolic disturbances identified**

- **Other chemicals (medications) have affected cholesterol metabolism without any adverse clinical effects**

- **Zheng et al. did not give details of how manually-collected breast milk was obtained; could not rule out contamination of milk from mothers' skin during collection**

- **CDC states that measurement of an environmental chemical in blood or urine does not mean, by itself, that the chemical causes disease**

CDC National Report on Human Exposure to Environmental Chemicals

# Need for Additional Studies

- **The authors of these important studies acknowledge the need to assess the importance of finding QACs in blood/breast milk by conducting further studies**
  - **Characterize the sources of QAC exposures**
  - **Confirm effects of QACs on human metabolic processes**
  - **Determine whether or not resulting metabolic alterations result in clinically-significant adverse health effects**

**Hrubec TC et al. Toxicol Rep 2021;8:646**
**Zheng G et al. Environ Sci Technol 2021;55:14689**
**Zheng G et al. J Expos Sci Environ Epidemiol 2022;32:682**

# Ability of Some Healthcare Pathogens to Become Tolerant or Resistant QACs

- **Staphylococci (including *S. aureus*), and especially some Gram-negative bacteria can develop tolerance or resistance to QACs**
  - **Tolerance: increased minimum inhibitory concentration (MIC)**
    - **Organism is usually still susceptive to QAC disinfectant/antiseptic products**
  - **Resistance: Able to survive in QAC concentrations present in products**
    - **Example: bacteria present in contaminated solution of antiseptic or disinfectant**
- **Mechanisms of tolerance/resistance include**
  - **Inate bacterial cell wall resists penetration of QACs**
  - **Production of efflux pumps**
  - **Changes in cell wall structure**
  - **Biofilm production by pathogen**

- **True QAC resistance is most common in *Pseudomonas, Burkholderia, Achromobacter, Serratia***

Maillard JY J Appl Microbiol 2022;133:3322
Partridge SR et al. Clin Microbiol Rev 2018;31:e00088-17
McCarlie S et al. Drug Resist Updat 2020;48:100672

**Table 3** Reported episodes of contaminated quaternary ammonium disinfectant or antiseptic. *Cite at line 341*

| Year | Author | Pathogen | Product Type | Type of Report |
|---|---|---|---|---|
| 1951 | Lowbury | *Pseudomonas pyocyanea* | Antiseptic | Infection outbreak |
| 1957 | Keown | *Pseudomonas aeruginosa* | Disinfectant | Infection outbreak |
| 1958 | Plotkin | *Pseudomonas* | Antiseptic | Infection outbreak |
| 1959 | Shickman | *Pseudomonas aeruginosa* | Disinfectant | Single infection |
| 1960 | Malizia | *Enterobacter aerogenes* | Antiseptic | Infection outbreak |
| 1961 | Lee | *Pseudomonas/ Achromobacter group* | Antiseptic | Infection outbreak |
| 1967 | Burdon | *Pseudomonas multivorans* | Antiseptic | No confirmed infections |
| 1969 | CDC* | *Pseudomonas kingii* | Antiseptic | Infection outbreak |
| 1970 | Hardy | *Pseudomonas EO-1* | Disinfectant | Infection outbreak |
| 1970 | Bassett | *Burkholderia cepacia* ** | Antiseptic | Infection outbreak |
| 1970 | Gilardi | *Pseudomonas EO-1* | Antiseptic | Outcome unclear |
| 1976 | Dixon | *Pseudomonas* species | Disinfectant | Infection outbreak |
| 1976 | Kaslow | *Burkholderia cepacia; Enterobacter* | Antiseptic | Pseudo-outbreak |
| 1976 | Frank | *Burkholderia cepacia* | Antiseptic | Infection outbreak |
| 1976 | Morris | *Burkholderia cepacia* | Antiseptic | Single infection |
| 1976 | Guinness | *Burkholderia cepacia* | Antiseptic | Infection outbreak |
| 1976 | Wishart | *Stenotrophomonas maltophilia* | Antiseptic | Infection outbreak |
| 1980 | Ehrenkranz | *Serratia marcescens* | Disinfectant | Infection outbreak; contaminated surfaces |
| 1981 | Fox | *Serratia marcescens* | Antiseptic | Infection outbreak (dogs and cats) |
| 1982 | Van Damme | *Serratia marcescens* | Antiseptic | Outbreak of bovine mastitis infections |
| 1984 | Sautter | *Serratia marcescens* | Antiseptic | Single infection |
| 1987 | Nakashima | *Serratia marcescens* | Antiseptic | Infection outbreak |
| 1988 | Gahrn-Hansen | *Achromobacter xylosoxidans* | Disinfectant | Infection outbreak |
| 1990 | Georgia DPH | *Mycobacterium chelonae* | Antiseptic | Infection outbreak |
| 1996 | Nagai | *Pseudomonas fluorescens* | Disinfectant | No infections |
| 1996 | Oie | *Burkholderia cepacia; Pseudomonas aeruginosa; Pseudomonas fluorescens* | Antiseptic and Disinfectant | No Infections |
| 1999 | Olson | *Pseudomonas aeruginosa* | Disinfectant | Infection outbreak |
| 2000 | Kaitwatcharachai | *Burkholderia cepacia* | Disinfectant | Infection outbreak |
| 2002 | Lehours | *Achromobacter xylosoxidans* | Disinfectant | Infection outbreak |
| 2003 | Tiwari | *Mycobacterium abscessus* | Antiseptic | Infection outbreak |
| 2003 | Gajadhar | *Pseudomonas* | Antiseptic | Survey |
| 2005 | Ebner | *Burkholderia cepacia* | Disinfectant | Pseudo-outbreak |
| 2005 | Fisher | *Pseudomonas aeruginosa* | Antiseptic | Infection outbreak |
| 2006 | Lo Cascio | *Burkholderia cenocepacia* | Disinfectant | Infection outbreak |
| 2007 | Siebor | *Pseudomonas fluorescens; Achromobacter xylosoxidans* | Disinfectant | Pseudo-outbreak |
| 2008 | Lee CS | *Burkholderia cepacia* | Antiseptic | Infection outbreak |
| 2010 | Hakuno | *Pseudomonas fluorescens;Burkholderia cepacia; Aeromonas* species | Antiseptic | No infections |
| 2014 | Kampf | *Achromobacter* species; *Serratia marcescens* | Disinfectant | Survey |
| 2015 | Kupfahl | *Achromobacter* species | Disinfectant | Survey |
| 2015 | Hugon | *Achromobacter denitificans* | Disinfectant | Infection outbreak; contaminated surfaces |
| 2016 | Tandel | *Burkholderia cepacia* | Antiseptic | Pseudo-outbreak |
| 2021 | FDA | *Burkholderia cepacia complex*<br>*Ralstonia pickettii* | Hand sanitizer | No reported infections |
| 2022 | Boyce | *Serratia marcescens; Achromobacter xylosoxidans* | Disinfectant | No infections; contaminated high-touch surfaces |

*** Centers for Disease Control and Prevention**

**** Originally classified as** *Pseudomonas cepacia (mulivorans)*

# Contaminated Disinfectants & Antiseptics

- **Causes of contamination**
  - Use of outdated products
  - Substantial over-dilution of concentrated solutions
  - Presence of organic material
  - Prolonged soaking of wipes with strong QAC-binding affinity

- **43 outbreaks of contaminated disinfectant/antiseptic resulted in:**
  - 26 outbreaks of infection
  - 3 single cases of infection
  - 4 pseudo-outbreaks
  - 3 surveys showing contamination of disinfectant buckets
  - 6 episodes of contamination without confirmed consequences
  - 1 episode with unclear outcome

- **Types of infection related to contaminated QACs**
  - Skin antiseptics (N = 24)
  - Surface disinfectants (N = 17)
  - Combined antiseptic/disinfectant (N=1)
  - Hand sanitizer (N = 1)

- **Most common pathogens**
  - *Pseudomonas* species (N = 17)
  - *Burkholderia* species (N = 13)
  - *Achromobacter* species (N = 8)
  - *Serratia marcescens* (N = 7)

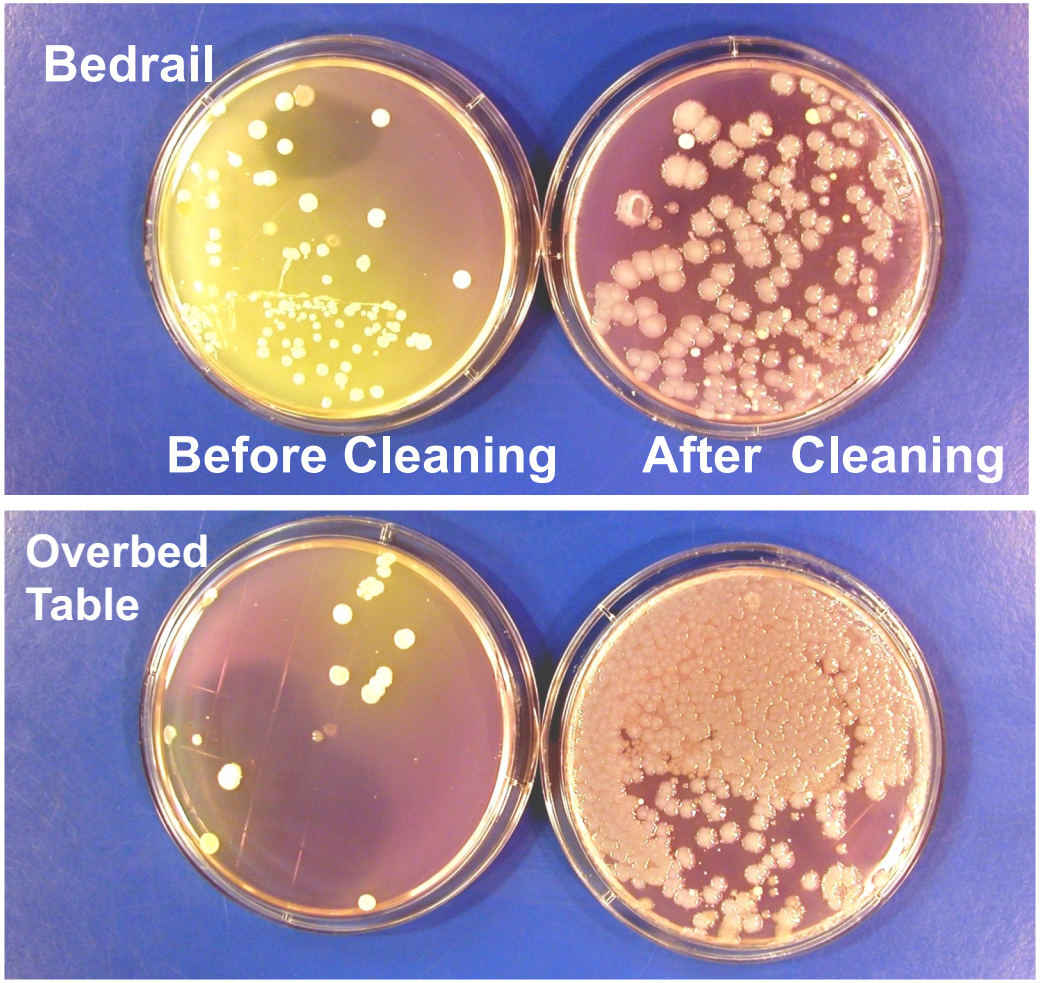
Boyce JM Antimicrob Resist Infect Control 2023;12:32

# Contaminated Disinfectants & Antiseptics

- **29 outbreaks of contaminated disinfectants or antiseptics resulted in infections**
  - Bloodstream infections (N = 15 episodes of contamination)
  - Wound infections (N = 5)
  - Skin abscesses (N = 2)
  - Septic arthritis (N = 2)
  - Meningitis (N = 2)
  - Urinary tract infection (N = 3)
  - Ear cartilage infections (N =1)
  - Respiratory tract (N = 1)
  - Intravenous catheters (N = 1)
- **More than one type of infection was reported in several episodes**
- **Contaminated surfaces resulted in healthcare personnel hand contamination in one episode**
- **Contamination of surfaces in patient rooms occurred in 3 episodes**

# Example of Contaminated In-Use Disinfectant

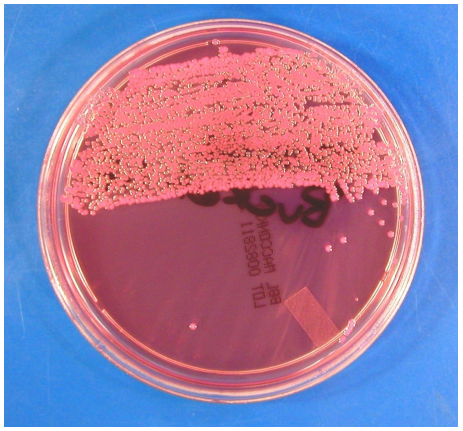
- **Cultures obtained in one patient's room <u>after</u> a housekeeper finished cleaning the room showed heavy growth of bacteria not present <u>before</u> room cleaning**



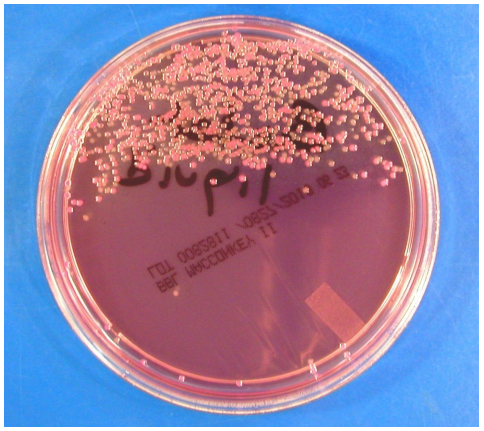

Boyce JM & Havill NH Am J Infect Control 2022;50:1296-1301

# Results

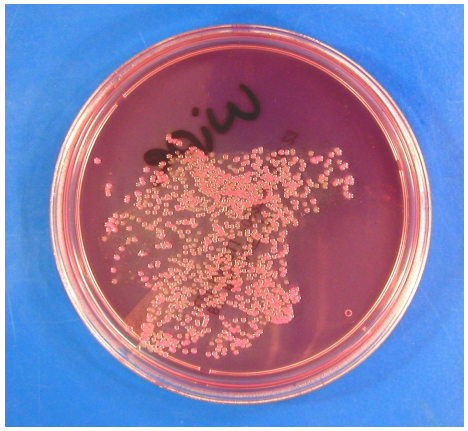
- **Heavy growth of Gram-negative bacteria was recovered on McConkey agar from the contaminated bucket, disinfectant, and wipe**



**Inside bucket lid**



**Disinfectant in bucket**



**Wipe removed from bucket**

- **All cultures of concentrated disinfectant, water for dilution, and automated dilution equipment were negative for the implicated pathogens**

- **Contaminated disinfectant contained 9.3 x $10^4$ CFU/ml of contaminants**

- **Isolates were identified as 2 strains of *S. marcescens* and a strain of *Achromobacter xylosoxidans***

# Microbiological Investigation

- **Pulsed Field Gel Electrophoresis was performed on the following isolates:**

  ***Achromobacter xylosoxidans***

  - Lane 1: from patient room
  - Lane 2: from disinfectant bucket

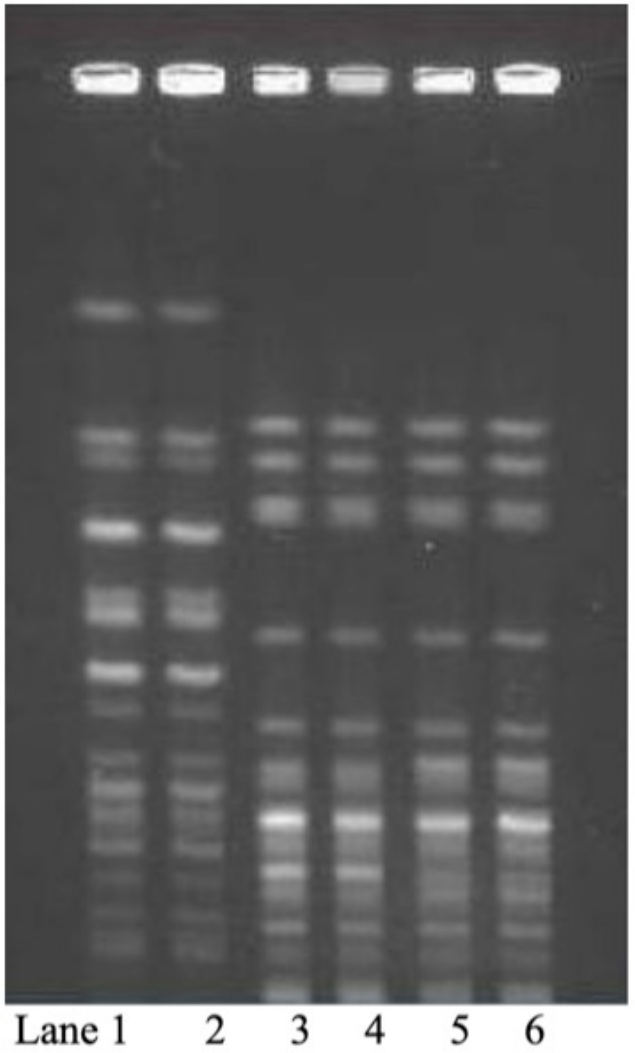
  ***Serratia marcescens* isolate #1**

  - Lane 3: from patient room
  - Lane 4: from disinfectant bucket

  ***Serratia marcescens isolate #2***

  - Lane 5: from patient room
  - Lane 6: from disinfectant bucket

- **Bacteria recovered from the patient room and from disinfectant were closely related, consistent with the disinfectant being the source of room contamination**



# Microbiological Investigation

- ***Serratia marcescens*** **strains recovered from the disinfectant contained genetic sequences identified as the following genes**
  - ***sdeAB, sdeXY, smfY*****, and *sugE*-like gene**
  - **Previously reported as encoding for quaternary ammonium resistance***

- **Other possible resistance mechanisms such as biofilm production were not studied**

- **Cause of contamination: failure to clean and dry bucket before adding new disinfectant**

Boyce JM & Havill NH Am J Infect Control 2022;50:1296-1301
* Chen J et al. J Antimicrob Chemother 2003;52:176
Shahcheraghi F et al. Biol Pharm Bull 2007;30:798
Kumar A et al. Antimicrob Agents Chemother 2005;49:1495
He GX et al. Antimicrob Agents Chemother 2011;55:3954

# Summary

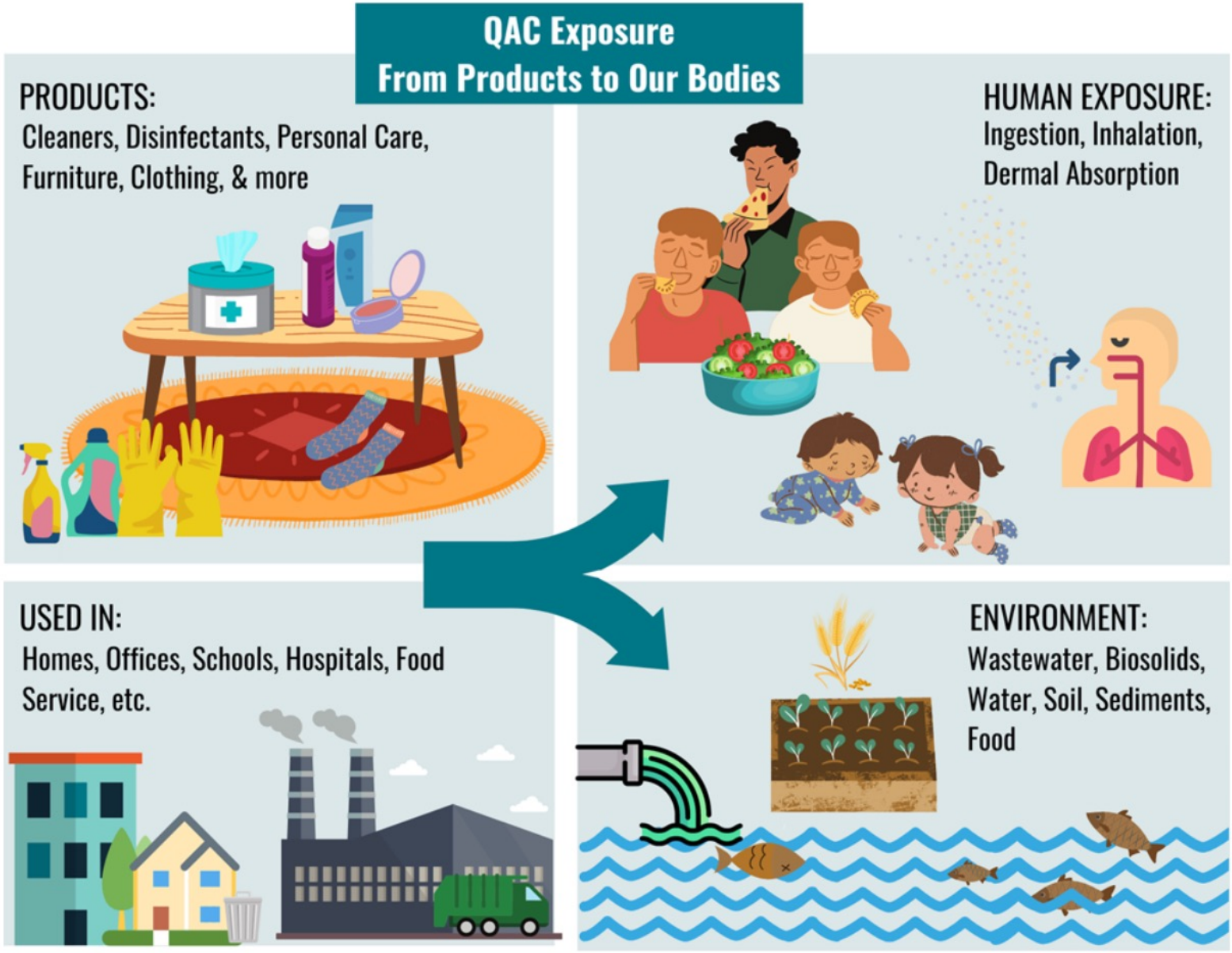
- **QAC disinfectants have a number of advantages which are responsible for their widespread use in healthcare and community settings**

- **Disadvantages include:**
  - **Limited antimicrobial activity against several important pathogens**
  - **Binding to certain wipe materials can compromise their efficacy**
  - **Safety and toxicity issues**
    - **Well-established dermal and ocular toxicity**
    - **Possible role in work-related asthma**
    - **Recently recognized presence in human blood and breast milk samples, which is currently of unknown clinical significance**
    - **Some pathogens can develop tolerance, or less commonly, true resistance to QACs**
    - **Propensity to become contaminated by Gram-negative bacteria if not used correctly**

# Recommendations

- **HCP who frequently used QAC-based disinfectants need education and periodic reminders about the importance of following manufacturers' Instructions for Use**

- **When using QAC disinfectants**
  - **Use appropriate PPE when diluting concentrated QAC solutions**
  - **Limit use of cotton towels and cellulose-based wipes when using QAC disinfectants, especially if wipes are left to soak in disinfectant bucket**
  - **Clean & dry disinfectant buckets before adding new disinfectant**
  - **Consider minimizing use of QAC disinfectant sprays; use in well-ventilated spaces**
  - **Review label claims of products to assure activity against pathogens of concern**




Arnold WA et al. Environ Sci Technol 2023;57:7645

# Examples of Efflux Pumps Conferring Resistance to QACs

**Table 2** Examples of efflux pumps conferring increased tolerance to quaternary ammonium compounds. *Cite at line 238*

| Pathogen | RND | MFS | ABC | SMR | MATE | PACE |
|---|---|---|---|---|---|---|
| E. coli | AcrAB-TolC | MdfA(Cmr), EmrB, EmrD | | EmrE, SugE | NorM, MdtK/YdhE | |
| Pseudomonas | Mex-Opr | | | QacE△1 | PmPM | |
| Serratia | SdeXY, SdeAB, SdeIJ, | SmfY | | | | |
| Burkholderia | Mex-Opr-like | | | | | AceI |
| Acinetobacter | | QacA, QacB | | QacE, QacE△1 | PmPM | AceI |
| Achromobacter | | | | | | |
| Proteus | | | | | PmPM | |
| Vibrio | | | | | PmPM | |
| Aeromonas | | | | QacE2 | | |
| Enterobacter | acrB | | | SugE | EmmdR/YeeO | |
| Klebsiella | | | | QacE | | |
| Salmonella typhimurium | AcrAB-TolC | | | | | |
| | | MFS | ABC | SMR | | |
| S. aureus | | NorA, QacA, Qac B; MepA MdeA | EfrAB | QacC,QacG,QacH, QacJ, QacE△1 | | |
| L. monocytogenes | | | | $EmrE_{Lm}$ | | |
| Enterococcus | | QacA/B | EfrAB | QacC, QacE△1 | | |

RND=resistance-nodulation-division; MFS=major facilitator superfamily; ABC=ATP-binding cassette; SMR=small multidrug resistance; PACE=proteobacterial antimicrobial compound efflux; MATE=multidrug and toxic compound extrusion

# Background

- **Monitoring disinfection practices is recommended by CDC, especially important in rooms of patients with MDROs**

- **Methods to monitor cleaning/disinfection include:**
  - **Fluorescent markers have been used by multiple hospitals**
  - **Adenosine triphosphate (ATP) bioluminescence assays are also used**
  - **Culturing surfaces to detect microbial contamination is less frequent**

- **DAZO fluorescent marker system is popular**

- **We compared DAZO system with an ATP system and aerobic colony counts in terminally cleaned patient rooms**

**CDC Options for Evaluating Environmental Cleaning 2010**
**Carling PC et a. Infect Dis Clin N Amer 2016;30:639**
**Deshpande A et al. Curr Opin Infect Dis 2017;19:32**

# Background

- **Rooms scheduled for terminal cleaning were disinfected with a quaternary ammonium (Quat) disinfectant**

- **5 high-touch surfaces (HTSs) in patient rooms are monitored**
  - **Bed rails, overbed table, TV remote, bathroom grab bar, toilet seat**

- **Sampling/marking protocol for each high-touch surface**
  - **Before terminal cleaning**
    - **DAZO fluorescent solution applied**
    - **Rodac agar plates with Dey-Engley neutralizer were used to sample surfaces**
    - **ATP reading obtained**
  - **After terminal cleaning (at least 10 min after completion)**
    - **Surface examined with black light to see if DAZO solution was removed**
    - **Rodac agar plates with Dey-Engley neutralizer were used to sample surfaces**
    - **ATP reading obtained**

**Boyce JM et al. Infect Control Hosp Epidemiol 2011;32:1187**

# Epidemiological Investigation

- **We suspected contamination of the Quat disinfectant, which has been reported on multiple occasions***
- **EVS manager was notified, and identified the housekeeper assigned to clean the patient's room that day**
- **Bucket used by the housekeeper to clean the affected room was obtained for microbiological investigation**
- **EVS cleaning/disinfection practices were reviewed**

* Weber DJ et al. Antimicrob Agents Chemother 2007;51:4217

# Epidemiological Investigation

- **Review of disinfectant preparation and use was conducted**
  - Concentrated disinfectant was mixed with water by automated system
  - Final in-use concentration was 660 ppm of Quat
  - Diluted disinfectant was delivered into plastic buckets used by housekeepers
  - Role of microfiber wipes was inserted into the bucket
  - Lid was placed on the bucket
  - Wipes were subsequently pulled through the lid, and used for wiping environmental surfaces

**Bucket used by implicated housekeeper**

# Epidemiological Investigation

**Search for clinical infections due to contaminating strains**

- **Computerized clinical microbiology laboratory records were searched for the previous 6-month period**

- **Searched for *Serratia* and *Achromobacter* clinical isolates with antimicrobial susceptibility patterns similar to the contaminating strains**

# Microbiological Investigation

## Environmental cultures

- **Sterile swabs were used to culture**
  - **In-use disinfectant from the housekeeper's bucket**
  - **Inside surface of the bucket**

- **Wipe removed from the bucket was cultured**

- **Swabs and the wipe were used to inoculate blood agar and McConkey agar plates, incubated at 37° for 24 hrs**

- **Identification and antimicrobial susceptibility of isolates recovered were performed using MicroScan system**
  - **Contaminating bacteria were identified as two strains of *Serratia marcescens* and one strain of *Achromobacter xylosoxidans***

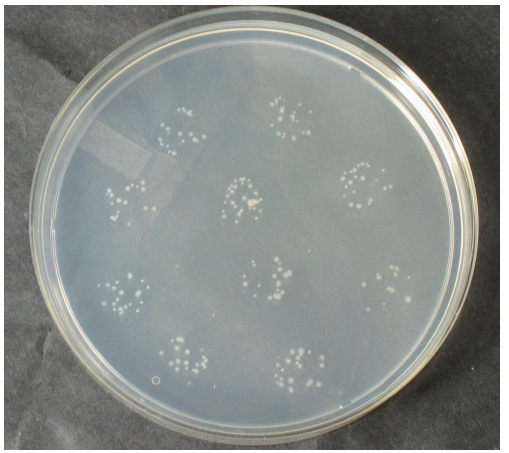
# Microbiological Investigation

## Environmental cultures

- **Cultures obtained in the automated dispensing station included:**
  - Inside surface of ends of hoses used to dispense concentrated disinfectant and for water used for dilution
  - Inoculated onto blood & McConkey agar

- **Samples of concentrated disinfectant & water were cultured by placing 1 ml of each liquid into trypticase soy broth**

- **Level of bacterial contamination of in-use disinfectant was determined using previously described methods***
  - 1:10 dilution of disinfectant was made in nutrient broth
  - Ten 200 µL aliquots were planted on nutrient agar plate
  - Incubated for 24 hrs, and colonies counted
  - Total colonies x 5 = number in 1 ml of 1:10 dilution
  - Then x 10 = number per ml of disinfectant



* Gajadhar T et al. Rev Panam Salud Publica 2003;14:193

# Microbiological Investigation

## Activity of Disinfectant Solution Against Pathogens

- **Determine if the contaminated disinfectant still had antimicrobial activity against pathogens**
  - **50 µL aliquots of contaminated disinfectant were inoculated onto:**
    - **Mueller-Hinton agar plate inoculated with 0.5 McFarland concentration of control strain of *S. marcescens* ATCC 13880 (susceptible to Quats)**
    - **Mueller-Hinton agar plate inoculated with 0.5 McFarland concentration of a suspension of *Staphylococcus aureus* 29213**
  - **Incubated at 37° for 24 hrs**
  - **Plates were examined to see if the contaminated disinfectant inhibited the growth of *Serratia* or *S. aureus* at the sites where the disinfectant was inoculated**

# Microbiological Investigation

## Biocidal Activity of Contaminated Disinfectant Against Contaminating Organisms

- **ASTM E-2197 quantitative carrier test method was used to compare the activity of the contaminated disinfectant toward**
  - **Strain of *S. marcescens* recovered from disinfectant**
  - ***S. marcescens* ATCC 13880**

## Survival of contaminating *S. marcescens* of hard surface

- **A wipe removed from the contaminated bucket was used to inoculate defined areas on a laboratory bench top; inocula were allowed to dry**
- **D/E contact plates were used to sample the surface after**
  - **15, 30,45, 60, 75, 90 and 105 minutes after inoculation**
- **Plates were incubated at 37° for 48 hrs; colonies counted**

# Microbiological Investigation

## Strain typing

- Pulsed field gel electrophoresis ( PFGE) was performed on
  - S. marcescens strains #1 and #2 from patient room and disinfectant
  - A. xylosoxidans from patient room and disinfectant
- Criteria for degree of genetic relatedness were those published by Tenover et al.*

## Mechanisms of quaternary ammonium resistance

- Whole genome sequencing was performed on 2 S. marcescens isolates at Walter Reed Army Institute for Research by Ion Torrent Personal Genome Machine, courtesy of Patrick T McGann, PhD
- Bioinformatics analysis was performed at the Sabeti Laboratory at Harvard University courtesy of Ryan Tewhey, PhD

* Tenover FC et al. J Clin Microbiol 1995;33:2233

# Microbiological Investigation

- **Retrieved 2 additional blue buckets and cultured them for possible bacterial contamination**

- **Cultured 10 White disinfectant buckets also used by EVS staff for bacterial contamination**

# Results

**Epidemiological investigation revealed**

- **An interview with the implicated housekeeper revealed**
  - **The housekeeper had used the same bucket for years**
  - **Did not clean the bucket in between re-filling with disinfectant**
  - **Only occasionally assigned to disinfect patient rooms**

- **Most of the EVS staff utilized a different type of disinfectant bucket, which were white-colored**

# Microbiological Investigation

- **Antimicrobial susceptibility testing revealed the following results:**

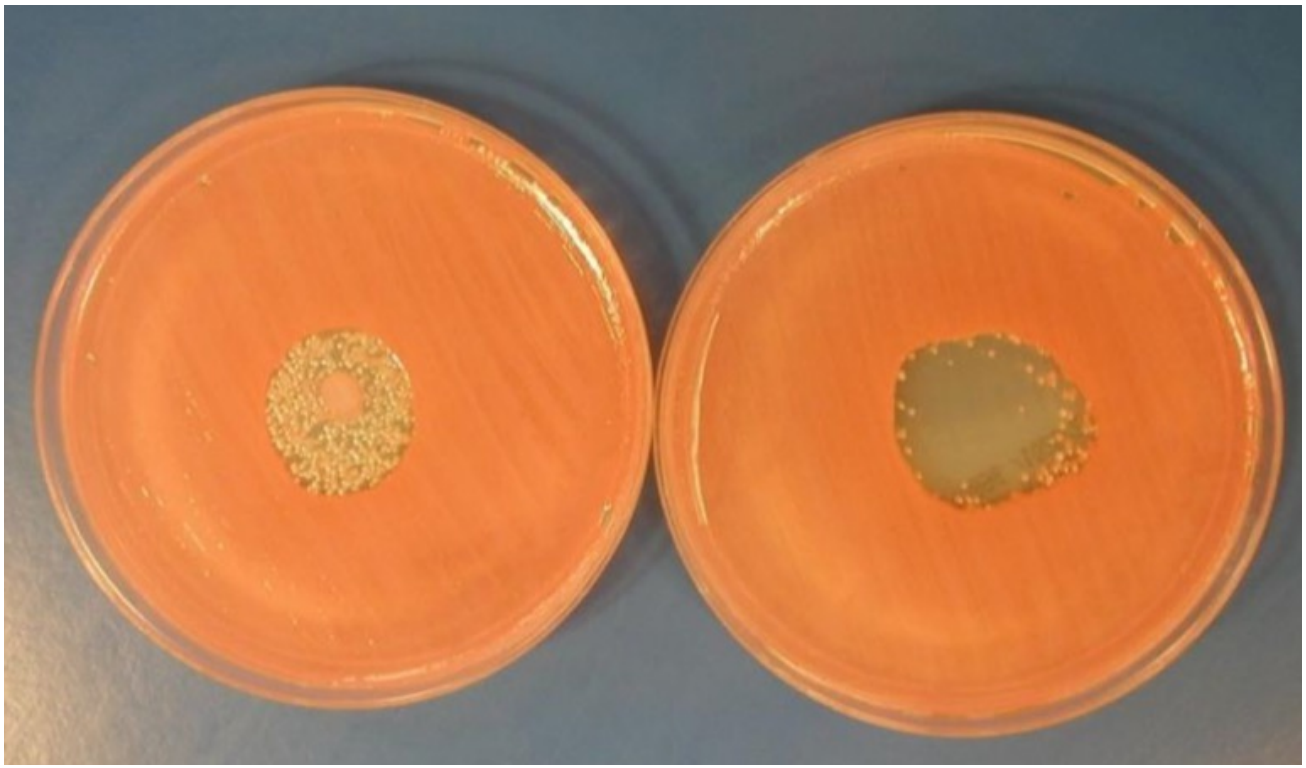
| Isolate | Antibiotics to Which Strain Was Resistant |
|---|---|
| Serratia strain #1 | Ampicillin, ampicillin-sulbactam, cefazolin, gentamicin and tobramycin, ceftriaxone, cefepime, and piperacillin-tazobactam |
| Serratia strain #2 | Ampicillin, ampicillin-sulbactam, cefazolin, gentamicin and tobramycin |
| Achromobacter | Ampicillin, cefazolin,ceftriaxone, cefepime, gentamicin, tobramycin, and piperacillin-tazobactam, ciprofloxacin |

- **Review of clinical microbiology laboratory records failed to identify any patients colonized/infected during the previous 6 months with *Serratia* or *Achromobacter* with similar antibiotic susceptibility patterns**

# Microbiological Investigation

- **Inoculation of contaminated disinfectant onto lawn of pigmented S. marcescens ATCC 13880 revealed zone of growth inhibition with contaminating pathogens growing inside zone of inhibition (left)**

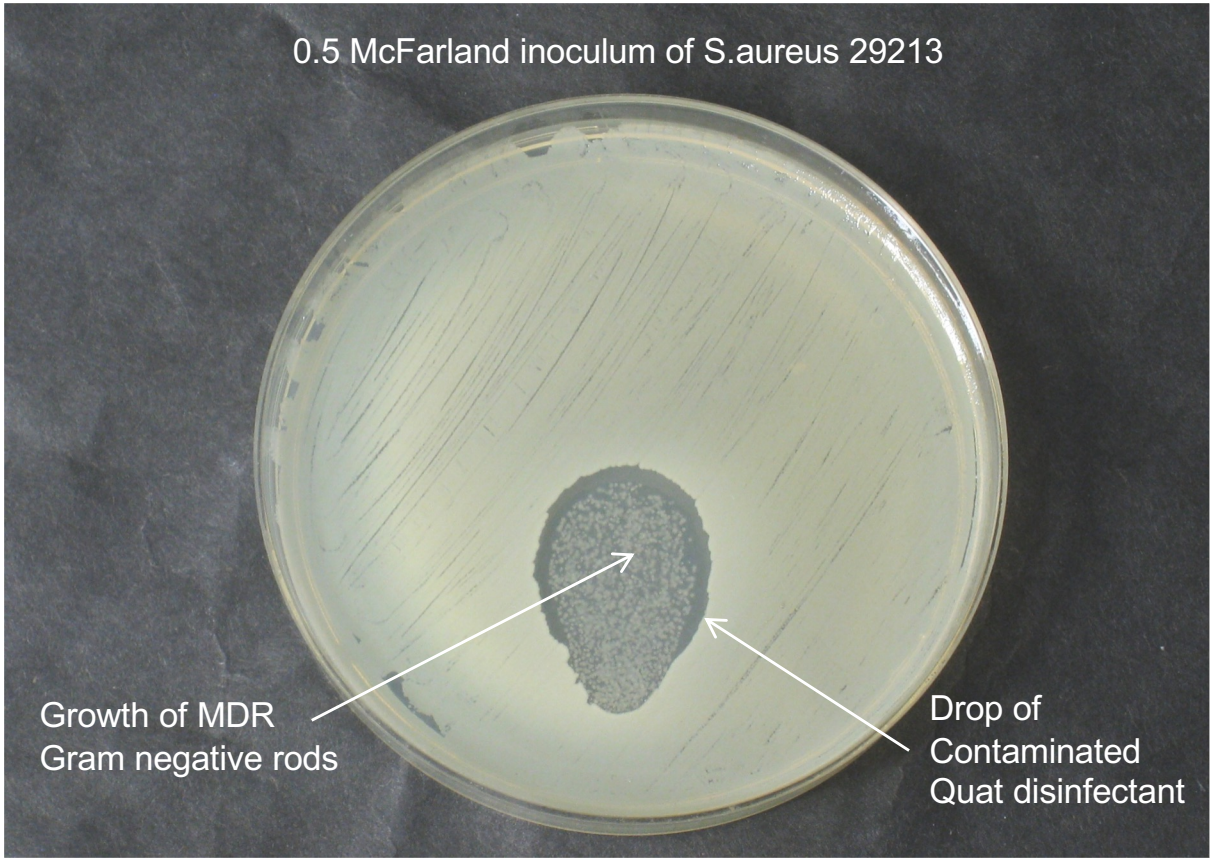
- **Uncontaminated disinfectant showed slightly larger zone of inhibition with only a small number of colonies growing inside zone (right)**



**Contaminated Quat** **Uncontaminated Quat**

# Microbiological Investigation

- **Inoculation of contaminated disinfectant onto lawn of *S. aureus* 29213 revealed zone of growth inhibition of *S. aureus* with contaminating pathogens growing inside zone of inhibition**
- **Inhibition of growth of *S. marcescens* ATCC 13880 and *S. aureus* 29213 provided evidence that contaminated disinfectant still had enough biocidal activity to inhibit standard strains of pathogens**



# Microbiological Investigation

- **Relative biocidal activity of the contaminated disinfectant against the 2 contaminating strains of *S. marcescens* and control strain *S. marcescens* ATCC 13880 using ASTM E-2197 carrier test method**
  - **$Log_{10}$ reductions of the contaminating *S. marcescens* strains were $10^2$ lower than $log_{10}$ reductions achieved against the control strain (i.e., demonstrating that the contaminating *Serratia* possessed Quat resistance determinants)**

- **Surprisingly, survival studies revealed that colony counts of *S. marcescens* decreased by 1 $log_{10}$ after 60 min, and showed no growth after 105 min**
  - **A few studies have also documented short survival times of *Serratia* on hard surfaces***

* Neely AN et al. J Burn Care Rehabil 2000;21:523
Hirai Y J Hosp Infect 1991;19:191

# Microbiological Investigation

- **Cultures of two additional blue buckets yielded bacterial contamination**
  - **Both grew *Pseudomonas* and *Achromobacter***
- **Cultures of 10 White disinfectant buckets used by EVS staff**
  - **All were no growth**
- **Reason for contamination of blue buckets was not determined**
- **Few remaining blue buckets in use were discarded**

# Discussion

- **Several aspects of our study were unique**
  - First to report genetic mechanisms of resistance among *Serratia* recovered from contaminated Quat disinfectants
  - Other studies of contaminated disinfectants involving other pathogens did not establish the genetic mechanisms of Quat resistance
  - We assessed the ability of the contaminating *Serratia* to survive on dry surfaces, unlike earlier studies of Quat-contaminated disinfectants
    - **Other laboratory studies found that *Serratia* can survive for days to weeks on dry surfaces***
    - **Possible factors affecting our results:**
      - the size of the inoculum (lower than other studies)
      - use of a contaminated wipe soaked with disinfectant to inoculate bench tops
      - using *Serratia* previously exposed to Quat disinfectant (unlike other lab experiments)
  - Limited survival of *Serratia* on surfaces & infrequent room cleaning by the implicated housekeeper may explain why no clinical infections were identified

*** Kramer A et al. BMC Infect Dis 2006;6:130**

# Discussion

- **Several aspects of our study were unique**
  - **We evaluated the remaining biocidal activity of the contaminated disinfectant, and showed that it still had substantial activity against standard pathogens (control strains of *Serratia* and *S. aureus*)**
    - **Survival in in-use disinfectant was not due to very low concentration of Quat disinfectant in the bucket**
    - **Previous studies have demonstrated that soaking wipes comprised of cellulose-based fibers (e.g., gauze, cotton towels, some types of disposable wipes) can significantly lower the biocidal activity of Quat disinfectants***
  - **This finding strengthened evidence that the contaminating bacteria possessed substantial resistance to Quats**

* Boyce JM et al. Infect Control Hosp Epidemiol 2016;37:340
Engelbrecht K et al. Am J Infect Control 2013:41:908
MacDougall KD et al. Infect Control Today 2006;10:62

# Discussion

- **Level of contamination ($9.3 \times 10^4$) is consistent with previous reports of contaminated Quat disinfectants**
  - **Range: 330 CFU/ml to $10^6$ CFU/ml**

- **In-use contamination of the disinfectant most likely occurred due to failure of the housekeeper to empty, clean, and dry the bucket before refilling with fresh disinfectant***

- **Other errors responsible for Quat contamination include:***
  - **Over-dilution of concentrated disinfectant solutions**
  - **Use of contaminated water to dilute concentrated solutions**
  - **Use of outdated products**
  - **Accumulation of organic material in disinfectant solution, which decreases the effectiveness of Quat disinfectants**

*** Weber DJ et al. Antimicrob Agents Chemother 2007;51:4217**

# Discussion

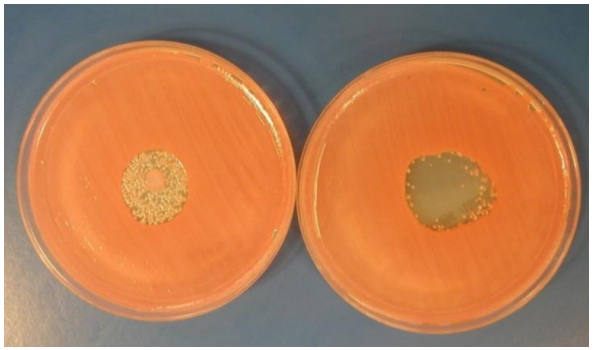
## Study limitations

- **Plating the contaminated disinfectant on McConkey agar without a neutralizer may have inhibited growth on the agar, thus underestimating the level of contamination**

- **The minimum inhibitory concentration (MIC) of disinfectant for the *Serratia* and *Achromobacter* strains was not determined**
  - **MICs of the *Serratia* strains were most likely significantly elevated, since the control strain has an MIC to benzalkonium chloride (another Quat) of only 12.5 ug/ml (ppm)**
  - **Usual in-use concentration of our Quat disinfectant was 660 ppm**
  - **The MIC had to be elevated to allow survival in the disinfectant bucket**

# Discussion

## Study limitations



- **The actual Quat concentration of the contaminated disinfectant was not tested, to assure that significant over-dilution did not occur**
  - **Unlikely based on zone diameters of contaminated and fresh disinfectant**

- **Available methods for estimating Quat concentrations include:**
  - **Qualitative Quat test strips (inexpensive, easy to use)**
  - **Quantitative titration kits (more expensive, more complicated, less easy to use)**


# Discussion

- **Quat disinfectants are among the most commonly used disinfectants used in healthcare settings**
  - **Broad range of antimicrobial activity, except poor activity against spores, mycobacteria, and non-enveloped viruses (e.g., norovirus), and suboptimal activity against *C. auris**
  - **Relatively safe, and inexpensive (esp. in dilutable form)**

- **However, compared to other hospital-grade disinfectants, they are more prone to contamination with Gram-negative bacteria**
  - **Multiple episodes of contamination of Quat antiseptics and disinfectants have been reported over a period of many years****

*Rutala WA et al. Am J Infect Control 2019;47:A96
Cadnum JC et al. Infect Control Hosp Epidemiol 2017;38:1240
Rutala WA et al. Infect Control Hosp Epidemiol 2019;40:380
** Weber DJ et al. Antimicrob Agents Chemother 2007;51:4217

# Reported Episodes of Quat Disinfectant Contamination

| Year | Author | Organism(s) | Outcome |
|---|---|---|---|
| 1980 | Ehrenkranz | ***Serratia marcescens*** | Infection outbreak; surface contamination |
| 1988 | Gahrn-Hansen | ***Achromobacter*** *xylosoxidans* | Infection outbreak |
| 1996 | Nagai | *Pseudomonas fluorescens* | No infections |
| 1996 | Oie | *Burkholderia cepacia, Pseudomonas aeruginosa* | No infections |
| 1999 | Olson | *Pseudomonas aeruginosa* | Infection outbreak |
| 2000 | Kaitwatcharachai | *Burkholderia cepacia* | Infection outbreak |
| 2002 | Lehours | ***Achromobacter*** *xylosoxidans* | Infection outbreak |
| 2005 | Ebner | *Burkholderia cepacia* | Pseudo-outbreak |
| 2006 | Lo Cascio | *Burkholderia cenocepacia* | Infection outbreak |
| 2007 | Siebor | ***Achromobacter*** *xylosoxidans, Pseudomonas fluorescens* | Pseudo-outbreak |
| 2014 | Kampf | ***Achromobacter*** *spp.,* ***Serratia marcescens*** | Survey of buckets |
| 2015 | Kupfahl | ***Achromobacter*** *spp* | Survey of buckets |
| 2015 | Hugon | ***Achromobacter*** *denitificans* | Infection outbreak, surface contamination |

# Discussion

## Why are Gram-negative bacteria responsible for most episodes of Quat contamination?

- **Unlike Gram-positive bacteria, Gram-negatives have an outer membrane that makes it more difficult for Quats to reach their target sites on the cytoplasmic membrane**

- **Some bacteria like *Burkholderia, and* some *Pseudomonads* and *Serratia* have chromosomally-encoded or plasmid-mediated efflux pumps that pump Quats out of cells**

- **Some strains of *Pseudomonas* have changes in their**
  - **Outer membrane proteins and lipopolysaccharide**
  - **Cytoplasmic membrane fatty acids that affect susceptibility**
  - **Decreased expression of porins related to Quat transport**
  - **Biofilm production**

# Discussion

- **Mechanisms of Quat resistance among *Achromobacter* have received little attention**

- **Intrinsic resistance is most likely related to**
  - **Outer membrane characteristics**
  - **Biofilm production**
  - **? Multidrug efflux pumps**

# Discussion

- **Binding of Quat disinfectants is generally not a problem with most pre-impregnated (ready to use) wipes**
  - **Especially true for wipes containing Quat + alcohol**

- **However, efficacy issues may occur with some Quat wipes**
  - **In one study, two commercially-available Quat-based wipes made of viscose material did not remove dry surface biofilms any better than equivalent materials impregnated with water**
    - **Viscose is a semi-synthetic material made from chemically-treated wood pulp**
  - **Polypropylene wipes impregnated with Quat eradicated dry surface biofilms > 100 times greater than viscose wipes***

*** Pascoe MJ et al. J Hosp Infect 2022;126:37**

# Discussion

- **In another study, one type of Quat disinfectant failed to adequately remove *S. aureus* from surfaces if used with microfiber or cotton cloths***

- **If using a preimpregnated wipe containing Quats as the only active agent ( not combined with alcohol), consider checking concentration of disinfectant released from the wipe (squeeze the wipe to collect fluid)**
  - **Check released fluid with Quat test strips**

*** Wesgate R et al. J Hosp Infect 2019;103:e25**

# Discussion

## Potential problem with automated dilution systems for disinfectants

- A survey of 33 automated dispensing systems revealed the following concentrations of a dilutable Quat dispensed
  - 0 ppm at 2 stations
  - < 200 ppm at 7 stations
  - 200-400 ppm at 17 stations
  - 400-600 ppm at 6 stations
  - One station was inoperable
- Manufacturer recommended a concentration of 660 ppm
- Investigation revealed
  - Variations in water pressure for making dilution
  - Problem with flow-control device of concentrate

Boyce JM et al. ICHE 2016;37:340

# Conclusions

- **Quat disinfectants are widely used in healthcare settings, and have a number of valuable characteristics**

- **However, disinfectants with 1 or more Quats as the only active agent(s) are prone to contamination by Gram-negatives**

- **EVS departments using liquid Quat disinfectants dispensed into buckets should**
  - **Have well-defined policies regarding care of reusable buckets**
    - **Buckets need cleaning and drying before being refilled with disinfectant**
  - **Provide staff with instructions about which type of wipes to be used, to avoid Quat binding**
  - **Consider periodic checks on in-use Quat disinfectant concentrations**
  - **Educate EVS staff regarding appropriate contact times and required PPE**

# Acknowledgements

**I would like to acknowledge Nancy Havill, MT, MHA, CIC, who is an infection preventionist, now at Yale New Haven Hospital, who performed the laboratory assays for the study.**

**Thank you for your Attention**

**Questions?**

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