AN ANALYSIS OF THE RISK AND RISK REDUCTION OF INFLUENZA VIRUS INFECTION THROUGH USE OF ANTIMICROBIAL PRODUCTS

By

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ABSTRACT

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Influenza is a pathogen of major concern, causing up to 79,000 deaths, 960,000 hospitalizations, and 49 million people sick per year in the US. One of the major route of transmission for influenza is by expelling viruses from coughing/sneezing onto surfaces, followed by transfer of viruses from surfaces to hands, and subsequently to facial mucous membranes.

Therefore, routine cleaning and disinfection of surfaces is an important part of the environmental management of influenza A. While the emphasis is generally on spraying hard surfaces and laundering cloth and linens with high temperature machine drying, not all surfaces can be treated in this manner. The quantitative microbial risk assessment (QMRA) approach was used to develop a stochastic risk model for estimating the risk of infection from indirect contact with porous surfaces, with and without surface pre-treatment with an antimicrobial spray product.

The data collected from laboratory combined with the risk model show that the risk of influenza A infection can be lowered by four logs when using an antimicrobial spray on a porous surface. Median risk associated with a single touch to a contaminated fabric was estimated to be 1.25×10^{-4} for the untreated surface, and 3.6×10^{-8} for the treated surface. This single touch scenario was used to develop a generalizable model, allowing to estimate risks by comparing different cases related to more realistic 15 to 30 minutes exposure scenarios associated with multiple surface/face touches. The results of this study demonstrate the effective risk reduction associated with treating porous surfaces that cannot be laundered at high temperatures.

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CHAPTER 1 – INTRODUCTION

INFECTION FROM INFLUENZA A, ONE OF THE MAJOR PATHOGEN ISSUES

Worldwide, infectious diseases are responsible for about 9.5 million deaths annually, representing 17% of global deaths (Ties Boerma, Colin Mathers, Carla AbouZahr, Somnath Chatterji, Daniel Hogan and Gretchen Stevens, assisted by Wahyu Retno Mahanani, Jessica Ho, 2015). In the US alone, infectious diseases are responsible annually for approximately 23.6 million visits to physician offices (*National Ambulatory Medical Care Survey : 2010 Summary Tables*, 2010), 3.9 million hospital outpatient department visits (National Center for Health Statistics, 2011), and a total cost of $120 billion (Levi, Segal, Lieberman, May, & St. Laurent, 2015).

Among infectious diseases, the influenza virus is one of the most common and significant causes of respiratory infections (WHO, 2016a). This RNA virus, which is subdivided into 4 types and multiple subtypes based on its surface protein types, is continuously monitored worldwide and is reported following the classic nomenclature [virus type]/[geographic origin]/[strain number]/[year of isolation]/[subtype]. With its tropical climate and its high density population, Asia is recognized as a sink source of continuously circulating viruses, allowing to constantly produce new seasonal variants that spread all over the world, mainly during the cold winter season and because of the human mobility (Bedford et al., 2015; Lemey et al., 2014; Russell et al., 2008; Wen, Bedford, Cobey, & Wen, 2016). Figure 1 shows the typical structure of an influenza A virus, an example of virus naming (Gallagher et al., 2018), and a simplified scheme of influenza global circulation adapted from the literature (Bedford et al., 2015; Lemey et al., 2014; Russell et al., 2008; Wen et al., 2016).

All the different types and subtypes of influenza viruses are known to yearly cause up to 500,000 deaths internationally (WHO, 2016a), making influenza a pathogen of high concern because of its annual occurrence; its potential to lead extremely broad and strong epidemics; and because of its significant yearly health and economic impacts. In the US, each annual influenza epidemic can infect 5 to 20% of Americans, lead between 140,000 and 960,000 hospitalizations and kill 12,000 to 79,000 people (CDC, 2019; Levi et al., 2015), while causing $10 billion estimated direct medical cost and $16 billion lost earnings (Molinari et al., 2007) (see Figure 2).

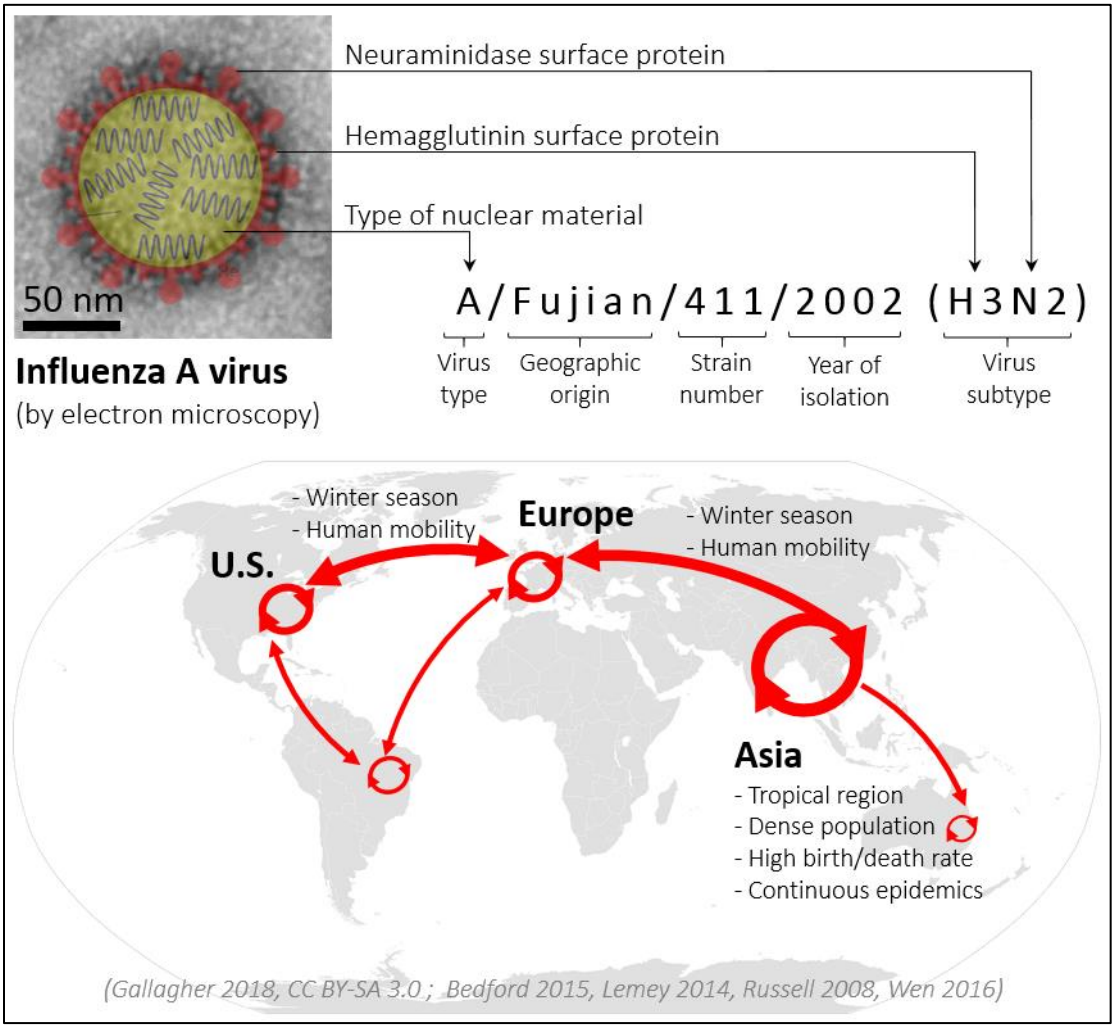
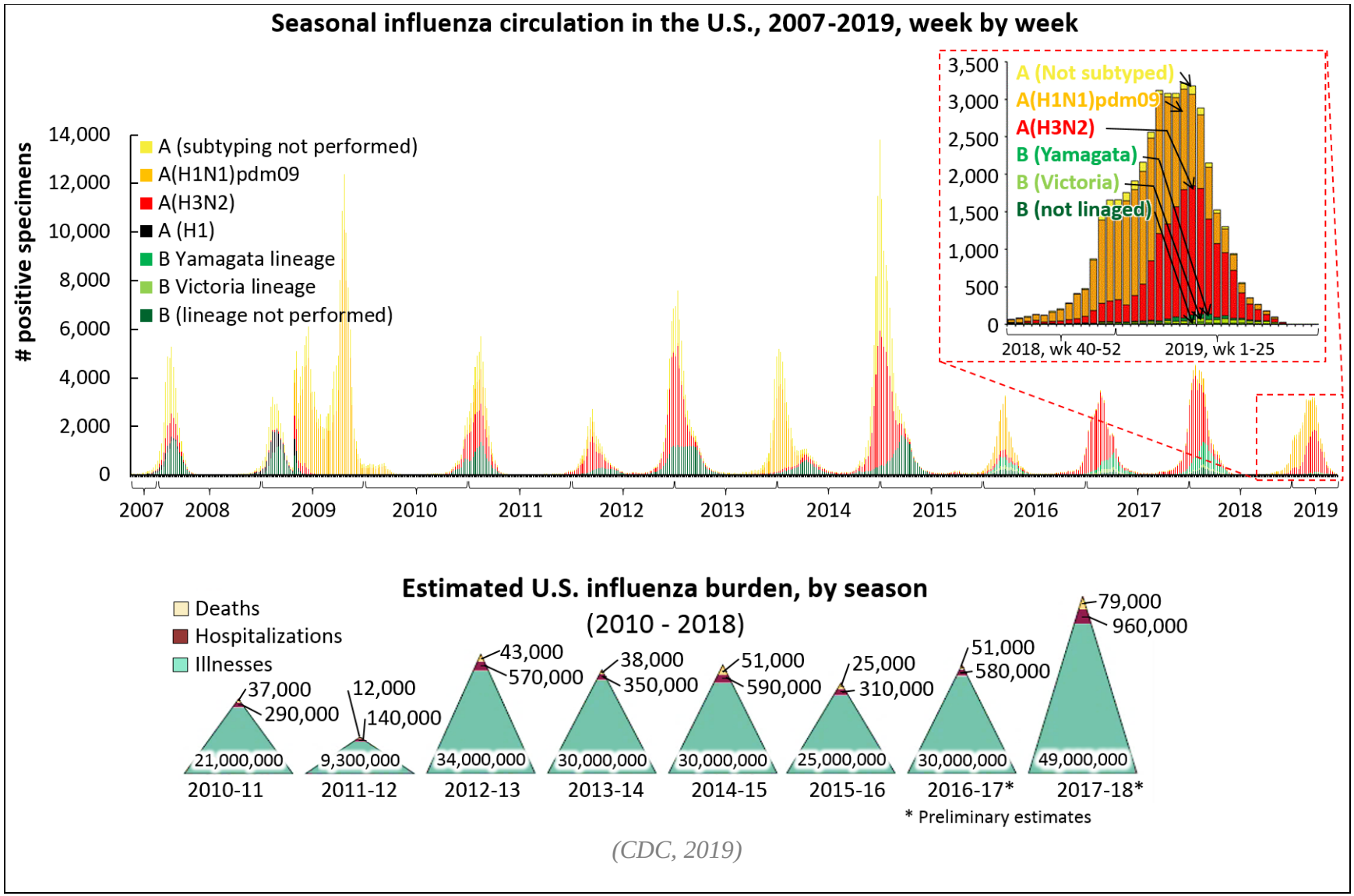


Figure 1. Influenza structure and annual global circulation from Asia to the rest of the world.



(CDC, 2019)

Figure 2. Seasonal influenza strain circulation and health burden in the United States.

MICROBIAL RISK ASSESSMENT APPROACHES

Different types of risk modeling approaches exist to characterize a risk of pathogen to spread, or a risk of human infection, illness or death. Risk techniques can be statistical or mechanistic, where the former is an induction approach driven by data statistics, while the later follow the deduction approach and results are more driven by how the model and pathway routes were constructed. Mechanistic models can be deterministic or stochastic, meaning parameters are defined with point values, or include probability distribution, respectively. Finally, risk models can brings solutions through analytical or numerical analysis. Analytical analysis relies on running some different equations that will bring a unique exact solution, while the numerical technique consists in iteratively running the model with equations that do not allow unique solutions, and testing at the same time if the problem can be solved, before stopping it when an optimized guessed solution is found.

Three main microbial risk assessments approaches are known for characterizing a risk of pathogen transmission or infection: the secondary transmission modeling, the risk matrix concept, and the Quantitative Microbial Risk Assessment (QMRA) approach (Collignon et al., 2016; EPA, 2014).

The secondary transmission modeling is based on a deterministic compartmental approach that use equations to describe population dynamics and estimate the risk of disease transmission between individuals (Eisenberg, Brookhart, Rice, Brown, & Colford, 2002; Keeling & Rohani, 2008; Kraay et al., 2018). This technique do not allow data gaps, is generally used for describing specific pathogen health issues, and cannot be used to estimate a risk of infection for a person.

The traditional risk matrix concept consists in scoring the likelihood and consequence of an event. This approach may rely almost exclusively on expert judgment to fill data gaps. The disadvantage of this method is that it provides only qualitative or semi-quantitative estimates, do not easily allow for inclusion of variability and uncertainty of input parameters and output risk estimates, and do not permit to fully reflect the whole pathogen infection pathway, as would do a mechanistic model.

Finally, the QMRA approach allows for risk characterization for a pathogen (Haas, Rose, & Gerba, 2014; WHO, 2016b), based on the exposure route and the dose-response model (Haas et al., 2014). It is widely used in industrial food safety and water quality, and has been used increasingly in occupational and hygiene risk assessments (Haas et al., 2014). Advantages of this approach is that it is mechanistic, conveniently permitting to identify each parameter for the full process of pathogen infection throughout all concerned environmental compartments. It also allows the model to be run deterministically (parameter defined with a simple point-value) or stochastically (parameter defined by a variable that follows a specific probabilistic distribution, allowing to reflect variability and uncertainty). A drawback of the QMRA approach is that it cannot includes data gaps: QMRA requires to recover from the literature a relevant value for each parameter. However, sometimes a research topic do not necessary have an estimate for all parameters. Fortunately, there are some ways to bypass this constraint: First, researchers can make a raw estimate of a parameter value by applying an important distribution to highlight the uncertainty on this parameter. Second, researchers can use a surrogate indicator by looking at parameters related to a similar pathogen. For instance, as SARS and MERS pathogens share structural similarities, some researchers used parameters related to the known SARS pathogen for modeling MERS or even influenza transmission (Otter et al., 2016).

THE PROBLEM

Influenza is known to be transmitted between humans through short distances, primarily by airborne droplet and contact routes (Brankston, Gitterman, Hirji, Lemieux, & Gardam, 2007; Nicas & Jones, 2009). The 2009 H1N1 pandemic reminded the world the important role hands and surfaces play in transmitting flu viruses (Goldmann, 2000). Since influenza A virus can survive several hours to up to 2 days on porous and non-porous surfaces (Bean et al., 1982; Greatorex et al., 2011), surface-to-hand following by hand-to-facial mucous contact appears to be a very probable event leading to flu transmission.

In this context, regularly cleaning hands and surfaces becomes a potential important mitigation solution for controlling flu transmission.

RESEARCH GAPS

To date, some studies investigated the impact of hand soaps on the reduction of influenza transmission. However, no study investigated the impact of antimicrobial sprays on the final risk reduction of infection from influenza.

RESEARCH OBJECTIVES

Knowing that influenza transmission is known to be mainly driven by short distances airborne droplet and contact routes (Brankston et al., 2007; Nicas & Jones, 2009), quantifying the impact of antimicrobial sprays used for cleaning various surfaces appear to be important, especially to study the effect on the virus removal from surfaces, and on the subsequent risk reduction of infection. This study is dedicated on addressing those two questions that were never investigated before.

CHAPTER 2 – LITERATURE REVIEW

A literature review was conducted to identify the viral pathogens that could be used as surrogates for the model, the conditions that lead to their survival on hard surfaces – named fomites, and previous work done to assess the risk posed to human health through indirect exposure from fomite contact.

INFLUENZA VIRUS CHARACTERISTIKS

The symptoms of flu are broad, consisting of sore throat, coughing, fever, headache, muscle aches, fatigue, diarrhea and vomiting (CDC, 2018). Influenza infections can result in relatively high morbidity and mortality rates, especially in sensitive subpopulations including children and the elderly (J. Rose, 2012). Three main types of influenza virus exist: A, B and C. Influenza C is less of a concern, since people infected with it acquire antibodies that provide immunity against this type for life. Both influenza types A and B constitute a higher threat, since people infected with a certain strain of type A or B viruses acquire immunity only to the particular strain. Furthermore, influenza A and B viruses regularly mutate to produce new strains; that can overcome the human immune system; and exhibit high infection rates during flu seasons. Comparatively, type B is fairly stable, but type A is highly unstable, and new strains of it arise constantly throughout the world (PhRMA Pharmaceutical Research and Manufacturers of America, 2013). The structure of influenza A viruses are complex and variable. As part of the virus family, Orthomyxoviridae, influenza viruses are enveloped viruses with segmented, negative-sense RNA genomes. Influenza A viruses vary by subtypes based on the antigenicity of the two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA) (see Figure 1).To date, influenza A viruses are divided into 18 HA and 9 NA subtypes, designated as H1-H18 and N1-N9 (Compans & Editors, n.d.). Viruses of the H5N1, H2N2, H3N2, and H1N2 subtypes have

circulated in humans over the past century. New subtypes such as H1N1 and H7N9 have emerged recently, in 2009 and 2013 respectively, being isolated from humans and poultry (*The U . S . Government & Global Emerging Infectious Disease Preparedness and Response*, 2014). Studies show that previous influenza pandemics, which occurred during the last century, especially H5, H7 and H9 avian influenza viruses, are serious candidates to cause the next human pandemics.

As with every respiratory virus, type A and B influenza viruses can be spread to humans through three modes of transmission. There is ongoing debate regarding which exposure route might be the most important, considering that different parameters may favor one or another route, such as the relative humidity, temperature, or level of indoor ventilation. Following concern about pandemic flu, research teams conducted a review of the literature on the transmission of influenza A in humans and concluded that influenza transmission mostly occurs over short distances and primarily by droplet and contact routes (Brankston et al., 2007; Nicas & Jones, 2009). Since the 2009 H1N1 pandemic, there is a real awareness that hands and surfaces may also be a transmission route for flu viruses (Goldmann, 2000). This transmission route appear to be plausible, since influenza A virus can survive several hours up to 2 days on porous and non-porous surfaces (Bean et al., 1982; Greatorex et al., 2011), making hand-to-surface contact a highly probable event leading to self-inoculation and infection through hand-to-face contact. Though the dose-response model was highly uncertain in their work, Nicas and Jones (Nicas & Jones, 2009) reported that of four exposure pathways studied, the virus-contaminated hand contact with facial membranes - eyes, nostrils, and lips mucosa – contributed substantially to influenza infection risk , with up to 93% when infectivity of the viruses contacting the mucus membranes is 1 to 1.

SURFACES AS A VECTOR OF INFLUENZA VIRUS TRANSMISSION

Generally, influenza virus can be spread through direct and indirect routes (see Figure 3). Two direct transmission routes exist: the first one, where an infected person shedding viruses directly expel viruses onto the facial membranes (eyes, nostrils, lips) of a susceptible individual; and the second one where the susceptible person get into physical contact with the infectious individual, such as by kissing him. Regarding the indirect route, two sub-routes can be defined: first, the case where the infected person expel some infectious droplets on his hands, then touch someone's hands, before this later susceptible individual self-inoculate himself by touching his facial membranes; second, where the infectious person shed infectious droplets on surrounding surfaces through coughing and sneezing (surfaces are here also named "fomites"), after what a susceptible individual comes in, touch the contaminated surfaces, and self-inoculate himself by touching his facial membranes. The final scenario may occur frequently in indoor environments where infected individuals are cared for, such as households and hospitals.

Indirect fomite transmission route is frequently considered to be an important transmission pathway, with several studies having previously reported the significance of fomite and facial touching frequency in influenza modeling (Jones, 2011; Li et al., 2009; Nicas & Jones, 2009). Influenza A virus has been isolated on multiple fomites - including common contact surfaces in houses, schools, day care centers and work places, reinforcing the indirect exposure route via fomite can play an important role in influenza spread and transmission (Boone & Gerba, 2005; Bright, Boone, & Gerba, 2010). Fomites are divided into 2 groups: nonporous fomites such as stainless steel, glass, plastic; and porous fomites such as cotton, paper, tissues, and clothes.

Poor hygiene is considered to be a factor in the transmission of community-based infections, including respiratory infections such as influenza (Bloomfield, Cookson, Falkiner,

Griffith, & Cleary, 2007). Indirect contact can largely be mitigated by effective hand washing/hand hygiene practices. However, interruption of the chain of transmission involving indirect contact via surfaces is the focus of a combination of both hand hygiene and surface sanitation. The Procter & Gamble Company develops multiple antimicrobial products sold all over the world to millions of people (Procter & Gamble Company, n.d.). Some of these products are used to enhance hygiene practices and reduce the transmission of infectious agents by inactivation of pathogens on treated surfaces. One of these products, an antimicrobial spray product for treating porous and non-porous surfaces is the subject of this study.

QMRA ON VIRUSES TRANSMISSION FROM FOMITE

In order to quantitatively estimate a human health risk associated with a specific pathogen, the QMRA approaches requires to follow four steps: (1) hazard characterization, consisting of data collection to understand the characteristics of the pathogen and host that lead to proliferation, transmission and adverse health outcomes; (2) exposure assessment, consisting of measurements and/or models of pathogen release, transport, attenuation and human exposure to quantify the magnitude of an exposure dose; (3) health effects assessment or dose-response, consisting of determining the mathematical relationship between a given exposure dose and risk of infection, illness or death; and (4) risk characterization, consisting of the calculation of risks using the quantified exposure dose and dose-response relationship along with a description of variability and uncertainty. When enough data are available, statistical modeling techniques like Monte Carlo analysis can be used to describe the variability and/or uncertainty in the input data and parameter estimates and propagate this uncertainty through the risk model to the final risk characterization

output. A number of logical and scientifically based assumptions are also often required and justified.

The remainder of this study describes the process followed to estimate the risks associated with contact with porous surfaces and to determine the risk reduction associated with using an antimicrobial spray product. Figure 3 & 5 summarizes the steps followed in the analysis for characterizing the risk with and without use of the antimicrobial spray. Many input factors are recognized to influence the transmission of influenza, and subsequently the risk of infection (Jones, 2011). Table 2 summarizes all input variables considered in this study and the intermediate calculations required to obtain the output risk distributions.

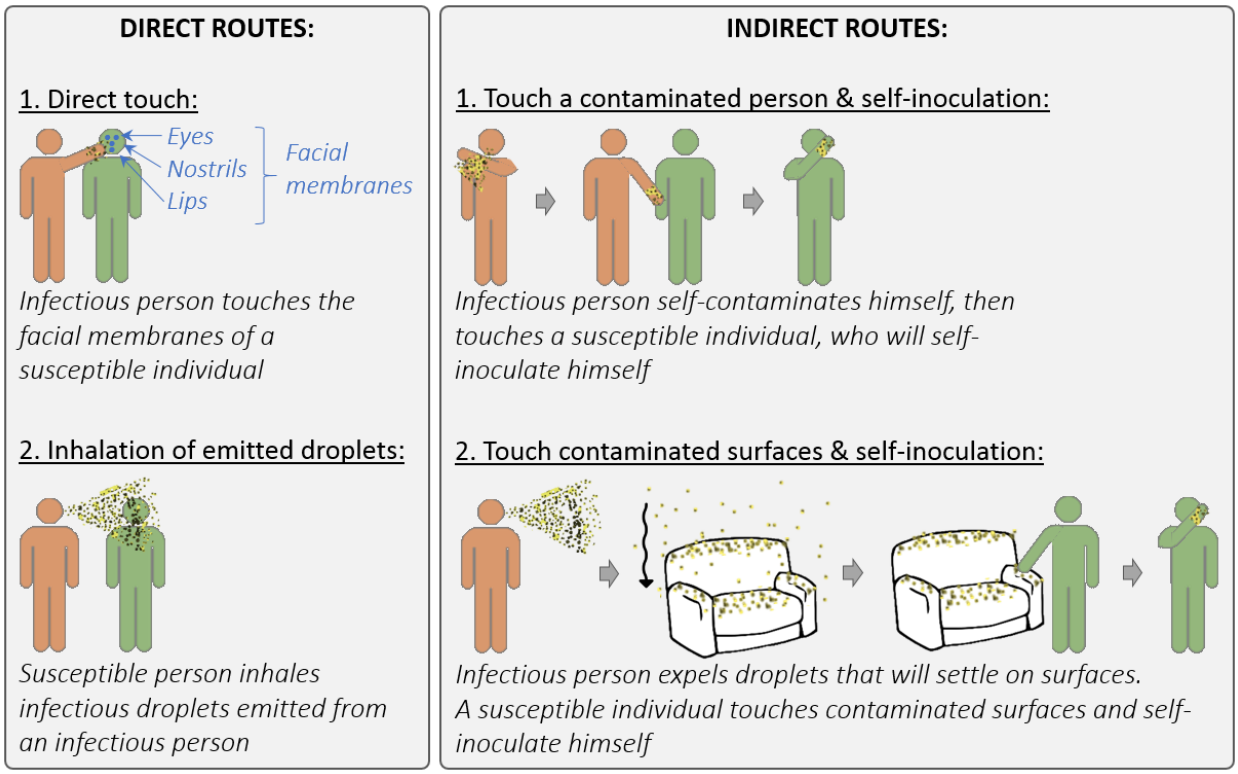


Figure 3. Indirect exposure route through contaminated fomite followed by self-inoculation.

CHAPTER 3 – RISK OF INFLUENZA INFECTION THROUGH CONTACT WITH CONTAMINATED SURFACE

METHODS

Laboratory experimental data

As shown in Figure 4, the laboratory experimental data are produced after following a defined protocol. First, a viral inoculum was prepared containing approximately 1 x10^9 $TCID_{50}$/ml with 5% of Fetal Bovine Serum (FBS).

The fabric carrier preparation consisted of the use of a 100% plain cotton fabric sourced from Japan Textile Evaluation Technology Council, cut into several pieces of 35 mm x 35 mm size squares. Each carrier was placed into a glass Petri dish, which contains a filter paper in the bottom to absorb any excess moisture during/after the following autoclaving step. Each Petri dish containing one carrier was sterilized by autoclaving (121°C for 15 minutes). The sterilized carriers were cooled at room temperature, dried completely (in a safety bench when needed), and stored at room temperature until use.

The carriers were inoculated in sets of five (five for each product treatment and five for a Phosphate Buffer Saline (PBS) negative control). A 50 µl aliquot of the prepared inoculum was transferred to the sterile carrier in the Petri dish using a micropipette. If necessary, sterile forceps were used to hold the carrier in place during the inoculation. The liquid aliquot was slowly and gently dispensed with the pipette tip.

The product treatments on the test carriers was done directly after the carrier was inoculated. Each carrier was treated with either the antimicrobial spray product according to the product usage instructions, or with the PBS control spray. The manufactured spray product

contains hydroxypropyl beta-cyclodextrin as the active compound. The sprayer nozzle was held toward the center of the carrier. The Petri dish containing the carrier remained flat on the lab bench surface. Trigger strokes was done firmly and completely.

After spraying, the body and edges of the carrier was kept flat against the bottom of the Petri dish. Each carrier was then held for a 20 minute exposure time at room temperature in an open Petri dish prior to being neutralized.

The carrier was aseptically transferred to a tube containing 20 ml neutralizer Soybean Casein Digest broth with Lecithin and Polyoxyethylene sorbitan monooleate (SCDLP). SCDLP neutralizing efficacy was validated. The neutralizer tube containing the carrier was vortexed 30 seconds. 0.1 ml of the extracted solution was subjected to subsequent viral titration by conducting appropriate dilutions of the extracted solutions via $TCID_{50}$ method. A test validation criterion was set by using the control fabric treated with PBS. If 1×10^4 $TCID_{50}$ or more were not recovered from the control, the test was considered void.

The 20 minutes air drying time for the product prior to neutralization and recovery was selected according to a Procter & Gamble internal survey (data not shown) and based on product labeling, which revealed that consumers are expected to wait about one hour after applying the spray on a fabric. Therefore, contact with treated fabric is likely to occur only after a drying time of at least one hour. In reality, an infected person may continue shedding viruses by coughing or sneezing and touching the fabric during the one hour or immediately following it so 20 minutes provides an average amount of treatment.

Data analysis was conducted on the five replicates reported in three experimental trials to determine an average $\log_{10}$ reduction for each experiment and an overall average (see Table 1).

Log_{10}-reductions were potentially underestimated (a conservative assumption), because they were calculated using the detection limit of 2.3 log_{10} from the laboratory method as a result of non-detects for each trial. Since each carrier was transferred to 20 ml neutralizer for extraction, and 0.1 ml of the extracted solution was subjected to subsequent viral titration, the detection limit was determined based on the ability to measure one remaining infectious viral particle on one carrier, PFU/carrier, which is equivalent to 1 PFU x 20 (ml)/0.1 (ml) = 200 PFU, or 2.3 log_{10} PFU/carrier.

On average for all three trials, the initial viral concentration applied was 6.93 log_{10} PFU/carrier (see Table 1) and on average the final viral concentration detected after PBS control treatment was 5.93 log_{10} PFU/carrier. Thus, the recovery percentage of the method is approximately equal to 5.93/6.93 = 85.6%. The remaining 14.4% may be due to irreversible binding. If the same percentage of recovery occurs with the product treatment, the final reported viral recovery would then only reflect the virus removal effect of the whole product. However, it is not necessary to distinguish between inactivation and irreversible binding when calculating risk associated with fomite contact as both phenomenon prevent exposure.

Based on the private nonprofit biological resource center American Type Culture Collection (ATCC American Type Culture Collection, 2012), conversions between PFU/ml and $TCID_{50}$/ml metric used in subsequent exposure dose calculations can be made by multiplying the $TCID_{50}$ titer by 0.7 to predict the mean number of PFU.

The described steps of the laboratory experimental protocol are illustrated in Figure 4. Results of viral concentration and log_{10} reduction are shown in Table 1.

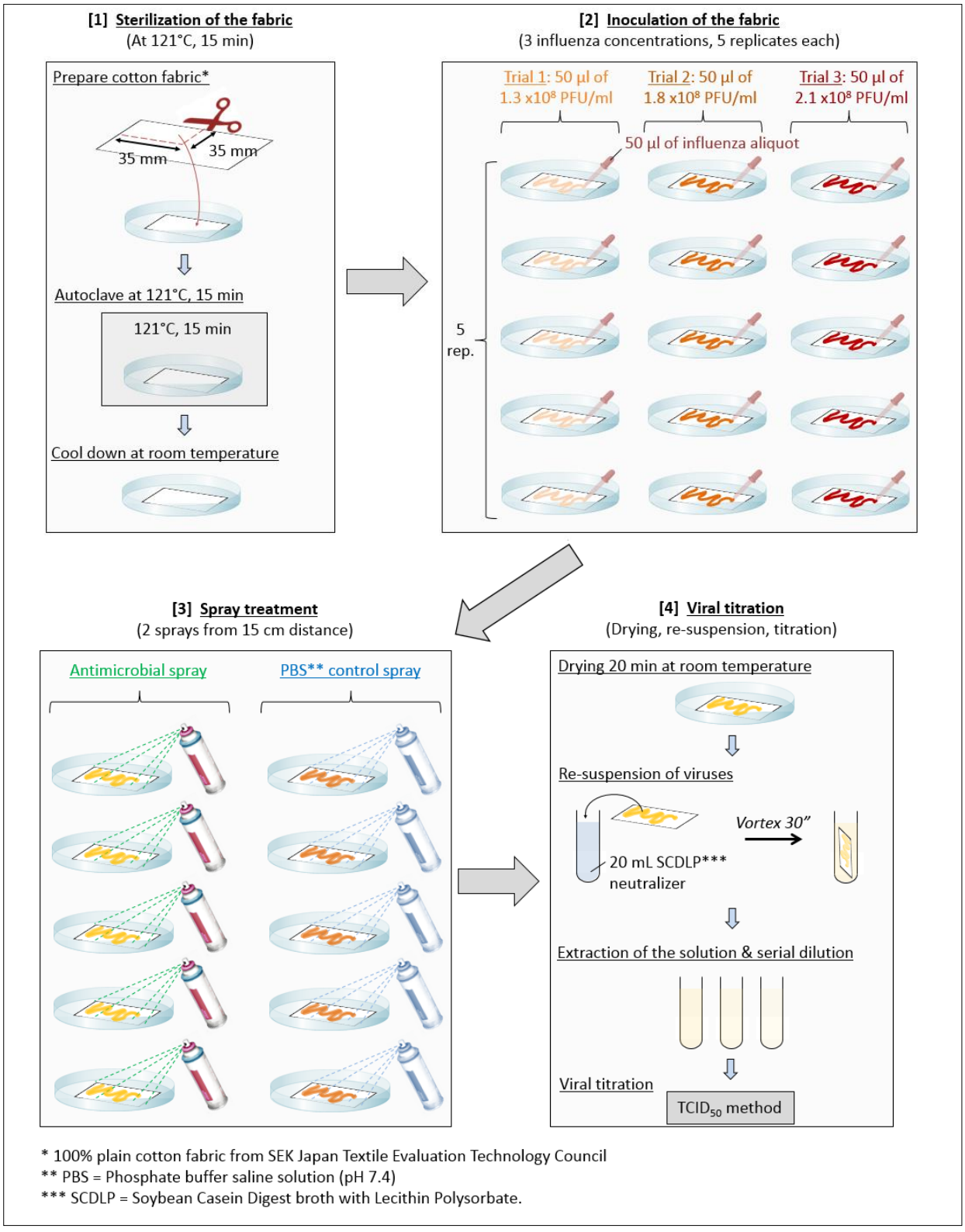


Figure 4. Laboratory tests to assess the removal of influenza viruses from cotton fabric, after the application of an antimicrobial spray on the surface.

Table 1. Raw data of virus removal from surface after antimicrobial spray treatment*

	Final concentration w/ PBS** (log_{10} PFU/carrier)	**Final concentration w/ spray product application** (log_{10} PFU/carrier)	**Reduction** (log_{10} PFU/carrier**)**
Trial 1: Initial amount applied – 50 µl of 1.3 x 10^8 PFU/ml = 6.81 log_{10} (PFU/carrier)			
	5.76	<2.30	3.46
	5.52	<2.30	3.22
	5.46	<2.30	3.16
	5.71	<2.30	3.41
	5.57	<2.30	3.27
Mean (log_{10} PFU/carrier)	**5.60**	**2.30**	**3.30**
Trial 2: Initial amount applied - 50µl of 1.8 x 10^8 PFU/ml = 6.95 log_{10} (PFU/carrier)			
	5.94	<2.30	3.64
	5.85	<2.30	3.55
	5.82	<2.30	3.52
	5.80	<2.30	3.50
	5.91	<2.30	3.61
Mean (log_{10} PFU/carrier)	**5.86**	**2.30**	**3.56**
Trial 3: Initial amount applied - 50µl of 2.1 x 10^8 PFU/ml = 7.02 log_{10} (PFU/carrier)			
	6.32	<2.30	4.02
	6.28	<2.30	3.98
	6.30	<2.30	4.00
	6.46	<2.30	4.16
	6.23	<2.30	3.93
Mean (log_{10} PFU/carrier)	**6.32**	**2.30**	**4.02**
Overall average	**5.93**	**2.30**	**3.63**

* Data provided from Procter & Gamble company.

** PBS: Phosphate Buffer Saline solution, containing no antimicrobial agent (negative control).

Exposure assessment

In this study, a non-dynamic model was built based on a single surface touch directly followed by self-inoculation through a single facial membrane touch (eyes, nostrils and lips). This base case scenario did not consider any viral decay on the surface (unless by the antimicrobial spray) or on the skin as further described. The observed average coughing rate of 105 times per hour (Jones, 2011) for persons with respiratory infection led to the assumption that the surface would be continuously contaminated with influenza A, justifying the omission of viral decay on surface. Several studies reported survival of viruses on the skin surface in units of time (Ansari, 1991; Bean et al., 1982; Grayson et al., 2009; Schurmann & Eggers, 1983). In order to account for the independency between the decay and the initial inoculum concentration in these studies, a series of linear models were developed from the published data for influenza A skin survival in order to calculate decay rates on skin. Based on these models an average survival time on the skin was determined to be 11.25 minutes. Since facial touches can occur as frequently as 2.5 times every 10 minutes (Hendley, Wenzel, & Gwaltney, 1973; Kwok, Gralton, & McLaws, 2015; Nicas & Best, 2008; Nicas & Jones, 2009), self-inoculation could reasonably happen before total viral decay on skin, thus providing justification for neglecting viral decay on the skin. Furthermore, a conservative worst-case scenario, would involve a plausible face touch occurring directly after a surface touch.

In addition to the generalizable model based on a single touch described above, simulations were evaluated for more realistic scenarios over extended periods of exposure time. Nicas and Jones (Nicas & Jones, 2009) analyzed a scenario using a Markov chain to describe the contamination of several fomites in a residential bedroom with a bed-ridden infected individual in which a susceptible person visits the infector for a period of 15 minutes. It has also been reported

that the exposure duration of visitors of patients in a hospital room can vary from 1 to 124 minutes, with a median exposure time of 14 minutes (Cohen, Hyman, Rosenberg, & Larson, 2012). The consideration of longer exposure durations results in multiple surface and facial contacts, where previously published rates for coughing/sneezing, surface and facial touches were applied (Nicas & Best, 2008; Nicas & Jones, 2009). Hence, considered frequencies were 12 coughs/hr (Loudon & Brown, 1967a), one surface touch/min (Nicas & Jones, 2009), and 2.5 face touches/min (Hendley et al., 1973; Kwok et al., 2015; Nicas & Best, 2008; Nicas & Jones, 2009). An additional duration of 30 minutes was also evaluated to determine whether the linearity of the process would always result in predictable risks within the low dose likely region of the dose-response curve.

The single touch, linear base case model was designed to be easily expandable to additional scenarios, by equations 1 and 2:

$$N_{Face,Spray-} = N_{Coughs/min} * t * V_{Saliva/event} * C_{Saliva} * F_{Air \rightarrow Surf.} * N_{Surf.\ touch/min} * F_{Surf \rightarrow Finger} * A_{Finger/fabric} * N_{Face\ touch/min} * F_{Finger \rightarrow Face} \quad (1)$$

$$N_{Face,Spray+} = N_{Coughs/min} * t * V_{Saliva/event} * C_{Saliva} * F_{Air \rightarrow Surf.} * F_{Red} * N_{Surf.\ touch/min} * F_{Surf \rightarrow Finger} * A_{Finger/fabric} * N_{Face\ touch/min} * F_{Finger \rightarrow Face} \quad (2)$$

where $N_{Face,Spray+}$ represents the viral exposure dose on facial membranes, with antimicrobial spray surface treatment, $N_{Face/spray-}$ is the exposure dose without treatment, $N_{Coughs/min}$ represents the frequency of coughing per minute, t represents the exposure time in minutes, $V_{Saliva/event}$ represents the volume of saliva expelled per cough or sneeze in ml, by an infected person, C_{Saliva} represents the concentration of influenza A in the saliva in $TCID_{50}$/ml, $F_{Air \rightarrow Surf.}$ represents the fraction of emitted droplets by cough or sneeze settling on the surface as a percent, F_{Red} represents the viral reduction on the surface induced by the use of antimicrobial spray as a percent, $N_{Surf.\ touch/min}$

represents the number of surface touches occurring per minute, $F_{Surf \rightarrow Finger}$ represents the surface-to-fingertip viral transfer efficiency in percent, $A_{Finger/fabric}$ represents the ratio of area (in cm^2) between one fingertip and the piece of porous fabric touched, $N_{Face\ touch/min}$ represents the facial membrane touch frequency per minute, and $F_{Finger \rightarrow Face}$ represents the finger-to-facial membrane viral transfer efficiency as a percent.

The literature suggests the volume of saliva expelled per cough or sneeze could be different (Duguid, 1946; Loudon & Roberts, 1966; Nicas & Jones, 2009; Papineni & Rosenthal, 1997). If a mean volume (V_{Saliva}) for coughs was calculated by multiplying the average droplet diameter, by the average number of droplets expelled per cough with respect to the droplet size distribution, a total saliva volume expelled per cough of 0.0065 ml would result. However, a higher mean volume of saliva expelled per cough was reported to be 0.044 ml (Nicas & Jones, 2009) so, the later larger volume for coughs was used to produce the most conservative estimates. For the volume of saliva expelled during a sneeze, a volume of 0.44 ml was used. This value was also previously used in the Nicas and Jones model (Nicas & Jones, 2009). The combination of three exposure times and two volumes of saliva expelled for coughing or sneezing events led to six different simulations.

The six possible scenarios evaluated can be described as below:

- (1) and (2): An instantaneous exposure with one cough or one sneeze, corresponding to an expelled volume of 0.044 or 0.44 ml (Nicas & Jones, 2009), followed by a direct surface and face touch (base scenario);
- (3) and (4): A 15 min exposure duration resulting in 3 coughs of 0.044 ml each or 3 sneezes of 0.44 ml each, 15 surface touches and 3.75 face touches;
- (5) and (6): A 30 min exposure period with 6 coughs of 0.044 mL each or 6 sneezes of 0.44 ml each, 30 surface touches and 3.75 face touches;

Pathogens are generally not uniformly distributed on surfaces but instead accumulate in clusters at different points. In this study, it was generally assumed that it is possible for a person touching an inoculated surface with his finger to collect all viruses from this surface. However, a distribution describing fingertip area was used to simulate both the human-to-human variability of finger size and variability in the spatial distribution of viruses on the surface, which was not formally considered.

The exposure dose calculations from source to outcome follow the flow described in Figure 3 & 5. Initially, the amount of viruses expected to be on the fabric surface was calculated. Then, a transfer rate was applied to calculate the number of viruses transferred from the surface to the fingers after contact with the infected surface. Finally, a transfer rate from hand to mucus membrane was applied to calculate the exposure dose to the receptor. These calculations were done with and without surface treatment for comparison.

Dose-response assessment

Mathematical functions for linking exposure dose from a particular exposure route to the likelihood of an adverse health outcome can be found from the literature or directly calculated from experiments. For this study, three beta-Poisson dose-response models were available on the QMRA Wiki (Huang, 2013), based on the raw data of three studies (Fan et al., 2009; B. Murphy et al., 1984, 1985). The general parameterization of the approximate beta-Poisson model is described in Equation 3:

$$P(d) = 1 - \left[1 + d * \frac{(2^{1/\alpha} - 1)}{N_{50}}\right]^{-\alpha} \quad (3)$$

where d is the exposure dose; α is a shape parameter with no biological meaning; N_{50} is the exposure dose at which 50% of the population is expected to have a positive response; and $P(d)$ is the probability or risk of infection.

Of the three models available for influenza on the QMRA Wiki, two models are based on influenza A attenuated strains that were administered to healthy human volunteers through the intranasal route. The third model was instead based on analysis on mice. Furthermore, each of the two human-based models specifically focused on the risk of infection, while the third dose-response model were constructed from a risk of death. In consequence, the fitting of the dose-response model were developed based on the two first listed models in the QMRA Wiki, focusing on the following specific strains: H1N1 A/California/10/78 attenuated strain and H3N2 A/Washington/897/80 attenuated strain (Fan et al., 2009; B. Murphy et al., 1985). The recommended model derived from those two studies has been defined as a beta-Poisson model, with a maximum likelihood estimates (MLE) of 9.45×10^5 and 0.58 for N_{50} and α dose-response parameters, respectively. In order to incorporate the uncertainty in the dose-response model, which can be attributed to inherent variability among hosts, strains or isolates, as well as uncertainty associated with extrapolation to the current scenario, a triangular distribution was defined for both parameters using the values representing the 5^{th}, MLE, and 95^{th} percentiles. For the α parameter, the 5^{th} and 95^{th} percentile values are equal to 0.424 and 0.915, respectively. For the N_{50} parameter, the 5^{th} and 95^{th} percentile values are 5.72×10^5 and 1.62×10^6, respectively.

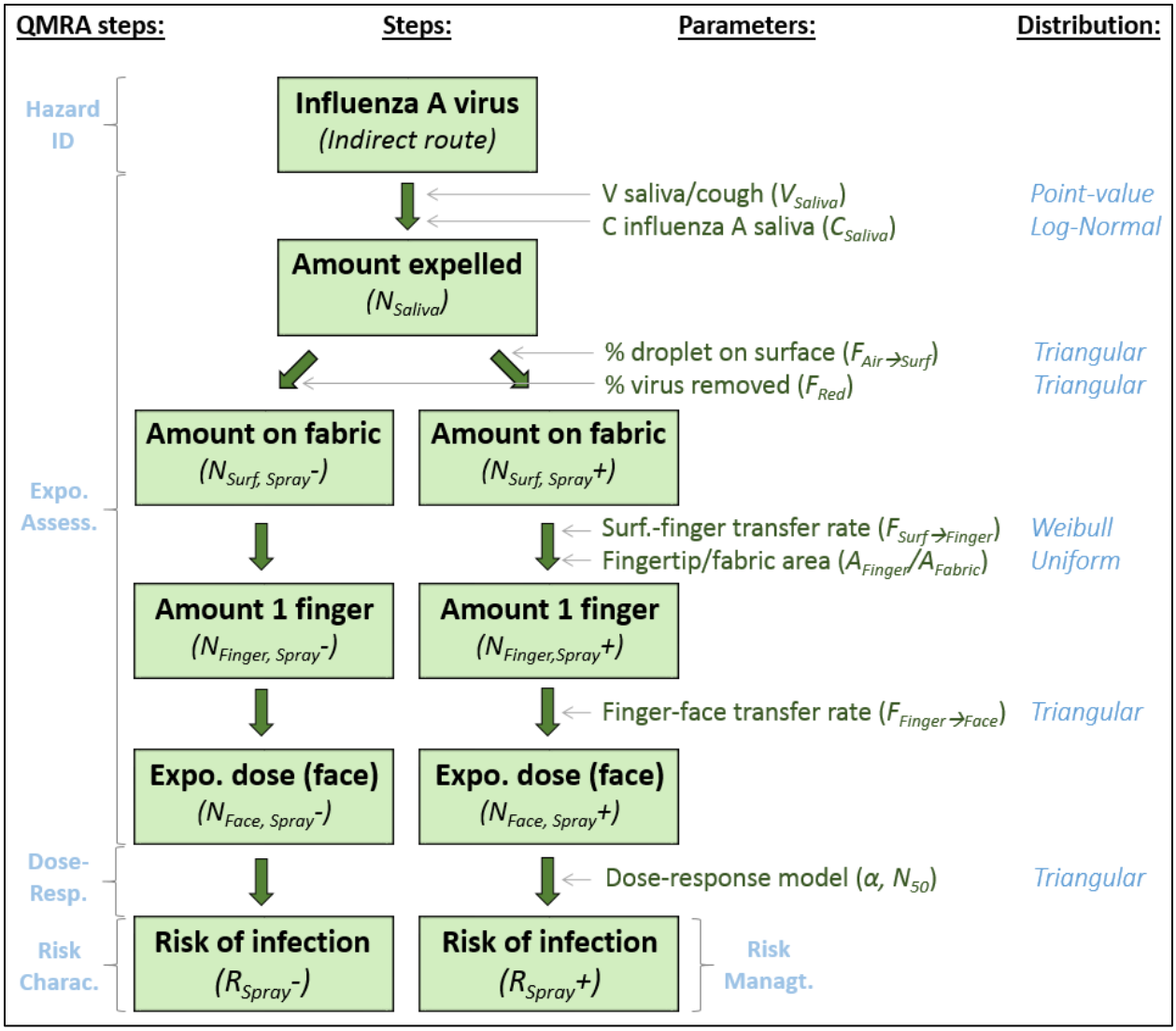


Figure 5. Top-down flowchart summarizing the QMRA approach used for the base model.

Table 2. Summary of the parameters and intermediate calculations

Parameters	Description	Central tendency [Unit]	Distribution for the model	Comments and sources
$V_{Saliva/event}$	Volume of saliva expelled per cough or sneeze.	0.044 or 0.44 [ml]	Point value	Highest volume (Nicas, Nazaroff, & Hubbard, 2005) taken from literature (Duguid, 1946; Loudon & Roberts, 1966; Nicas et al., 2005; Papineni & Rosenthal, 1997).
C_{Saliva}	Concentration of influenza A in saliva, from an infected person (median value of distribution).	9.30×10^6 [$TCID_{50}$/ml]	Log-Normal	Median value, based on 6 values taken from 3 studies (Mukherjee et al., 2012; B. R. Murphy, Chalhub, Nusinoff, Kasel, & Chanock, 1973; Nicas & Jones, 2009). Log-normal distribution has been applied in the model.
N_{Saliva}	Amount of influenza A viruses in saliva expelled during a cough or sneeze. (median value).	4.09×10^5 [$TCID_{50}$]	Calculated	Calculation: $N_{Saliva} = V_{Saliva} * C_{Saliva}$
$F_{Air \rightarrow Surf.}$	Fraction of expelled droplets from cough and sneeze, depositing on surfaces (median value).	75.4 [%]	Triangular	Based on 2 studies (Nicas & Jones, 2009; Rusin, Maxwell, & Gerba, 2002)proposing 100% and 51% respectively. Use of a triangular distribution for the model.
F_{Red}	Fraction of influenza reduction on fabric, due to the use of antimicrobial spray (median value).	99.9725 [%]	Triangular	Based on Procter & Gamble: 3 analyses, 5 replicates each (= 15 values), after applying a triangular distribution. See Figure 4.
$N_{Surf,Spray-}$ $N_{Surf,Spray+}$	Amount of influenza A on fabric without and with spray surface treatment (median values).	3.07×10^5 ; 88.61 [$TCID_{50}$/fabric]	Calculated	Calculation: $N_{Surf,Spray-} = V_{Saliva} * C_{Saliva} * F_{Air \rightarrow Surf}$ Calculation: $N_{Surf,Spray+} = N_{Surf,Spray-} * F_{red}$
$F_{Surf. \rightarrow Finger}$	Surface-to-finger transfer efficiency (median value of raw data).	0.436% [%]	Weibull	Based on 10 values from influenza A, PRD-1 phage and MS2 coliphage (Bean et al., 1982; Lopez et al., 2013; Rusin et al., 2002), with fitted Weibull distribution.
A_{Finger}	Fingertip area distribution (median value of distributed data).	4.58 [cm^2]	Uniform	Based on 8 values taken from 4 studies (Murai, Lau, Pereira, & Pho, 1997; Nicas & Jones, 2009; Peters, Hackeman, & Goldreich, 2009; J. B. Rose, Gurian, Haas, Weir, & Eisenberg, 2013). A uniform distribution has been applied for the model.
A_{Fabric}	Area of the porous fabric tested in laboratory.	12.25 [cm^2]	Point value	Surface area of the porous surface tested in laboratory (3.5 * 3.5 cm^2 100% cotton fabric).
$N_{Finger,Spray-}$ $N_{Finger,Spray+}$	Amount of influenza A on one fingertip, without and with spray surface treatment (median).	555 ; 0.16 [$TCID_{50}$/fingertip]	Calculated	Calculation: $N_{Finger,Spray-} = N_{Surf,Spray-} * F_{Surf \rightarrow Finger} * A_{Finger}/A_{Fabric}$ Calculation: $N_{Finger,Spray+} = N_{Surf,Spray+} * F_{Surf \rightarrow Finger} * A_{Finger}/A_{Fabric}$
$F_{Finger \rightarrow Face}$	Finger-to-facial membrane transfer efficiency (median value of raw data).	19.74 [%]	Triangular	Based on 2 values from 2 studies (Jones, 2011; Rusin et al., 2002). A triangular distribution has been applied.
$N_{Face,Spray-}$ $N_{Face,Spray+}$	Exposure dose, without and with antimicrobial spray surface treatment (median values).	106 ; 0.03 [$TCID_{50}$]	Calculated	Calculation: $N_{S1,Face,Spray-} = N_{Finger,Spray-} * F_{Finger \rightarrow Face}$ Calculation: $N_{S1\text{-}Face,Spray+} = N_{Finger/Spray+} * F_{Finger \rightarrow Face}$
α	Dose-Response parameter - Pathogen survival probability (median value).	0.655 [-]	Triangular	Value from the QMRA Wiki webpage (Huang, 2013), based on 2 studies (B. Murphy et al., 1984, 1985), with triangular distribution applied for the model, from 5th, median to 95th percentiles (median values of distributed data shown here). See Eq. 3.
N_{50}	Dose-Response parameter - Dose at which 50% of the population is expected to be affected.	1.07×10^6 [-]	Triangular	

Risk characterization

A Monte Carlo analysis was conducted, using the Crystal Ball® program (Oracle, Redwood Shores, CA). The number of simulation runs for each model scenario was 100,000 as this exceeds the number of recommended trials to obtain sufficient accuracy in contribution to variance in the sensitivity analysis (Haas et al., 2014; Oracle Company, 2013). In order to generate reproducible results, a random seed was set requiring the software to use the same sequence of random numbers generated for each scenario tested. The Monte Carlo analysis incorporated probability distributions for each uncertain input parameter listed in Figure 5. Table 2 provides a description of the input parameters; the treatment of variability and/or uncertainty through the assumption of a probability distribution (i.e. uniform, triangular, Weibull, and log-normal) when appropriate given the available data; and the sources of information/data. A minimum number of data points for each input parameter are required to fit a probability distribution function. In most cases, this minimum threshold was not met.

Table 2 also provides a list of the intermediate calculations leading to the risk characterization. Propagation of the uncertainty and variability in the input parameters to the output parameters lead to a final distribution of the risk for the scenarios evaluated. The lower bound (5^{th} percentile), median (50^{th} percentile) and upper bound (95^{th} percentile) of the risk estimates were used to summarize the risk distributions.

In Appendix, details of data recovered from the literature review are shown for each input parameter.

RESULTS

Calculation of surface, finger and facial (exposure) doses

A triangular distribution was developed to describe the product viral reduction data ranging from 99.95% to 99.99% (Table 2). These observed reduction values are consistent with other reductions reported after household sanitation (Sexton, 2013; Tamimi, Carlino, Edmonds, & Gerba, 2014; Tamimi, Edmonds-Wilson, & Gerba, 2015). The risks reported below should be interpreted as "less than" the values calculated because after treatment, all samples were negative and reductions were based on the detection limit.

Based on three relevant studies (Mukherjee et al., 2012; B. R. Murphy et al., 1973; Nicas & Jones, 2009), six values of influenza viral concentration in saliva (C_{Saliva}) were found. Influenza A viral concentrations in saliva can naturally be different from person to person for two reasons: (1) the stage of infection in which the infected person falls (e.g. incubation, prodromal, illness and convalescence stages), which lead to different rates of virus production; and (2) the inherent person-to-person variability in production of viruses at similar infection stages. According to the concentration distribution observed from the data reviewed, a log-normal distribution was used to emphasize the higher probability of encountering lower concentration values than higher ones. The parameter values set for the log-normal distribution of the concentration in saliva were the location, the median and the 95th percentile of the raw data concentrations, which were respectively equal to 600, 1.11 x10^{7} and 2.45 x10^{8} $TCID_{50}$/ml. The derived median influenza A dose in saliva was determined to be 9.30 x10^{6} $TCID_{50}$.

Based on two studies (Loudon & Brown, 1967b; Nicas & Jones, 2009), an average fraction of droplets ($F_{Air \rightarrow Surface}$) from coughs and sneezes depositing on surfaces was estimated to be

75.5%. A triangular distribution was used based on the minimum, maximum and mean values extracted from the literature.

The amount of influenza on the surface was calculated with and without application of the antimicrobial spray, using following equations 4 and 5.

$$N_{Surf,Spray-} = V_{Saliva} * C_{Saliva} * F_{Air \rightarrow Surf} \quad (4)$$

$$N_{Surf,Spray+} = N_{Surf,Spray-} * F_{Red} \quad (5)$$

The median calculated values for the influenza dose on the treated fabric was 88.61 and 3.07 x10^5 $TCID_{50}$/fabric for the untreated fabric.

Based on ten surface-to-finger transfer efficiency values ($F_{Surf \rightarrow Finger}$) found in the literature for influenza A viruses, and surrogate pathogens PRD-1 phage and MS2 coliphage (Bean et al., 1982; Lopez et al., 2013; Rusin et al., 2002), transfer ranged from 0.0005 to 2.3%. Fitdistrplus package (Delignette-muller & Dutang, 2015) from R v3.5.3 software (R Foundation for Statistical Computing, 2013) was used, to find out the distribution that will best fit the data, by using the maximum likelihood estimation method. The best-fit distribution found was a Weibull distribution, with location, scale and shape being equal to 0.002755, 0.003109 and 0.553901, respectively.

Based on eight values from four studies (Murai et al., 1997; Nicas & Jones, 2009; Peters et al., 2009; J. B. Rose et al., 2013), reported fingertip area (A_{Finger}) was found to range from 2 to 7.16 cm^2 with a median of 4.87 cm^2. The studies reviewed only focused on adult fingertips area, and adults are likely in care giving roles versus children. A uniform distribution was defined for this input parameter.

The amount of influenza viruses on the hand after touching the porous surface was calculated with and without application of the antimicrobial on the surface using the following equations:

$$N_{Finger,Spray-} = N_{Surf,Spray-} * F_{Surf \rightarrow Finger} * A_{Finger}/A_{Fabric} \quad (6)$$

$$N_{Finger,Spray+} = N_{Surf,Spray+} * F_{Surf \rightarrow Finger} * A_{Finger}/A_{Fabric} \quad (7)$$

The median dose of influenza on the fingertip, with treatment was 1.62×10^{-1} and without antimicrobial spray, was determined to be 555 $TCID_{50}$/fingertip. Distributions of these parameters are shown in Figure 6 (Boxplots C).

An estimation of the finger-to-facial membrane (eyes, nostrils and lips) transfer efficiency for influenza ($F_{Finger \rightarrow Face}$) was done based on two values from two studies (Jones, 2011; Rusin et al., 2002). Since very little information is reported in the literature regarding this parameter, a triangular distribution was set. The median was defined as 19.745%.

The facial mucus membranes are the points of entrance of viruses into the human body. With the following equations, the dose of influenza virus entering the facial membranes was calculated with surface treatment (Equation 1) and without surface treatment (Equation 2).

The calculated median exposure doses of influenza for a treated or an untreated surface were respectively equal to 3.07×10^{-2} and 1.06×10^{2} $TCID_{50}$. As stated earlier, the above exposure dose calculation is attributable to an indirect exposure through contact of contaminated surface followed by a self-inoculation. It does not represent the total magnitude of an exposure for a susceptible person in close proximity to an ill individual.

Figure 6 shows all the influenza A dose calculations across each step in the exposure pathway: in saliva (Boxplot A), on fabric (Boxplot B), on one fingertip (Boxplot C) and on the facial membranes mouth, lips and nostrils (Boxplot D). Figure 7 shows the exposure doses over time (0, 15 and 30 min), when sneezing or coughing with or without surface pre-treatment with antimicrobial spray product.

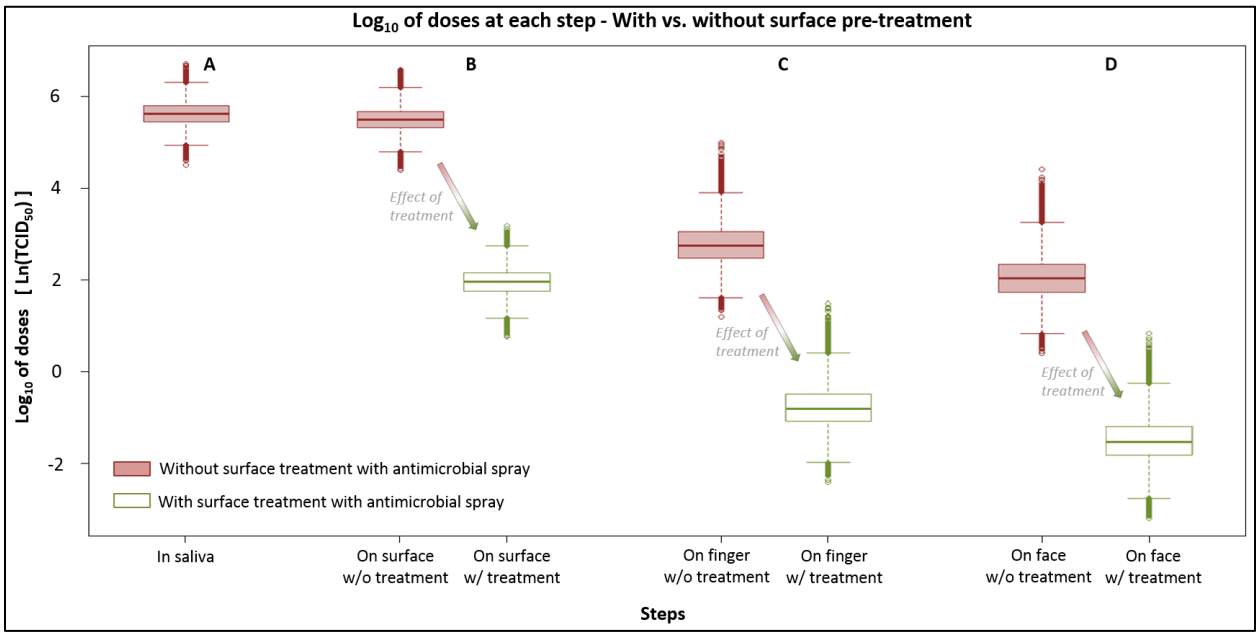


Figure 6. Distribution of dose values at each exposure step, for the base model (instantaneous exposure duration, with one cough, one surface touch, and one single face touch). Plots obtained after running 100,000 Monte Carlo trials.

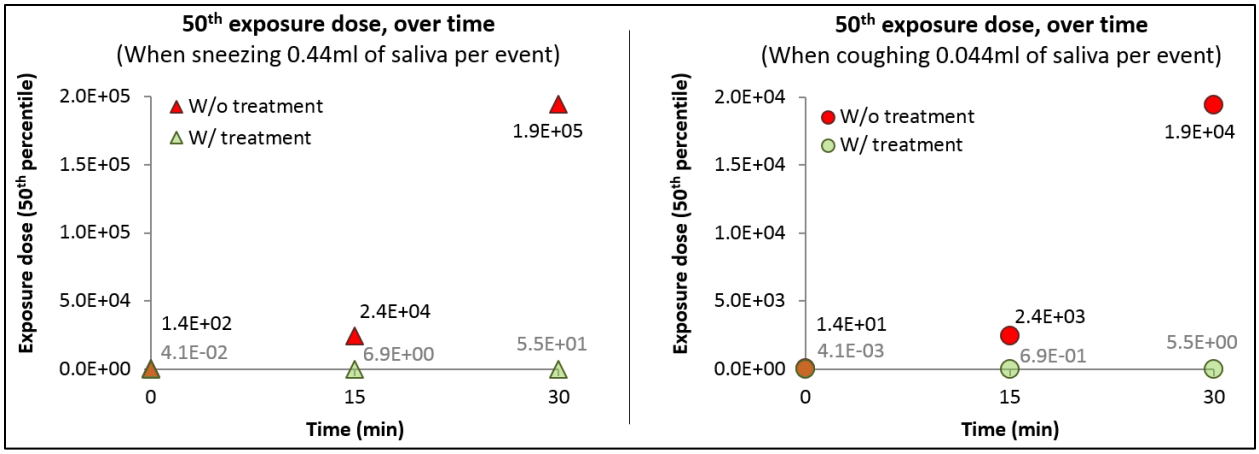


Figure 7. Exposure doses over time, when sneezing or coughing, with or without surface pre-treatment with antimicrobial spray product.

Risk characterization

A distribution of risk estimates was computed to describe the probability of infection with and without surface treatment for all 6 scenarios. It should be noted again that the percentage of viral log-reduction on the surface associated with surface pre-treatment was based on the limit of detection, so it follows that the actual risk for each scenario would be less than the reported values.

The histograms in Figure 8 illustrate the distribution of the risk of infection for a person instantaneously self-inoculating himself via fomite contact, after someone else spread viruses by coughing one time and expelling 0.044 ml of saliva (base scenario). It can be noticed that, without antimicrobial spray surface treatment, the median risk of infection for the base scenario associated with one cough was found to be 1.25×10^{-4} (approximately 1 infections in 100,000) with a lower and upper bound (5^{th} and 95^{th} percentiles) at 2.51×10^{-5} and 9.19×10^{-4} respectively. With surface treatment, median risk of infection for one cough goes down to 3.64×10^{-8}, with a lower and upper bound at 6.67×10^{-9} and 2.80×10^{-7} respectively. Therefore, it can be concluded that porous surface treatment with antimicrobial spray can reduce the risk of infection by 4-orders of magnitude, corresponding to the efficacy of the treatment. Comparable reduction level is observed for the same base scenario, but with a sneeze as an expelling event (see Table 3).

The expected results are for a single surface and face touch, showing that low exposure doses fall within the linear low-dose region of the dose-response curve. More realistic exposure durations with multiple surface and face touches show higher risks, with exposure doses falling outside of the linear low-dose region (see Figure 9), indicating that though the process is linear, the efficacy of the product may result in non-linear risk reduction, especially for the upper bound 95^{th} percentile risk estimates. For all the six scenarios described earlier, the exposure doses and associated risks are summarized in Figure 9 and Table 3, respectively.

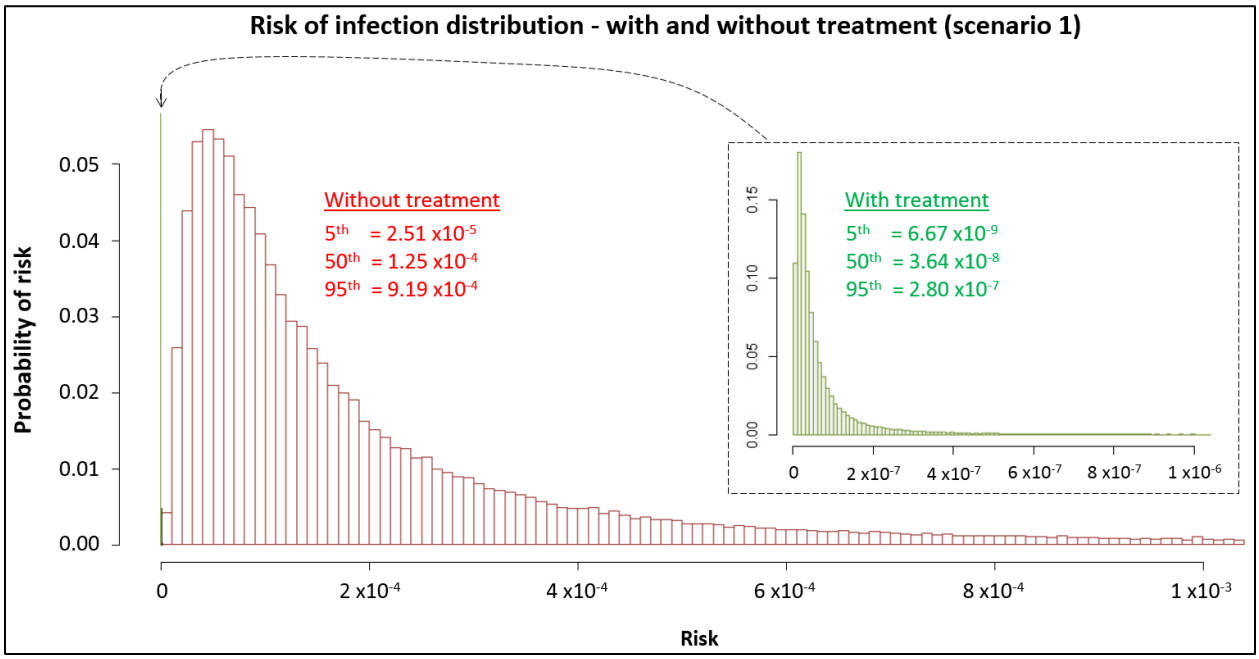


Figure 8. Histogram of the risk distribution for influenza A infection, for the base model (instantaneous exposure duration, with one cough, one surface touch and one single face touch), with and without treatment. Plots obtained after running 100,000 Monte Carlo trials.

Table 3. Risk levels calculated for each scenario considered, with and without surface treatment.

Scenario		Risk			Dose	Parameters changed for each scenario			
#	Trt	5^{th}	50^{th}	95^{th}	50^{th}	Time (min)*	Event^{+}	# surface touches$^{\Delta}$	# face touches$^{\Phi}$
1	Trt-†	2.51×10^{-05}	1.25×10^{-04}	9.19×10^{-04}	1.06×10^{02}	0	1 cough	1	1
	Trt+‡	6.67×10^{-09}	3.64×10^{-08}	2.80×10^{-07}	3.07×10^{-02}				
2	Trt-	2.51×10^{-04}	1.25×10^{-03}	9.10×10^{-03}	1.06×10^{03}	0	1 sneeze	1	1
	Trt+	6.67×10^{-08}	3.64×10^{-07}	2.80×10^{-06}	3.07×10^{-01}				
3	Trt-	4.22×10^{-03}	2.06×10^{-02}	1.30×10^{-01}	1.79×10^{04}	15	3 coughs	15	3.75
	Trt+	1.13×10^{-06}	6.14×10^{-06}	4.73×10^{-05}	5.18×10^{00}				
4	Trt-	4.03×10^{-02}	1.67×10^{-01}	5.44×10^{-01}	1.79×10^{05}	15	3 sneezes	15	3.75
	Trt+	1.13×10^{-05}	6.14×10^{-05}	4.73×10^{-04}	5.18×10^{01}				
5	Trt-	3.26×10^{-02}	1.39×10^{-01}	4.98×10^{-01}	1.43×10^{05}	30	6 coughs	30	7.5
	Trt+	9.01×10^{-06}	4.91×10^{-05}	3.78×10^{-04}	4.14×10^{01}				
6	Trt-	2.39×10^{-01}	5.63×10^{-01}	8.57×10^{-01}	1.43×10^{06}	30	6 sneezes	30	7.5
	Trt+	9.01×10^{-05}	4.91×10^{-04}	3.76×10^{-03}	4.14×10^{02}				

† Trt- & ‡ Trt+ = Without & with antimicrobial spray pre-treatment of surface.

***** Time duration of 15 and 30 minutes were considered, as Nicas and Jones (Nicas & Jones, 2009) reported a plausible scenario of a person visiting someone sick in a residential bedroom for a period of 15 minutes, while another study found that the exposure time of visitors in hospital goes from 1 to 124 minutes, with a median duration of 14 minutes (Cohen et al., 2012).

$^{+}$ Cough frequency used were the reported 12 times/hr (Loudon & Brown, 1967a), though other frequencies have been reported, going from 56 to 116 coughs/ hour (Jones, 2011; Kuhn, Hendley, Adams, Clark, & Gwaltney, 1982; Paul, Wai, Jewell, Shaffer, & Varadan, 2006).

$^{\Delta}$ 1 surface touch/min frequency was used, as reported from the literature (Nicas & Jones, 2009).

$^{\Phi}$ 2.5 face touches/10 min was used, based on the literature (Hendley et al., 1973; Kwok et al., 2015; Nicas & Best, 2008; Nicas & Jones, 2009).

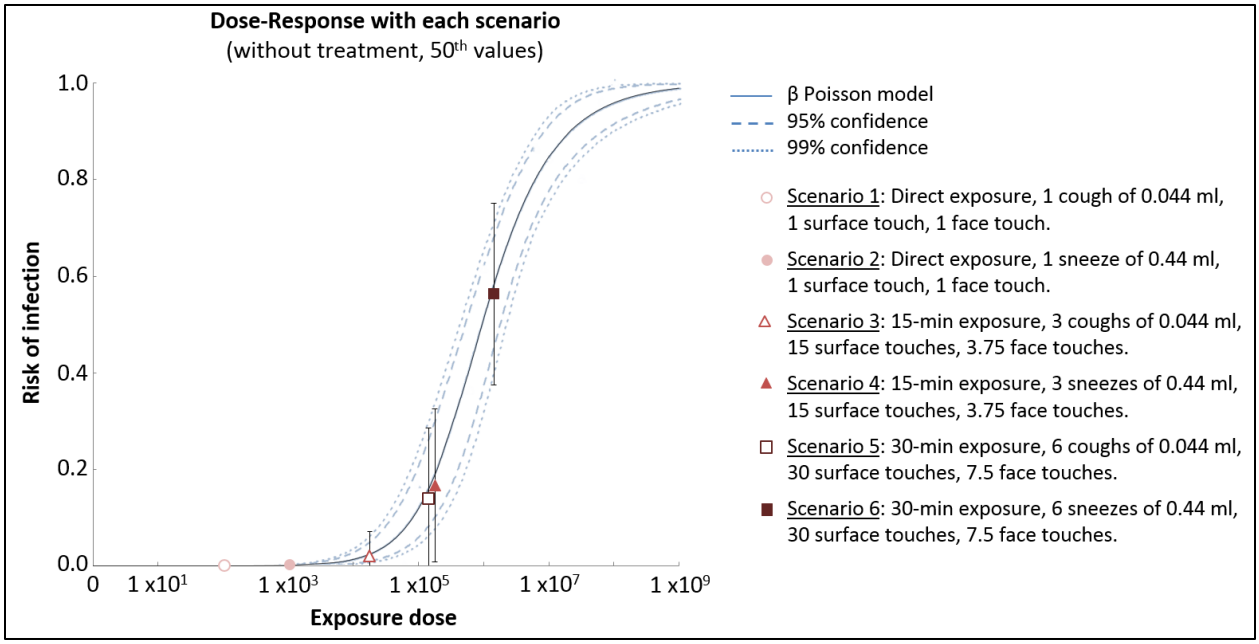


Figure 9. Calculated exposure doses and associated risks for all 6 scenarios, without surface treatment.

It can be observed that risk significantly increase with the exposure time. For instance, a person exposing himself during 30 minutes instead of few seconds to influenza by touching untreated porous surfaces contaminated from a sick person coughing in the room, will see his median risk of infection increasing of a 3-orders of magnitude, going from about 0.01% to 14% respectively (see scenarios 1 and 5 in Table 3). If the person decides to leave the room after 15 minutes, his median risk of infection will be of about a probability of 2% (see scenario 3, Table 3).

Also, for a same exposure time, such as 15 minutes, a person setting in the same room of a influenza A infected patient, could have a median risk of infection through fomite contact ranging from 2% to 17%, depending on the patient shedding activity, by comparing coughing and sneezing event respectively (see scenarios 3 and 4 in Table 3).

Additionally, it can be observed that for all exposure durations and shedding rates from infected patients, an exposed person through fomite contact can minimize his risk of infection by a 4-orders of magnitude by treating porous surfaces in the room with antimicrobial spray. For instance, for a 15 minutes exposure duration with a coughing patient, treatment of surfaces can reduce the medina risk of infection from 2% to 0.0006% (see scenarios 3 Trt- and 3 Trt+ in Table 3).

It appears that the risk associated with scenario 4 without surface treatment (see scenario 4 Trt- in Table 3) relatively follows the same conditions used in the influenza A risk assessment estimated for hand contact published by Nicas and Jones (Nicas & Jones, 2009): Both models consider a 15 minute exposure period for a person near another person coughing three times, with similar viral saliva concentration of about 10^7 $TCID_{50}$/ml. The comparison of the calculated median risk from this present study (1.67×10^{-1}) to the risk reported in Nicas and Jones as 45% of the total risk, 1.1×10^{-2} (or higher if the infectivity ratio is closer to 1:1 in that study) indicates that the actual risk for this route could be substantially higher than previously estimated.

Lastly, the relative risks presented in the Nicas and Jones paper indicated that surface contact presents the highest component of total influenza risk, making this present study an important contribution to the literature as it better characterizes risk associated with textile contact, by applying at the same time a revised dose-response model (Fan et al., 2009; B. Murphy et al., 1985).

Sensitivity analysis

A sensitivity analysis of the single touch base case risk model was conducted. Sensitivity charts quantify the influence of each input parameters on the variability and uncertainty in the output risk distributions and helps identify which input parameters might be refined through future research. Crystal Ball calculates sensitivity by computing rank correlation coefficients between every assumption and forecast, while the simulation is running. Crystal Ball (Oracle Company, n.d., 2013) squares the rank correlation coefficients and normalize them to 100% (Figure 10). This sensitivity analysis revealed that uncertainty in the model is mainly due to variability of two parameters: the surface-to-fingertip transfer efficiency and the influenza concentration in saliva. These two parameters account together for 70% of the variability. These results can be explained by the relatively high range of values reported in the literature for each of these parameters. The primary driver of variability, surface-to-finger influenza transfer rate, is also subject to inherent variability, as many factors can influence this parameter, including the viral species itself, the type of porous fabric, the air temperature and relative humidity, and the level of pressure applied on the surface during the touch (Julian, Leckie, & Boehm, 2010). The second variable, concentration of influenza in saliva, is expected to vary based on the stage of illness of the donor. It is well established that viral shedding rates change from infection to illness to recovery. While more refined estimates for these values would reduce uncertainty in the risk calculations, inherent variability cannot be reduced. Furthermore, the absence of the point-value input parameter – volume of saliva expelled per cough or sneeze - in the sensitivity analysis does not necessary means that its estimation is fully satisfying. Because it is also used for estimating the initial contamination on the surface, further investigation may also be warranted. This additional work may have the greatest potential for reducing true uncertainty in the risk estimates.

Regarding the influence of the distributional assumptions for each input parameter, a comparison of different possible distributions given the available data was done, testing uniform, log-normal, triangular and normal distribution. The sensitivity analysis did not change significantly across the distributional changes. The selection of each input distribution was done to fit the observed pattern of the data and to produce risk estimates consistent with the assumptions described above.

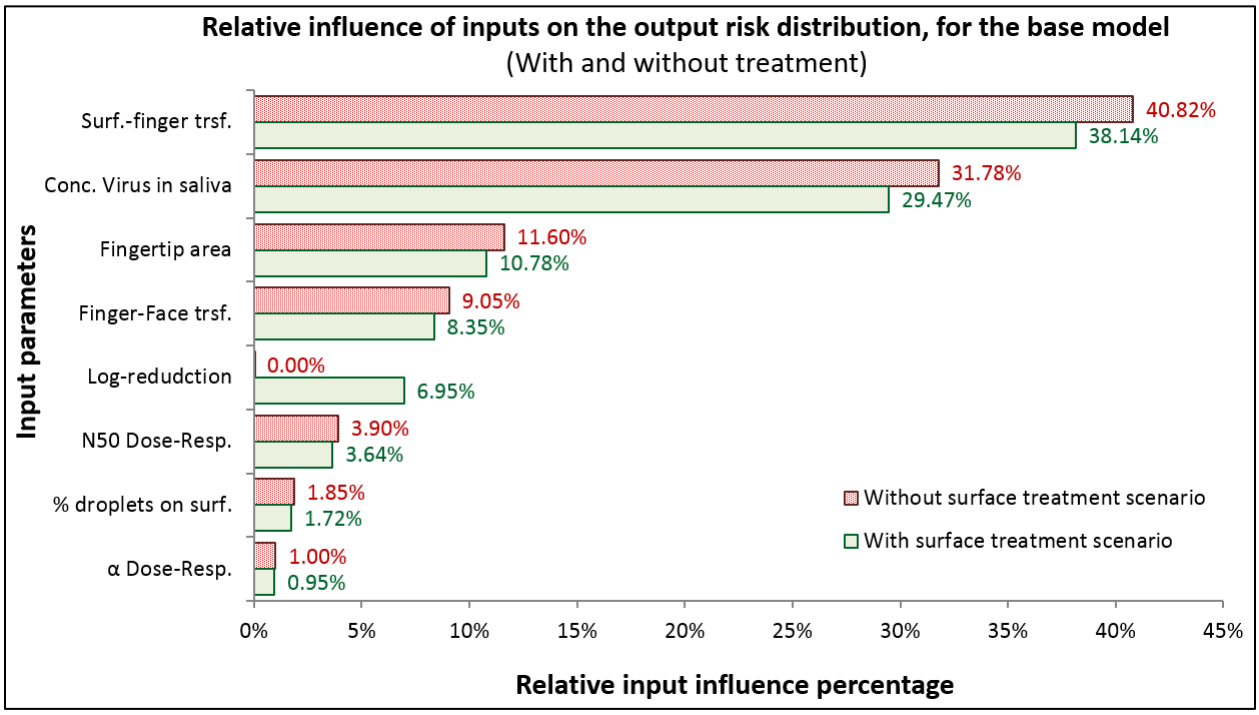


Figure 10. Sensitivity analysis of input parameters, for the base model (instantaneous exposure duration, one cough, one surface touch and one single face touch).

CHAPTER 4 – CONCLUSIONS AND FUTURE WORK

CONTRIBUTIONS

Influenza transmission modeling is critical for estimating the risk of infection, especially during flu outbreak season. Indirect transmission via fomite, consisting of self-contamination from facial touch after a contact with some contaminated surfaces, has been proven to be an important cause of influenza transmission (Bean et al., 1982; Nicas & Jones, 2009). The information used in this analysis was based on the best available scientific data and is useful for informing risk management strategies to prevent influenza cases. Current recommendations focus on hand washing (Wong, Cowling, & Aiello, 2014), disinfection of commonly touched nonporous surfaces and laundering cloth and linens with high temperature machine drying (Jeong, Bae, & Kim, 2010; Sakaguchi et al., 2010). This study showed that the use of antimicrobial sprays on fabrics may have a significant impact on risk reduction of the indirect transmission of influenza through surfaces, and led to a scientific publication (Chabrelie, Mitchell, Rose, Charbonneau, & Ishida, 2018).

Second, this study highlighted the fact that the risk of infection is mostly sensitive to two parameters: (1) the concentration of influenza virus in saliva, and (2) the surface-to-finger transfer rate (see Figure 10 on the sensitivity analysis). Such information is important for researchers and risk assessors, suggesting that investigating in more details the distribution pattern of these parameters could help to minimize the uncertainty and/or variability of the estimated risk. Variation of concentration of virus in saliva of an infected person is believed to be only due to natural variability, since people can have different immune systems abilities, or be in different

infectious stage. In consequence, additional research on viral concentration in saliva might not bring more precise risk estimation. However, conducting additional research on the surface-to-finger transfer rate for influenza virus specifically might be an interesting work, since the variation of this parameter is believed to be mainly due to uncertainty, instead of natural variability.

Third, the base model developed in this study validated the fact that the risks of influenza infection associated with a single touch of an inoculated porous fabric followed by a direct facial touch with one fingertip is a concern. Median risk value calculated for this simple baseline scenario was determined to be 1.25×10^{-4}, which can be considered as a relative low risk. Additionally, the use of the antimicrobial spray product on a porous surface significantly reduces this risk by 4-orders of magnitude, leading to a final median risk of 3.64×10^{-8}, equivalent to approximately 4 infections in 100 million, for the single surface and face touch base scenario. However, the risk of infection should be considered with an understanding of the potential for multiple touches by multiple fingers in realistic scenarios, potentially leading to higher risk of infection. The comparison of the baseline instantaneous single surface and face touch scenario, with a 15-minute and 30-minute exposure duration with associated time-dependent number of surface and face touches showed risk of infection could increase to a maximum median value of 56%, which is highly concerning.

These risk estimates for single and multiple surface and face touches scenarios were based on a point estimate of coughing frequency of 0.2 times/minute (12 times/hr) (Loudon & Brown, 1967a), though higher values have also been reported, ranging from 0.856 to 1.93 times/minute (56 to 116 times/hr) (Kuhn et al., 1982; Paul et al., 2006). Similarly, the expelled saliva volumes of 0.044 or 0.44 ml per event were based on previous studies, but sneezing has been reported to produce even higher volumes of saliva, up to 0.55 ml per event (Duguid, 1946). Thus, it is

reasonable to assume that realistic exposure through contact with porous fabric would result in even higher risks.

In addition, the developed model in this study used a proposed new dose-response model that were derived from two studies (Fan et al., 2009; B. Murphy et al., 1985), bringing substantial information to future risk assessors, regarding this parameter.

Finally, the developed risk model showed that scenarios describing realistic exposure durations from 15 to 30 minutes, with subsequent multiple surface and face touches, brought risk estimates falling outside of the linear low-dose region of the dose-response model (see Figure 9). This observation lead to the conclusion that industrial companies producing products designed to reduce viral content on surfaces might be interested to not only claim the viral load reduction on surface (EPA, 2018), but also the final related calculated risk reduction. With risk reduction claim being believed to better transcribe the positive impact of a developed industrial antimicrobial product.

ASSUMPTIONS AND LIMITATIONS

First assumption made in the developed model consisted in excluding the natural decay rate of influenza on the porous surface and on the skin, in order to simulate a static condition is supposed to be a conservative assumption. It was considered a reasonable assumption, given that an ill person may consistently shed viruses by coughing and sneezing, leading to a continuous viral loading on surfaces. Hence, the exposed person, like a caregiver, may frequently touch the continuously contaminated surfaces beyond the single fingertip used for estimation in this study. It is therefore possible that developing a more complex dynamic model would then have no major

impact on the risk estimation. Furthermore, reported decay rates of virus on surface (Bean et al., 1982; Greatorex et al., 2011) or skin (Ansari, 1991; Grayson et al., 2009; Schurmann & Eggers, 1983) show wide different ranges, as shown in Figure 11.

Second, the laboratory tests were conducted on a 100% cotton porous fabric, studying the effect of an antimicrobial spray product on such surface. However, it imaginable that viral removal from spray usage may be different on non-porous surface, compare to on porous surface (Kraay et al., 2018; Otter et al., 2016).

Third, it has been shown that desorption of viral particles from a porous surface may occurs (Gerba, 1984). In this study, the desorption/re-suspension event has not been taken into account, as the study were exclusively focused on an indirect transmission through surface touch only. By considering the additional virus airborne route and the indirect inhalation route through virus re-suspension, risk of infection may potentially reach higher levels.

Finally, a spatial distribution of viruses on surface is relatively difficult to model, with viral loading on surfaces believed to be subject to a large degree of variability. This variable was not directly taken into consideration in this study, but the beta-Poisson dose-response model does consider the Poisson distribution of microorganisms in a given dose. Deposition from coughing or sneezing over a larger fabric area could result in lower risks depending on the distribution, while larger areas of contamination and touching the surface with multiple fingers would increase risks.

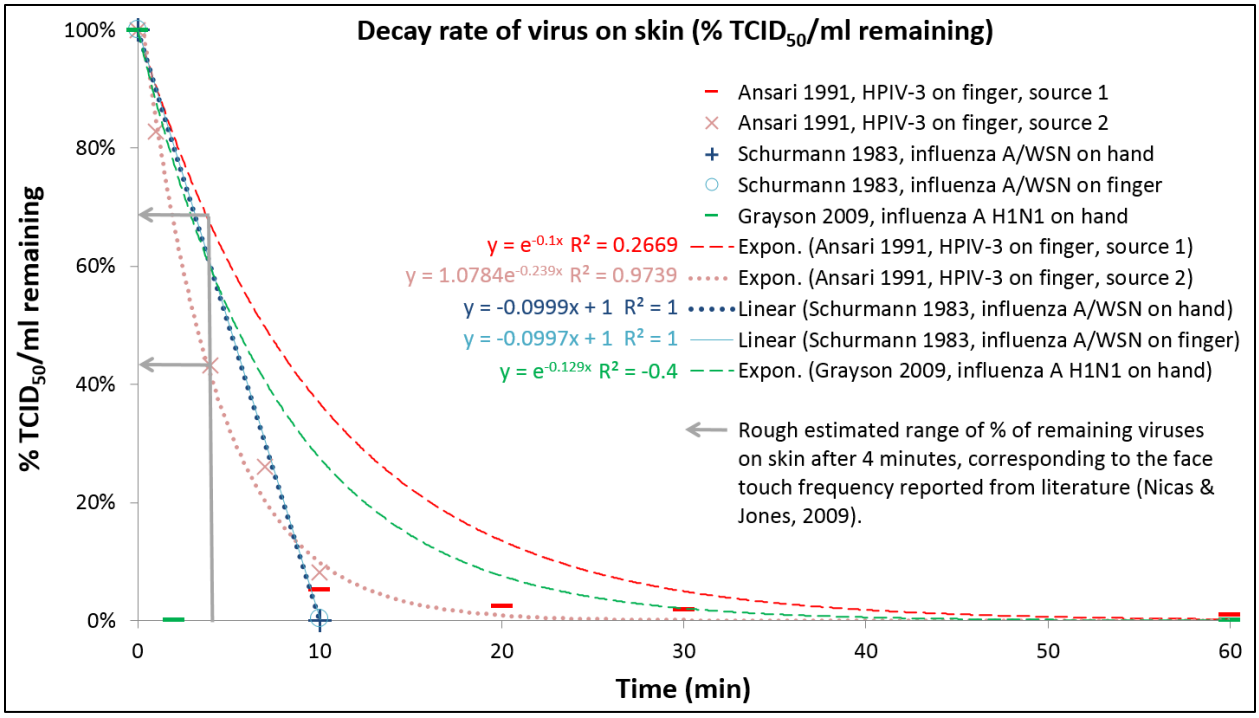


Figure 11. Decay rates of human parainfluenza virus 3 (HPIV-3) and influenza A/WSN on skin. Data recovered from literature review (Ansari, 1991; Grayson et al., 2009; Schurmann & Eggers, 1983).

POSSIBLE FUTURE WORK

The developed risk of infection characterization and risk reduction from usage of antimicrobial spray on to surface as pre-treatment, were calculated for a scenario were an infected person shed influenza virus onto surrounding porous surfaces (100% cotton fabric being considered as a good surrogate to represent any porous surfaces), followed by a self-inoculation of another person through contact with these contaminated porous surfaces. Hence, this model did not consider the possible virus transmission through porous surfaces other than 100% cotton, and through non-porous surfaces, such as steel or plastic surfaces for example (Kraay et al., 2018; Otter et al., 2016). Extending the model by including the risk related to self-contamination though contact with such other surfaces could be interesting, in order to have a more complete and generalizable model. Doing so would require recovering additional parameters, such as the virus load reduction after application of antimicrobial spray on those surfaces, and the transfer rate of viruses from non-porous surface to hand.

As transmission of viruses through close air contacts is considered to a possible important pathway (Brankston et al., 2007; Nicas & Jones, 2009), including this second transmission route may be relevant to consider as well.

Another possible improvement could be to develop a dynamic model that would consider continuous addition of viruses over time into the system (on porous and non-porous surfaces), along with a continuous viral removal process from viral decay on surfaces and/or from air ventilation, as conducted by some other researchers for bacterial pathogens.

APPENDIX – INPUT PARAMETER VALUES AND DETAILED INFORMATION

Parameter	Distribution applied in the model	Details of values extracted from the literature
$V_{Saliva/event}$	Point-value • For 1 cough: 0.044 ml. • For 1 sneeze: 0.44 ml.	Highest values from the most recent study done in this field was kept (Nicas et al., 2005). Other reported values found from literature were hence not considered: 0.00755 ml/cough and 0.549/sneeze (Duguid, 1946), and 0.00539/cough (Loudon & Roberts, 1966). Data from Papineni & Rosenthal 1997 (Papineni & Rosenthal, 1997) were not considered as well, since they did not analyze droplets greater than 8µm of diameter, while in reality, 99.9% of droplets are believed to be greater than this diameter (Nicas et al., 2005)
C_{Saliva}	Log-Normal • Location = 600 $TCID_{50}$/ml • Mean = 11,075,000 $TCID_{50}$/ml • 95% = 24,550,000 $TCID_{50}$/ml	Values retrieved and used for defining the distribution: 600 and 20,000,000 $TCID_{50}$/ml from influenza A concentration found in human nasal washes (B. R. Murphy et al., 1973); 10,000 and 100,000,000 $TCID_{50}$/ml from the reported influenza virus concentration in saliva (Nicas & Jones, 2009)
$F_{Coughs/hr}$	Point value • 12 times/hr	Kept cough frequency were the reported 12 times/hr (Loudon & Brown, 1967a), though other frequencies have been reported, going from 56-116 times/ hour (Kuhn et al., 1982; Paul et al., 2006) to as high as 105 coughs/ hour (Jones, 2011).
$F_{Air \rightarrow Surf.}$	Triangular • Min = 51% • Likeliest = 76% • Max = 100%	The minimum and maximum values of 51% and 100% came from two studies (Loudon & Roberts, 1966; Nicas & Jones, 2009). As no specific indication on the possible distribution pattern was found from the literature, a triangular distribution was set.
$R_{Decay\ surface}$	Parameter excluded from the model	The frequency of coughing – and subsequently the frequency of surrounding surface inoculation – is reported to range from 12 coughs per hour (Loudon & Brown, 1967a), to 56-116 times per hour (Kuhn et al., 1982; Paul et al., 2006) to as high as 105 coughs per hour (Jones, 2011). In addition, one study states that influenza viruses survive from 8 to 12 hours on porous surfaces (Bean et al., 1982). In consequence, it has been assumed that surfaces are continuously contaminated with influenza A virus, and viruses do not have time to decay.
F_{Red}	Triangular • Min = 99.9503% • Likeliest = 99.9725% • Max = 99.9905%	Values were recovered from the laboratory tests done by Procter & Gamble (see Table 1). Percentage of viral log reduction on the 100% cotton fabric was calculated using the formula: $1\text{-}10^{-\log \text{reduction}}$. Since no suggested distribution was found from the literature, and because three values were recovered, a triangular distribution was set. See Figure 4.

$F_{Surf.\ touch/min}$	Point value • 1 surface touch/min	The literature gave a surface touch frequency of one time/minute (Nicas & Jones, 2009).
$F_{Surf.\rightarrow Finger}$	Weibull • Location = 0.002755 • Scale = 0.0033109 • Shape = 0.553901	The porous surface to skin transfer rate efficiency values were retrieved from the following sources: 0.251% of influenza A viruses transferred from porous surface (paper tissue) to hand (Bean et al., 1982). 0.005%, 0.0005% and 0.03% of PRD-1 phage transferred from 100% cotton laundry to hand, 50-50% cotton-polyester laundry to hand, and dishcloth to hand, respectively (Rusin et al., 2002). 0.03% and 0.3%, 0.3% and 2.3%, 0.4% and 0.7% of MS2 coliphage transferred from 100% cotton under low and high humidity, from 100% polyester under low and high humidity, and from paper currency under low and high humidity, respectively (Lopez et al., 2013). Phages such as MS2 phage are known to be usable as surrogate for influenza virus (Coulliette et al., 2014). Value range was observed to be left-skewed. A distribution fit was run by using the fitdistrplus package (Delignette-muller & Dutang, 2015) in R v3.5.3 software (R Foundation for Statistical Computing, 2013). The best-fit distribution was found to be the Weibull distribution.
$R_{Decay\ skin}$	Parameter excluded from the model	Decay rates of human parainfluenza virus 3 (HPIV-3) and influenza A/WSN on skin, according to the literature (Ansari, 1991; Grayson et al., 2009; Schurmann & Eggers, 1983). See Figure 11. The total viral decay on skin is reported to widely vary, from a range of 10 to 60 minutes. Since reported face touch frequency is of one time per 4 minutes, this parameter was considered not necessary to include, as 40 to 70% of viruses would survive on skin over this 4-minute period (Hendley et al., 1973; Kwok et al., 2015; Nicas & Best, 2008; Nicas & Jones, 2009). Hence, conservative assumption was made to consider a full 100% viral survival on skin.
A_{Finger}	Uniform • Min = 2.00 cm^2 • Max = 7.16cm^2	A literature reviewed allowed to identify 8 values estimating the area of a human fingertip. Two sources reported a fingertip area of 2 cm^2 (Nicas & Jones, 2009; J. B. Rose et al., 2013). Murai et al. 1997 studied human volar face of fingers from fresh Asian cadavers and listed fingertip areas for each human finger, with values going from 6.66, 7.16, 6.71, and 5.49 cm^2 for the index, middle, ring and little finger, respectively (Murai et al., 1997). Finally, one study analyzed the fingertip sizes of 97 participants and estimated an average fingertip area of 3.60 cm^2 for women, and 4.25 cm^2 for men (Peters et al., 2009).
A_{Fabric}	Point-value • Min = 12.25 cm^2	The area of the 100% cotton fabric used were used to calculate the A_{Finger}/A_{Fabric} ratio, in order to estimate the fraction of viruses on the tested fabric that would be exposed to be transferred on a fingertip after a single touch. The area of the tested cotton fabric pieces were recovered from the laboratory tests done by the industrial company (see Table 1 and Chapter 3, "Laboratory experimental data" section).

$F_{Face\ touch/min}$	Point value • 2.5 face touches/10 min	The literature reported a single face touch frequency of 2.5 times every 10 minutes (Hendley et al., 1973; Kwok et al., 2015; Nicas & Best, 2008; Nicas & Jones, 2009).
$F_{Finger \rightarrow Face}$	Triangular • Min = 5.49% • Likeliest = 19.75% • Max = 33.9%	Two values were extracted from two studies. Jones et al. 2011 found that the skin-to-skin transfer of rhinovirus HH of 5.49% in average could be representative of influenza transfer during skin-to-skin contact (Jones, 2011). Rusin et al. 2002 proposed a fingertip-to-lips transfer efficiency of 33.9% for phage PRD-1 (Rusin et al., 2002). Because of no further information found, these values were assumed to be the minimum and maximum of a triangular distribution, while the average was chosen as the likeliest value.
α	Triangular • Min = 4.24 $x10^{-1}$ (5^{th}) • Likeliest = 6.40 $x10^{-1}$ (average) • Max = 9.15 $x10^{-1}$ (95^{th})	A best-fit β-Poisson dose-response was found in the QMRA Wiki webpage (Huang, 2013), derived from two studies that provided raw data (B. Murphy et al., 1984, 1985) which correlated the risk of infection to intranasal influenza concentration in humans. This recommended best-fit dose-response was developed after a statistical test run to estimate the model. A triangular distribution was applied for each parameter, using the 5^{th} and 95^{th} percentiles as min and maximum values, while the average value was considered for the likeliest value of the triangular distribution. See Eq. 3.
N_{50}	Triangular • Min = 5.72 $x10^{5}$ (5^{th}) • Likeliest = 1.07 $x10^{6}$ (average) • Max = 1.62 $x10^{6}$ (95^{th})	

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