Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination☆

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SUMMARY

Viruses with pandemic potential including H1N1, H5N1, and H5N7 influenza viruses, and severe acute respiratory syndrome (SARS)/Middle East respiratory syndrome (MERS) coronaviruses (CoV) have emerged in recent years. SARS-CoV, MERS-CoV, and influenza virus can survive on surfaces for extended periods, sometimes up to months. Factors influencing the survival of these viruses on surfaces include: strain variation, titre, surface type, suspending medium, mode of deposition, temperature and relative humidity, and the method used to determine the viability of the virus. Environmental sampling has identified contamination in field-settings with SARS-CoV and influenza virus, although the frequent use of molecular detection methods may not necessarily represent the presence of viable virus. The importance of indirect contact transmission (involving contamination of inanimate surfaces) is uncertain compared with other transmission routes, principally direct contact transmission (independent of surface contamination), droplet, and airborne routes. However, influenza virus and SARS-CoV may be shed into the environment and be transferred from environmental surfaces to hands of patients and healthcare providers. Emerging data suggest that MERS-CoV also shares these properties. Once contaminated from the environment, hands can then initiate self-inoculation of mucous membranes of the nose, eyes or mouth. Mathematical and animal models, and intervention studies suggest that contact transmission is the most important route in some scenarios. Infection prevention and control implications include the need for hand hygiene and personal protective

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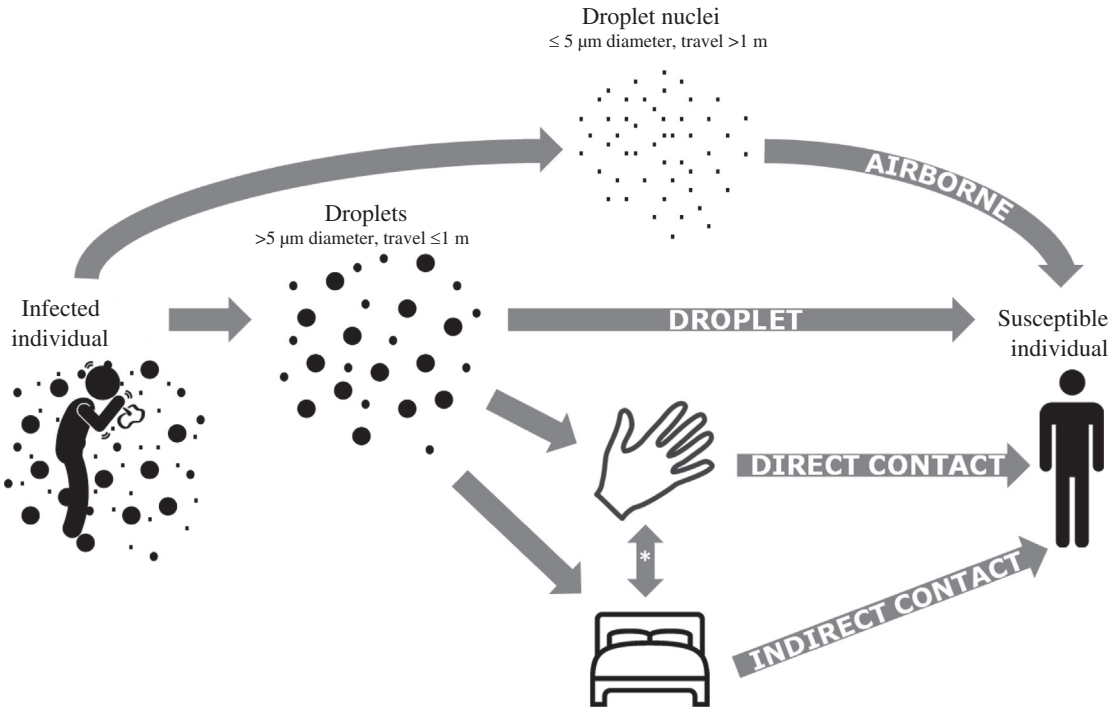
equipment to minimize self-contamination and to protect against inoculation of mucosal surfaces and the respiratory tract, and enhanced surface cleaning and disinfection in healthcare settings.

Introduction

A number of viruses with pandemic potential have emerged in recent years. The 2002 emergence of severe acute respiratory syndrome coronavirus (SARS-CoV), 2009 pandemic of H1N1 influenza, continued circulation of influenza H5N1 and H5N7 strains, and the recent emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV) illustrate the current threat of these viruses.[1–4]

Despite fundamental differences in their structure and epidemiology, these pandemic viral threats share a number of important properties. They are zoonotic enveloped RNA respiratory viruses that rarely transmit between humans in their native form, but could mutate to allow more efficient human-to-human transmission. This was illustrated by the 2002–2003 SARS pandemic and the 2009 H1N1 influenza pandemic.[3,4] Frequent and accepted transmission routes are 'droplet transmission', where droplets (>5 μm diameter, travelling <1 m) containing viable viruses make contact with the nose, mouth, eyes, or upper respiratory tract, and 'airborne transmission', where droplet nuclei (≤5 μm diameter, which can travel >1 m) are inhaled by susceptible individuals (Figure 1).[5–8] The role of 'direct contact transmission' (not involving contaminated surfaces) and 'indirect contact transmission' (involving contaminated surfaces) in the spread of these viruses with pandemic potential has been controversial (Figure 1).[6–8] However, several reviews and models have suggested that indirect contact transmission is the predominant transmission route for some respiratory viruses, including influenza, in some settings.[7–9]

Contaminated surfaces are an established route of transmission for important nosocomial pathogens including *Clostridium difficile*, meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Acinetobacter baumannii* and norovirus, which share the capacity to survive on surfaces for extended periods.[10–12] There is a general perception that enveloped viruses, such as influenza and human coronaviruses including MERS-CoV and SARS-CoV, have a very limited capacity to survive on dry surfaces.[13–15] However, several studies suggest that SARS-CoV, MERS-CoV and influenza virus have the capacity to survive on dry surfaces for a sufficient duration to facilitate onward transmission.[16–18] SARS-CoV and surrogates, and influenza virus can also survive in environmental reservoirs such as water, on foods, and in sewage for extended periods.[19–25] Here, we review the studies evaluating influenza and human coronavirus survival on dry surfaces, field



* Transmission routes involving a combination of hand & surface = indirect contact.

Figure 1. Transmission routes: droplet, airborne, direct contact, and indirect contact. (Indirect contact: routes involving a combination of hand and surface.) Definitions of 'droplet' and 'droplet nuclei' are from Atkinson *et al.*[5]

investigations that have performed surface sampling for these viruses, and we consider the importance of contaminated surfaces in the transmission of these viruses.

Search strategy

PubMed searches without date or language restrictions were performed on November 22nd, 2014 using the following search terms: [coronavirus or influenza] survival surface OR fomite transmission OR surface contamination OR disinfection transmission. Studies evaluating contamination of any surface were included. A total of 254 articles were identified using these search terms (Appendix A). Articles were also identified by hand-searching of bibliographies and related articles on PubMed.

Survival on dry surfaces

Tables I and II summarize in-vitro studies evaluating the capacity of human coronaviruses (including SARS-CoV and MERS-CoV) and influenza to survive when inoculated on to dry surfaces. Important methodological differences include variation in the choice of virus species and strain, method used to detect virus, deposition mode, titre and volume applied, surface substrate, suspending medium, temperate and relative humidity (RH), and drying time. These differences mean that direct comparison of reported survival times between studies is often not meaningful. In some of the reviewed studies, these factors have been experimental variables, allowing comment on the influence of the method used to detect virus, species and strain, titre, substrate, suspending medium, and temperature/RH on drying time (Tables I and II).

Notwithstanding differences in methodology, some common themes emerge. Survival times for SARS-CoV, MERS-CoV, and surrogates such as transmissible gastroenteritis virus (TGEV) are generally measured in days, weeks, or months.[16,26,28–30,43] Survival times for influenza virus are generally shorter, often measured in hours rather than days.[16,32–34] However, some studies have reported considerably longer survival times for influenza virus, measured in days rather than hours.[35,36,39–42] This apparent conflict is most likely explained by experimental factors. The difference in survival capacity between influenza virus and that of SARS-CoV and MERS-CoV is best illustrated by van Doremalen *et al.* who tested both H1N1 influenza and MERS-CoV.[16] Viable MERS-CoV was recovered after 48 h, with a half-life ranging from ~0.5 to 1 h. By contrast, no viable H1N1 was recovered after 1 h under any of the conditions tested.

SARS-CoV and MERS-CoV appear to have an unusual capacity to survive on dry surfaces compared with other human coronaviruses (229E, OC43, and NL63).[17,28,27,31,44] SARS-CoV, like the non-enveloped adenovirus comparator, survived for more than six days when dried on to Petri dishes compared with human coronavirus HCoV-229E, which survived for less than 72 h.[28] Although data are limited, it appears that MERS-CoV may survive on surfaces for longer than most human coronaviruses.[16] Since other human coronaviruses do not share the unusual survival properties of SARS-CoV, TGEV and mouse hepatitis virus (MHV) are often used as surrogates.[26,43,45]

No study has tested more than one strain of SARS-CoV or MERS-CoV. However, some studies have tested more than one strain of influenza, highlighting considerable strain variation.[18,35,39,42] Further work is necessary to evaluate the importance of strain variation in influenza and coronavirus survival.

There appears to be a 'dose response' in terms of survival, with more concentrated viral suspensions surviving longer than less concentrated suspensions.[29,33,39] For example, SARS-CoV survived on disposable gowns for 1 h at 10^4 $TCID_{50}$/mL vs 2 days at 10^6 $TCID_{50}$/mL.[29] Similarly, H3N2 influenza survived on bank notes for 1 h at 1.1×10^5 $TCID_{50}$/mL vs 2 days at 8.9×10^5 $TCID_{50}$/mL.[39]

Substantial variation in survival times is evident for coronaviruses and influenza on different surface substrates.[30,34,37,41] Coronaviruses and influenza both have the capacity to survive on a wide range of porous and non-porous materials, including metals, plastics (such as light switches, telephones, perspex, latex, rubber, and polystyrene), woven and non-woven fabrics (including cotton, polyester, handkerchiefs, and disposable tissues), paper (including magazine pages), wood, glass, stethoscopes, tissue, Formica®, bank notes, tiles, eggs, feathers, and soft toys.[16,27,31–34,39,41,43] The properties of different surfaces are likely to influence survival times. For example, the survival of influenza dried on to copper surfaces was considerably shorter than on stainless steel.[40]

Several studies have evaluated the capacity for SARS-CoV (and the surrogate TGEV), and influenza virus to survive on materials widely used as personal protective equipment (PPE) such as gowns, gloves, and respirators.[29,37,43] For example, TGEV survived on isolation gowns, nitrile and latex gloves, N95 respirators, and scrubs with a $<10^2$ reduction for >4 h, and was detected on some items after 24 h.[43] One study showed that H1N1 influenza virus dried on to various materials could be transferred to the hands of volunteers for at least 24 h following inoculation on some surfaces, with clear implications for the acquisition of viable viruses on the hands of healthcare personnel during the removal of PPE.[42] A more recent study identified viable pandemic H1N1 influenza after six days on coupons made from N95 respirators.[18]

The suspending medium used to dry the viruses on to surfaces is another important factor influencing survival times.[18,28,39,46] For example, adding mucus increased the survival time of influenza dried on bank notes from hours to up to 17 days.[39] A related variable is the mode of deposition of the viruses. Most studies dried a small volume of a known concentration of virus in a cell culture medium. However, several studies have evaluated the use of deposited virus from clinical specimens, which may be more representative of the clinical scenario and tends to result in shorter survival times.[32,33,39]

In all studies that tested varying temperature and RH, lower temperature and RH favoured the survival of both coronaviruses and influenza.[16–18,26,35,36,38]

Different methods have been applied to detect virus — most often cell culture assays but also RNA detection using polymerase chain reaction (PCR) or indirect methods such as fluorescence or haemagglutinin assays.[27,33,34,37,40] Intact viral RNA appears to remain detectable on surfaces for longer than viruses that retain the ability to infect cells.[32,33,42] Since PCR assays only detect a small portion of RNA they cannot be used to replace culture-based methods in determining viability.

Experimental factors that have been shown to influence virus viability *in vitro* are likely to have important implications for virus survival on hospital surfaces. For example, the titre

Table I
Survival of SARS-CoV, MERS-CoV, and surrogates on dry surfaces

Study	Year	Location	Test virus	Load applied	Substrate(s)	Suspending medium	Volume applied (μL)	Temperature (°C)/RH (%)	Drying time (min) for time 0 sample	Results
van Doremalen *et al.*[16]	2013	USA	MERS-CoV	10^5	Steel and plastic	Cell culture medium only	100	Variable	10	Viable virus detected after 48 h at 20°C/40% RH. Less survival at 30°C/80% RH (8 h) and 30°C/30% RH (24 h). Half-life ranged from ~0.5 to 1 h.
Chan *et al.*[17]	2011	Hong Kong	SARS-CoV	10^5	Plastic	Cell culture medium only	10	Variable	Until visibly dry	SARS-CoV survived for 5 days with <10-fold reduction in titre at room temperature and humidity, and was viable for >20 days. The virus was more stable at lower temperatures (28 vs 38°C) and lower humidity (80–89% vs >95%). The reduction in viral titre was similar in suspension compared with virus dried on surfaces.
Casanova *et al.*[26]	2010	USA	TGEV	$>10^3$	Latex/nitrile gloves, N95 respirator, hospital scrubs, isolation gowns	Cell culture medium only	10	20/50	0	TGEV survived with $<10^2$ reduction on all items after 4 h and was detected on some items after 24 h
Casanova *et al.*[19]	2009	USA	TGEV, MHV	10^5	Stainless steel discs	Cell culture medium only	10	Variable	Until visibly dry	Both TGEV and MHV could survive in excess of 28 days under some conditions, with lower temperature and relative humidity resulting in improved survival. TGEV and MHV did not differ significantly in their survival properties.
Muller *et al.*[27]	2008	Germany	HCoV-NL63, human metapneumovirus	Not specified	Latex gloves, thermometer caps, stethoscopes, plastic table	Cell culture medium only	Not specified	Ambient	Not specified	Viable virus not detected after drying; viral RNA detectable for up to 7 days
Rabenau *et al.*[28]	2005	Germany	SARS-CoV, HCoV-229E, herpes simplex virus, adenovirus	10^6–10^7	Polystyrene Petri dish	Cell culture medium ±20% fetal calf serum	500	Ambient	Until visibly dry	SARS-CoV, adenovirus and herpes simplex virus survived >6 days. HCoV-229E survived for <72 h. The addition of FCS made little impact on survival times.

Lai *et al.*[29]	2005	China	SARS-CoV	Dilution series (10^2—10^4)	Paper, disposable gowns, cotton gowns	Cell culture medium + 2% fetal calf serum	5	Ambient	Until visibly dry	There was a dose response in terms of survival times of all materials, with more concentrated inocula surviving longer. Survival times ranged from 5 min (10^2 load on a cotton gown) to 2 days (10^4 load on disposable gown).
Duan *et al.*[30]	2003	China	SARS-CoV	10^6	Wood board, glass, mosiac, metal, cloth, paper, filter paper, plastic	Cell culture medium only	300	Ambient	No time 0 sample	Viability was assessed semiquantitatively and SARS-CoV was able to survive, albeit with reduced infectivity, for >72 h on all surfaces tested, and for >120 h on metal, cloth and filter paper. Additionally, virus survived for >72 h on cotton cloth in an experimentally dried enclosure.
Sizun *et al.*[31]	2000	Canada	HCoV-229E, HCoV-OC43	10^3	Aluminium, cotton gauze, latex gloves	Cell culture medium only	10	Ambient	Until visibly dry (15—45 min)	Viability fell to below detectable levels after 6 h for 229E and 2 h for HCoV-OC43.

SARS, severe acute respiratory syndrome; CoV, human coronavirus; MERS, Middle East respiratory syndrome; RH, relative humidity; TGEV, transmissible gastroenteritis coronavirus; MHV, mouse hepatitis virus.

and volume of virus applied to surfaces will be influenced by the type and volume of respiratory secretion, as will the suspending medium. The temperature and RH of the hospital environment is likely to be controlled to comfortable levels, meaning that some of the extremes of temperature and relative humidity tested *in vitro* may not be so relevant in the field.

Survival in aerosols

Respiratory virus symptoms such as sneezing and coughing result in the generation of virus-containing particles, in a size continuum from 1 to 500 μm.[47,48] Whereas the generation of small droplet nuclei has traditionally been associated with 'aerosol-generating procedures', several recent studies have identified aerosols (droplet nuclei, ≤5 μm diameter) in the vicinity of patients infected with influenza who are not undergoing recognized aerosol-generating procedures.[49—51] Coronaviruses especially have the ability to survive for long periods in aerosols. For example, HCoV-229E aerosol remained infectious for six days at 20°C and 50% RH.[52] One study has evaluated the survival of MERS-CoV aerosols, finding a 7% reduction over 10 min (at 40% RH).[16] By contrast, H1N1 suffered a 95% reduction over the same time period, suggesting that influenza virus may be less robust as an aerosol than coronaviruses. However, other studies have shown extended survival times for influenza aerosols (surviving up to 36 h).[53—55]

Environmental contamination in field settings

A number of studies have performed environmental sampling for influenza or SARS in field settings (Table III). No studies have yet been published evaluating MERS-CoV contamination in field settings.

The major limitation with field studies is the use of PCR to detect viral RNA, which is best seen as a marker of virus shedding rather than indicating the presence of viable virus on surfaces, which must be confirmed by the recovery of viruses able to infect cells. In a number of influenza virus studies, a considerably lower rate of detection was identified by viral culture than by PCR, and in one study no viable virus was detected by culture despite the detection of influenza virus RNA.[56—58] Similarly, regarding SARS, two studies have detected environmental reservoirs of SARS-CoV RNA by PCR, but no viable virus by culture.[44,63]

Three studies have evaluated influenza contamination of surfaces in healthcare settings. A UK study detected influenza virus RNA on two (0.5%) of 397 samples from surfaces around infected individuals, one of which grew viable influenza.[57] More than half of the patients in the study were receiving antiviral medication, which may have reduced shedding. Influenza virus RNA was recovered from 38.5% of 13 environmental surfaces around hospitalized patients in Mexico.[61] In one case, one out of five surfaces (a bed rail) was positive from a patient's room 72 h after patient discharge and terminal cleaning. Pappas *et al.* sampled toys in the waiting room of a general paediatric practice, finding that only one out of 59 toys was contaminated with influenza RNA.[59] However, a higher proportion of toys was contaminated with picornavirus RNA (19.2%), including four out of 15 after cleaning. The identification of viral RNA on surfaces after cleaning and disinfection may be a marker of ineffective cleaning and disinfection.

Table II
Survival of influenza viruses on dry surfaces

Study	Year	Location	Test virus	Load applied	Substrate (s)	Suspending medium	Volume applied (μL)	Temp (°C)/RH (%)	Drying time (min) for time 0 sample	Results
van Doremalen *et al.*[16]	2013	USA	H1N1 (human isolate)	10^5	Steel and plastic	Cell culture medium only	100	Variable	10	No viable virus recovered after 4 h. No difference between plastic and steel.
Coulliette *et al.*[18]	2013	USA	H1N1 (pandemic strain)	10^4	Coupons from N95 respirators	Cell culture medium/2% FBS/mucin	100	Variable	60	10^2 $TCID_{50}$ per coupon recovered from time 0 samples (after drying). Viable virus was recovered after 6 days with a 10-fold reduction. Viral survival was longer in FBS and mucin compared with cell culture medium. Lower absolute humidity favoured longer survival.
Zuo *et al.*[32]	2013	USA	Avian influenza H9N9	Liquid spike (10^4—10^5)	Three non-woven fabrics	Cell culture medium only	20	Ambient	0 min; until visibly dry; 30 min after visibly dry	Viable virus survival for >1 h on each of the materials tested; survival times varied significantly by material. Survival on hydrophilic nylon lower than on hydrophobic materials. Choice of eluent did not significantly affect recovery. Virus recovery following deposition as an aerosol was considerably lower.
Mukherjee *et al.*[33]	2012	USA	Field study of 20 influenza-infected individuals	Participants coughed or sneezed on hands then touched surfaces	Door handle, telephone, pillowcase, cotton handkerchief	n/a	n/a	Ambient	n/a	Virus RNA recovered from three door handles and one telephone; no samples were tissue culture positive.
			H1N1 (recovered from two participants)	Dilution series (10—10^5)	Formica, vinyl, stainless steel, cotton pillowcase, facial tissue	Cell culture medium only	20	Ambient	5	Viable virus detected by tissue culture from some hard surfaces at higher applied load for up to 1 h; no viable virus detectable by tissue

									culture after 1 h; virus RNA detectable after 1 h on some surfaces.
Greatorex *et al.*[34]	2011	UK	H1N1 (PR8)	10^6	Common porous and non-porous household materials	Cell culture medium plus 1% bovine serum albumin	10	17–21/23–24	0 (drying times ranged from 5 min to 7 h)	Viral RNA detected with minimal reduction on most surfaces over 24 h; viral infectivity falls away more rapidly, with infective virus at low titre detectable from most surfaces at 4 h but from only stainless steel at 9 h
			H1N1 (AH04): recent clinical isolate	10^4		Cell culture medium only				Semiquantitative fluorescence assay indicated the presence of virus at 4–24 h on hard surfaces but <4 h on porous surfaces.
Dublineau *et al.*[35]	2011	Paris	H1N1 seasonal and pandemic strains	10^5–10^6	Watch glass	Cell culture medium only	50	Variable	5–17 h	Both viruses survived for >3 days under all conditions tested; pandemic H1N1 survived for >7 days at 35°C and 2 months at 4°C.
Wood *et al.*[36]	2010	USA	H5N1	10^6	Glass and galvanized steel	Cell culture medium only	100	4/variable	60	Influenza stable at low temperature, regardless of humidity, with 13-day survival and reduction by factor of <1 on both substrates. Surface survival not tested at room temperature.
Sakaguchi *et al.*[37]	2010	Japan	H1N1	10^4	Personal protective equipment: rubber gloves, N95 mask, surgical mask, Tyvek gown, coated wood, steel	Cell culture medium only	500	25.2/55	0	The haemagglutinin titre of the virus remained stable on all surfaces up to 24 h. The virus remained infective by $TCID_{50}$ on all materials up to 8 h, and on rubber for up to 24 h.

(*continued on next page*)

Table II (*continued*)

Study	Year	Location	Test virus	Load applied	Substrate (s)	Suspending medium	Volume applied (μL)	Temp (°C)/RH (%)	Drying time (min) for time 0 sample	Results
McDevitt *et al.*[38]	2010	USA	H1N1 (PR8)	10^4—10^5	Stainless steel	Purchased virus suspension	50	Variable	Until visibly dry (~30 min)	Virus survival assessed at 15, 30 and 60 min at variable temperature 55—65°C) and relative humidity (25—75%). Virus survived for >60 min with a $10^{1.5}$ reduction at the lowest temperature/humidity combination (55°C/25%). Linear association between increasing humidity and logarithmic reduction.
Thomas *et al.*[39]	2008	Switzerland	H3N2 (2 strains), H1N1 and influenza B	10^3—10^8	Bank notes	Cell culture medium only	50	21—28 (avg. 22)/30—50	Dried under laminar airflow; time not specified	Survival varied by strain from 3 h to 3 days, depending on the virus tested.
			Spiked pooled negative nasopharyngeal secretions		Bank notes	Cell culture medium only	50	21—28 (avg. 22)/30—50	Dried under laminar airflow; time not specified	Higher inocula survived for longer on surfaces; the addition of respiratory mucus significantly increased survival, usually from hours to up to 17 days.
			Influenza-positive nasopharyngeal secretions		Bank notes	Cell culture medium only	50	21—28 (avg. 22)/30—50	Dried under laminar airflow; time not specified	Infective influenza recovered from 7/14 (50%) of notes after 24 h, 5/14 (36%) of notes after 48 h, and in one case, after 12 days.
Noyce *et al.*[40]	2007	UK	H1N1	10^6	Stainless steel or copper	Cell culture medium only	20	20—24/50—60	Not specified	10^5 viable virus recovered from stainless steel after 24 h vs 10^2 viable virus on copper after 6 h
Tiwari *et al.*[41]	2006	USA	Avian influenza virus, avian metapneumovirus	10^4	Steel, wood, tile, tire, gumboot, feather, egg shell, egg tray, plastic, latex, cotton and polyester	Cell culture medium only	10	Ambient	Until visibly dry (~30—40 min)	Both viruses survive for up to 72 h on most surfaces tested. Influenza survived for up to 6 days on latex and feather.

Bean *et al.*[42]	1982 USA	H1N1 and influenza B clinical isolates	10^2–10^4	Steel, plastic, cotton handkerchief, paper tissue, magazine page, cotton panamas	Cell culture medium only	100	26–29/35–56	Up to 1.5 h	Viruses survived for 48–72 h on non-porous surfaces (steel and plastic) and for shorter periods on porous surfaces. Influenza A survived significantly longer than influenza B. Viruses dried on to surfaces could be transferred to hands from all surfaces for 15 min, and from steel for 24 h.

FBS, fetal bovine serum; TCID, tissue culture infectious dose; avg., average.

Several studies have evaluated influenza RNA or viable influenza in homes, day-care centres and elementary schools.[58,60,62] The proportion of sites contaminated with influenza virus RNA varied from 3% to >50% in these studies, with evidence of seasonal variation in the study by Boone *et al.*[62] In Bangkok, households randomized to a handwashing intervention had a lower proportion of sites contaminated with influenza virus RNA than did control households (11.1% of 45 vs 24.4% of 45).[58]

Influenza RNA was detected on 15% of the 1862 environmental samples collected from bird markets in Indonesia, and almost half of the markets (47%) were contaminated at one or more site(s).[56] Viable influenza was cultured from 4.6% of 280 samples tested. Markets that slaughtered birds, as well as one particular province, were associated with contamination, whereas zoning of poultry activities and daily disposal of solid waste were protective.

Two studies have evaluated SARS-CoV contamination. A study of areas used to care for patients with SARS in Bangkok and Taipei found that 38.1% of 63 sites were contaminated with SARS-CoV RNA.[44] Furthermore, 6.4% of 31 public areas were also contaminated with SARS-CoV RNA. A lower rate of contamination was identified at a Canadian hospital, where 3.5% of 85 surfaces in SARS units were contaminated with SARS-CoV RNA.[63] Viral culture did not detect viable SARS-CoV from any of the surfaces in these studies. A study of public surfaces in Jeddah Airport, Saudi Arabia, identified human coronavirus RNA from three (7.5%) of 40 surface samples. No viral culture was performed in the study.[64]

Importance of contaminated surfaces in transmission

Direct and indirect contact transmission is an established transmission route for several respiratory and gastrointestinal viruses, including rhinovirus, respiratory syncytial virus, norovirus, and rotavirus.[7,47,65–67] However, the importance of indirect contact transmission (contact transmission involving contaminated surfaces; Figure 1) in the spread of respiratory viruses, including influenza, SARS-CoV and MERS-CoV, compared with other transmission routes is uncertain.[6–8,68]

For contaminated surfaces to play a role in transmission, a respiratory pathogen must be shed into the environment, have the capacity to survive on surfaces, transfer to hands or other equipment at a concentration above the infectious dose, and be able to initiate infection through contact with the eyes, nose or mouth.[11]

Human coronaviruses and influenza are shed in respiratory secretions.[14,69] They can also survive in the gastrointestinal tract and have been associated with diarrhoea, which causes widespread environmental dissemination.[14,69–74] In the case of SARS-CoV, viral loads in nasopharyngeal (up to 10^6/mL) and stool (up to 10^9/g) specimens may be high.[69] Titres of influenza in nasopharyngeal specimens (generally ranging from 10^5 to 10^7, but can be up to 10^{11} copies/mL) and stool specimens (up to 10^7/g) exhibit a similar range.[57,74–76] Emerging data suggest that MERS-CoV are shed in approximately equal quantities to SARS-CoV.[77,78] By contrast with the high titre shed from the respiratory and gastrointestinal tracts, the infectious dose may be low. For example, the infectious dose for influenza can be <1 $TCID_{50}$, and <20 plaque-forming units for SARS-CoV.[13,79]

Table III
Field sampling for influenza and human coronaviruses including SARS-CoV environmental contamination

Study	Year	Setting and location	Sites sampled	Sampling method	No. of samples	No. positive (%)	Notes
Influenza							
Indriani *et al.*[56]	2010	Live-bird markets, Indonesia	27 sites were sampled at 83 live-bird markets for avian influenza (H5N1)	Cotton swabs; PCR for viral RNA and viral culture	1862 (PCR)	280 (15)	39 (47%) markets contaminated at one or more site. Structured questionnaire to assess risk factors for contamination. One province and markets that slaughtered birds associated with contamination; zoning of poultry activities and daily disposal of solid waste were protective.
					280 (culture)	13 (4.6)	
Killingley *et al.*[57]	2010	Influenza-infected adults in hospital and community settings in and around Nottingham, UK	19 patients (daily) and their immediate environment (every other day) were sampled.	Moistened cotton swabs; PCR for viral RNA and viral culture	397	2 (0.5)	Live virus recovered from 1/2 positive surfaces. 54% of subjects took an antiviral drug, which may have influenced shedding. Duration of virus shedding had a mean of 6.2 days and a range of 3—10 days.
Simmerman *et al.*[58]	2010	90 children with influenza in Bangkok, Thailand. Households were randomized to obtain handwashing education or not.	Six household items in 90 households	Moistened rayon tipped swabs; PCR for viral RNA and viral culture	540	18 (3.3)	16 (17.8%) of the 90 households had one or more samples positive for influenza by PCR. Nine TV remotes, six toys, two bathroom knobs and one light switch had positive results. No viable virus was detected by culture.
Pappas *et al.*[59]	2010	Toys in the waiting room of a general paediatric practice in Virginia, USA	Hard surfaces and fabric toy samples on three separate occasions	Moistened swab; samples tested for picornavirus, RSV and influenza by PCR	52	1 (1.9)	19.2% of the toys were contaminated with picornavirus RNA.
Bright *et al.*[60]	2010	Surfaces in three elementary school classrooms in Seattle, Washington, USA	Standardized surfaces sampled in the morning, at midday and in the afternoon.	Moistened swabs; PCR for viral RNA	54	13 (24.1)	Also, norovirus RNA was found on 16.4% of 55 surfaces sampled.
Macias *et al.*[61]	2009	Hospital in Mexico City, Mexico	Samples collected from hands and surfaces in the rooms of patients with confirmed influenza	Swabs; PCR for viral RNA	13	5 (38.5)	In one case, 1/5 surfaces (a bed rail) was positive from a patient's room 72 h after patient discharge and terminal cleaning. 5/6 samples from patient hands were positive for influenza.
Boone and Gerba[62]	2005	Homes and day-care centres in Tucson, Arizona, USA	Samples from eight homes	Moistened swabs; PCR for viral RNA	92	35 (38.0)	None of 33 surfaces sampled during summer months vs 59% of 59 samples during March.
			Samples from 14 day-care centres		218	—	Influenza was detected on 23% of surfaces during the autumn and 53% during the spring.

Human coronavirus						
Booth *et al.*[63]	2005	Hospitals in Toronto, Canada	19 rooms in SARS units and 'control' areas not housing SARS patients	Moistened swabs; PCR for viral RNA and viral culture	85	3 (3.5)	Positive sites were a bed table, a television remote control and a refrigerator handle in a nurses' medication station. All swabs were culture negative. Two (5%) of 40 air-slit samples were positive for SARS-CoV.
Dowell *et al.*[44]	2004	Hospitals in Bangkok, Thailand and Taipei, Taiwan	SARS-infected patient areas (patient rooms, nursing stations, emergency department)	Moistened swabs; PCR for viral RNA and viral culture	63	24 (38.1)	All swabs were culture negative.
			Public areas		31	2 (6.4)	
Memish *et al.*[64]	2014	Jeddah airport, Saudi Arabia	Various frequently touched items in public areas	Moistened swabs; PCR panel for viral culture	40	3 (7.5)	Human coronavirus (OC43/HKU1) RNA was identified from surfaces. Influenza B virus RNA was identified from 1/18 air samples, but was not identified on surfaces.

SARS-CoV, severe acute respiratory syndrome coronavirus; PCR, polymerase chain reaction.

SARS-CoV, MERS-CoV and influenza virus can survive on dry surfaces for extended periods, particularly when suspended in human secretions (Tables I and II), and may contaminate hand-touch sites in the field (Table III).

Viral and bacterial surface contamination can be transferred to hands, and serial transfer to a number of surfaces from contaminated hands may occur.[11,42,80–85] For example, Bean *et al.* calculated that an infectious dose of virus could be transmitted for at least 2 h and possibly up to 8 h from stainless steel surfaces to hands.[42]

In order for the virus to initiate indirect contact transmission, oral inoculation or contact with mucous membranes must occur to transfer sufficient viruses. Nasal inoculation is a frequent route for establishing influenza and SARS infection.[86–90] Whereas oral inoculation has not been reported for SARS, it may occur for influenza and other viruses.[13,91,92]

Thus, the steps necessary to facilitate indirect contact transmission of both SARS-CoV and influenza are established. Although data are more limited for MERS-CoV, it appears to have the key properties to facilitate indirect contact transmission.

Determining which route is most important is challenging, but it seems that direct contact, indirect contact, droplet and airborne transmission do occur with both SARS-CoV and influenza viruses on occasion.[8,68] Few data are available evaluating transmission routes for coronaviruses, but the relative importance of the various routes for influenza virus has been evaluated through mathematical models, animal models, and intervention studies.[9,93,94]

Several mathematical models have been applied to SARS transmission, but none has considered an environmental route.[93,95] However, some influenza transmission models have evaluated the relative importance of airborne, droplet, and contact influenza transmission.[9,96,97] Two of these models conclude that contact transmission of influenza is at least as important as airborne or droplet spread, whereas one study found that contact transmission was negligible compared with other routes.[9,96,97] However, it is important to note that the relative contribution of contact, droplet, and airborne transmission depends on a combination of viral factors (e.g. capacity to survive on surfaces), host factors (e.g. frequency of hand contact with the nose) and environmental factors (e.g. size of enclosure and density of shedders). Varying these and other parameters will change the relative contribution of the various transmission routes.[9]

Several influenza transmission models have compared the importance of indirect contact transmission (involving surface contamination) with direct contact transmission (that occurs independently of surface contamination).[98,99] One model indicates that indirect transmission via contaminated surfaces generates touch frequency-dependent patterns whereas transmission via the air generates human density-dependent patterns.[98] Another model compared the involvement of droplet-contaminated versus hand-contaminated surfaces.[99] Droplet-contaminated surfaces were more likely to be involved in transmission than hand-contaminated surfaces (~10-fold difference), and large surfaces (such as table tops) had a higher transmission potential than small surfaces (such as door handles). A number of simplifying assumptions were made, which may be unsound — for example, that people touch portions of the fomite homogeneously, and that pathogens on fomites are homogeneously distributed. Also, transportation of

contamination from one type of fomite to another via human hands was not modelled. Notwithstanding these limitations, the study provides some useful data on indirect contact transmission of influenza.

An alternative approach is the use of animal models. For example, a guinea-pig model evaluated the relative contribution of airborne, droplet, and indirect contact transmission.[94] Indirect contact transmission was evaluated by placing uninfected animals in cages vacated by experimentally infected animals without changing bedding, food dishes, and water bottles. Animals were exposed to these cages for 24 h and tested for infection using nasal washings. Around a quarter of exposed guinea-pigs became infected, which was less efficient than transmission through airborne and droplet experiments (25–100% efficiency). Experimental contamination of surfaces in the cages was unable to establish infection. Another guinea-pig model showed that increasing the temperature to 30°C blocked aerosol but not contact transmission of influenza.[100] This provides further evidence that the relative importance of the various transmission routes is context dependent.

A small number of studies have demonstrated that interventions in field settings to improve surface or hand hygiene reduce influenza transmission, demonstrating the importance of contact transmission.[63,101,102] For example, introducing regular cleaning using disinfectant wipes reduced the rate of respiratory and diarrhoeal disease in elementary schools.[60]

Implications for cleaning and disinfection, and infection prevention and control in healthcare settings

The likely contribution of droplet, direct and indirect contact, and to a lesser extent the airborne route in the transmission of influenza, SARS and MERS dictates that each route must be separately addressed by infection prevention and control interventions. The use of a surgical mask will protect the respiratory tract from droplets, an N95 (FFP3) respirator will protect the respiratory tract from droplet nuclei, and gloves, gowns and eye protection will prevent contact with mucous membranes and contamination of clothing or hands for subsequent nasal inoculation.[103] Emerging literature suggests that doffing PPE presents a challenging risk for the acquisition of important viruses on hands.[104,105] Thus, protocols should be in place for minimizing the risk of contamination of hands and clothing, and hand hygiene should be performed following removal of PPE.

The extended survival of influenza virus, SARS-CoV and MERS-CoV on surfaces (Tables I and II) and some evidence of contamination in field settings (Table III) argue for enhanced disinfection, particularly at the time of patient discharge.[59,61] A range of hospital disinfectants are active against SARS-CoV and surrogates, and influenza, including alcohol, hypochlorites (bleach), quaternary ammonium compounds, and hydrogen peroxide, although inactivation is time and concentration dependent and will be influenced by other factors such as type of contaminated surface, specific product, and protein load.[28,45,106,107] However, in-vitro disinfectant effectiveness is a poor predictor for the elimination of contamination from surfaces if cleaning/disinfection is inadequate, which is often the case in hospitals.[108,109] Thus, there may be a role for automated room disinfection (ARD) systems, such as hydrogen peroxide vapour and ultraviolet (UV) light, when patients known to be infected with pandemic influenza or coronaviruses are discharged.[45,108]

Table IV
Calculating the time that an infectious aerosol shed by a patient infected with Middle East respiratory syndrome coronavirus could survive

Shed titre	Time to reach 20 virus particles
1,000,000	26 h
100,000	20 h
10,000	15 h
1000	9 h
100	4 h

The calculation assumes an infectious dose equal to severe acute respiratory syndrome coronavirus (<20 plaque-forming units) and a decay rate of 7% over 10 min in a room with no air changes.[13,16] The calculation used the following equation: $P(t) = P_0e - rt$, where $P(t)$ = the amount of some quantity at time t, P_0 = initial amount at time $t = 0$, r = the decay rate, t = time (number of periods).

There may be the potential for extended survival of an infectious viral aerosol in patients' rooms following their discharge. Using MERS-CoV as an illustrative example, infectious aerosol above the infectious dose could be present after the discharge of the patient for up to 26 h, assuming no air changes in the room and depending on the shed titre (Table IV). ARD systems address both contaminated air and surfaces, which may be important if infectious aerosol above the infectious dose remains following patient discharge.

Another consideration is the requirement for large quantities of N95 (FFP3) respirators in the event of a pandemic of influenza or MERS/SARS. Stockpiles of N95 respirators required for a pandemic are large, and stock shortages were acknowledged during the 2009 N1H1 influenza pandemic.[110] Both influenza virus and SARS-CoV surrogates have been shown to survive for extended periods on N95 respirator material.[18,37,43] This survival represents a barrier to the reuse of N95 respirators. One approach is to disinfect the N95 respirators. Several candidate technologies have been evaluated for the disinfection of N95 respirators; UV light, hydrogen peroxide vapour, and ethylene oxide show most promise.[111]

Conclusion

We reviewed the capacity of viruses with pandemic potential, influenza SARS-CoV and MERS-CoV, to survive on dry surfaces. The experimental methods used to test survival are important, but it seems that surface survival of SARS/MERS-CoV is greater than that of influenza virus. Important factors that influence the survival of these viruses on surfaces include: strain variations, a 'dose–response' relationship between the titre applied and survival time, the surface substrate (including the ability to survive on materials used to make PPE), the suspending medium (with the addition of mucus increasing substantially the survival time of influenza), the mode of deposition, temperature and RH, and the method used to determine the presence of the virus (specifically culture versus the use of PCR to detect viral RNA). All three viruses are able to survive in an aerosol for a considerable length of time (>24 h), which may have important infection control implications.

Environmental sampling has been performed for influenza virus and human coronaviruses (including SARS-CoV) in a number of field settings. Most studies have used PCR to detect viral RNA, which may not necessarily represent the presence of viable virus, but should be seen as a marker of virus shedding. Some studies have demonstrated the presence of viable influenza virus on surfaces using cell culture. There is a wide range in terms of the frequency of sites contaminated with influenza virus or SARS-CoV RNA, ranging from $<5\%$ to $>50\%$, including hand-touch sites.

The importance of indirect contact transmission is uncertain compared with other transmission routes, principally direct contact transmission, droplet, and airborne routes. Influenza virus, SARS-CoV and probably MERS-CoV are shed into the environment at concentrations far in excess of the infective dose, they can survive for extended periods on surfaces, and sampling has identified contamination of hospital surfaces. Contaminated surfaces could result in onward contamination of hands or equipment, which could then initiate inoculation through contact with the nose, eyes, or mouth. Thus, the steps required for indirect contact transmission are established. Mathematical modelling, animal models, and intervention trials suggest that contact transmission may be the most important route for influenza, but that this is context dependent.

The infection prevention and control implications of these findings include the need to wear appropriate PPE to account for contact, droplet and airborne routes, paying particular attention to the risk of contamination of hands and clothing during PPE removal. The potential for inadequate distribution and contact time during manual cleaning and disinfection, combined with the risk of extended survival of infectious aerosol, may argue for the use of ARD systems. These systems may also have a role in disinfection and reuse of N95/FFP3 respirators.

Viruses with pandemic potential including influenza, MERS-CoV, and SARS-CoV can survive for extended periods on dry surfaces, cause contamination in field settings and may require enhanced cleaning and disinfection to assure effective infection prevention and control.

Conflict of interest statement
J.A.O. is a consultant to Gama Healthcare. All other authors have no conflict to declare.

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None.

Appendix A. PubMed searches

coronavirus survival surfaces (June 11th, 2013: 9 studies)
influenza survival surfaces (June 11th, 2013: 29 studies)
coronavirus fomite transmission (June 20th, 2013: 8 studies)
influenza virus fomite transmission (June 20th, 2013: 43 studies)
coronavirus surface contamination (June 20th, 2013: 4 studies)
influenza virus surface contamination (June 20th, 2013: 14 studies)
disinfection influenza transmission (June 04th, 2014: 112 studies)
disinfection SARS transmission (June 04th, 2014: 35 studies)
Updated May 21st, 2014

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